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RIJKSINSTITUUT VOOR ZIEKTE- EN INVALIDITEITSVERZEKERING
DIENST GENEESKUNDIGE VERZORGING
Comité voor de evalutie van de medische praktijk inzake geneesmiddelen

The rational use of medication for the treatment of migraine

Literature review: full report

Consensus conference
May 25th 2023
Auditorium Lippens (Royal Library)
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This literature review was performed by BCFI/CBIP

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Table of contents

1 Abbreviations

APC: ASA + paracetamol + caffeine
ASA: acetylsalicylic acid
CHD: coronary heart disease
CI: confidence interval
CO: crossover RCT
CVD: cardiovascular disease
DB: double blind
HIT-6: Headache Impact Test–6
HR: hazard ratio
HRQoL: Health Related Quality of Life
ITT: intention-to-treat analysis
MA: meta-analysis
MCID: minimal clinically important difference
MD: mean difference
MIDAS: Migraine Disability Assessment Questionnaire
MSQ: Migraine-Specific Quality of Life Questionnaire v2.1
n: number of patients
N: number of studies
NA: not applicable
NR: not reported
NS: not statistically significant
NT: no statistical test
OL: open label
PG: parallel group
PO: primary outcome
QoL: Quality of life
SAE: Serious adverse event: Serious adverse event was defined as any untoward medical occurrence that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability/incapacity.
SB: single blind
SD: standard deviation
SF-36 : 36-Item Short Form Health Survey
SS: statistically significant
VAS: Visual Analogue Scale

2 Methodology

2.1 Introduction

This literature review was conducted in preparation of the consensus conference **"The rational use of medication for the treatment of migraine"** which will take place on the 25th of May 2023.

2.2 Questions to the jury

The questions to the jury, as they were phrased by the organising committee of the RIZIV/INAMI are:

1. **a.** Wat is migraine? Hoe te diagnosticeren? Hoe te onderscheiden van andere soorten hoofdpijn? Welke zijn de verschillende vormen van migraine?
   a. Qu'est-ce que la migraine ? Comment la diagnostiquer ? Comment la différencier des autres céphalées ? Quels sont les différents types de migraines ?

   b. Wat zijn de mogelijke oorzaken/uitlokkende factoren van (deze verschillende vormen van) migraine en migraineaanvallen?
   b. Quelles sont les causes/déclencheurs possibles de (ces différentes formes de) migraines et des crises de migraine ?

2. **a.** Welke behandelingen en/of welke farmaceutische klassen hebben een aangetoond effect op migraineaanvallen?
   a. Quels traitements et/ou quelles classes pharmaceutiques ont un effet prouvé sur les crises de migraine ?

   b. Welke behandelingen en/of welke farmaceutische klassen hebben een aangetoond effect op het voorkomen van migraine(aanvallen)?
   b. Quels traitements et/ou quelles classes pharmaceutiques ont un effet prouvé dans la prévention de la migraine (crises) ?

   c. Welke zijn hun mogelijke ongewenste effecten (incl. bij gebruik op langere termijn)?
   c. Quels sont leurs éventuels effets indésirables (y compris après utilisation à long terme) ?

   d. Welke zijn hun mogelijke contra-indicaties?
   d. Quelles sont leurs éventuelles contre-indications ?

3. Aanpak van migraine in verschillende populaties:
   Prise en charge de la migraine dans différentes populations :

   a. Volwassenen. Welke is de aanbevolen aanpak
      Adultes. Quelle est la prise en charge recommandée

      i. van migraineaanvallen? / des crises de migraine ?

      ii. om aanvallen te voorkomen? / pour prévenir les crises ?

b. Kinderen en adolescenten. Welke is de aanbevolen aanpak
Enfants et adolescents. Quelle est la prise en charge recommandée

   i. van migraineaanvallen? / des crises de migraine ?

   ii. om aanvallen te voorkomen? pour prévenir les crises ?

c. Ouderen. Welke is de aanbevolen aanpak
Personnes âgées. Quelle est la prise en charge recommandée

   i. van migraineaanvallen? / des crises de migraine ?

   ii. om aanvallen te voorkomen? pour prévenir les crises ?

d. Menstruatiegebonden migraine. Welke is de aanbevolen aanpak
Migraine menstruelle. Quelle est la prise en charge recommandée

   i. van menstruele migraineaanvallen? / des crises de migraine menstruelles ?

   ii. om menstruele aanvallen te voorkomen? / pour prévenir les crises menstruelles ?

   iii. wat met hormonale contraceptie? / quid de la contraception hormonale ?

e. Zwangerschap en lactatie. Welke is de aanbevolen aanpak
Grossesse et allaitement. Quelle est la prise en charge recommandée

   i. van migraineaanvallen? / des crises de migraine ?

   ii. om aanvallen te voorkomen? / pour prévenir les crises ?

4. Hoe patiënten met migraine optimaal opvolgen?
Comment suivre de manière optimale les patients souffrant de migraine ?

   a. qua effect van de behandeling(en) (incl. juiste moment van evaluatie, duur, afbouw en stopzetting van de behandeling, tools om de effectiviteit te evalueren, …)?
   en termes d'effet du ou des traitement(s) (y compris le bon moment pour évaluer le traitement : sa durée, sa réduction posologique, son arrêt, les outils pour évaluer son efficacité, etc.) ?

   b. qua mogelijke ongewenste effecten (rekening houdend met eventuele comorbiditeiten)?
   en termes d'effets indésirables éventuels (en tenant compte d'éventuelles comorbidités) ?

   c. Rolverdeling/samenwerking 1e, 2e en 3e lijn?
   Répartition des rôles/coopération 1e, 2e et 3e ligne ?

5. Welke kan de rol zijn van andere gezondheidszorgberoepen (andere artsen dan huisartsen en neurologen, apothekers, psychologen, verpleegkundigen, kinesitherapeuten, …) bij de hulp aan migrainepatiënten?
Quel pourrait être le rôle des autres professionnels de la santé (médecins autres que généralistes

et neurologues, pharmaciens, psychologues, infirmiers, kinésithérapeutes, …) dans l'accompagnement des patients migraineux ?

6. Zijn de huidige terugbetalingsregels van de specialiteiten ter behandeling van migraine up-to-date?
   Les règles actuelles de remboursement des spécialités dans le traitement de la migraine sont-elles à jour ?

2.3 Research task of the literature group

The organising committee has specified the research task for the literature review as follows:

- To discuss **selected guidelines**.
  - See 2.3.1 for guideline inclusion criteria.
- To perform a literature review:
  - To search and report relevant **RCTs or systematic reviews/meta-analyses of RCTs,** and for certain questions**, observational studies,** to provide an answer to certain research questions.
  - See 2.3.2 for information on study type inclusion criteria and 2.3.3 for search details.
- To discuss information from **additional sources** for information on safety, contra-indications, specific subgroups, precautions and monitoring.
  - See section "11 Additional safety information from other sources".

In the table below, we provide an overview of the research task of the literature group per jury question. We also indicate in what chapter the results can be found.

Question 1 **a.** Wat is migraine? Hoe te diagnosticeren? Hoe te onderscheiden van andere soorten hoofdpijn? Welke zijn de verschillende vormen van migraine? **a.** Qu'est-ce que la migraine ? Comment la diagnostiquer ? Comment la différencier des autres céphalées ? Quels sont les différents types de migraines ? **b.** Wat zijn de mogelijke oorzaken/uitlokkende factoren van (deze verschillende vormen van) migraine en migraineaanvallen? **b.** Quelles sont les causes/déclencheurs possibles de (ces différentes formes de) migraines et des crises de migraine ?
• This question will be answered by an expert-speaker.
Question 2 **a.** Welke behandelingen en/of welke farmaceutische klassen hebben een aangetoond effect op migraineaanvallen? **a.** Quels traitements et/ou quelles classes pharmaceutiques ont un effet prouvé sur les crises de migraine ?

b. Welke behandelingen en/of welke farmaceutische klassen hebben een aangetoond effect op het voorkomen van migraine(aanvallen)?
b. Quels traitements et/ou quelles classes pharmaceutiques ont un effet prouvé dans la prévention de la migraine (crises) ?

c. Welke zijn hun mogelijke ongewenste effecten (incl. bij gebruik op langere termijn)?
c. Quels sont leurs éventuels effets indésirables (y compris après utilisation à long terme) ?

d. Welke zijn hun mogelijke contra-indicaties?
d. Quelles sont leurs éventuelles contre-indications ?

- The literature group will discuss the selected **guidelines**. This discussion can be found in chapter 5.1 and 5.2.
- The literature group will perform a literature search of **RCTs or systematic reviews/meta-analyses** of RCTs. The results of the literature search can be found in chapter 6 to 9 and details in appendix 12-15.
- The literature group will provide additional information from **observational studies** for cardiovascular adverse events in older people with migraine in chapter 10 (and appendix 16).
- **Additional sources** (see 2.3.2) will also be consulted for safety outcomes. The results of additional sources can be found in chapter 11.
- An expert speaker will provide comments and additional information.

Question 3

Aanpak van migraine in verschillende populaties:
Prise en charge de la migraine dans différentes populations :

a. Volwassenen. Welke is de aanbevolen aanpak
Adultes. Quelle est la prise en charge recommandée

iii. van migraineaanvallen? / des crises de migraine ?

iv. om aanvallen te voorkomen? / pour prévenir les crises ?

b. Kinderen en adolescenten. Welke is de aanbevolen aanpak
Enfants et adolescents. Quelle est la prise en charge recommandée

v. van migraineaanvallen? / des crises de migraine ?

vi. om aanvallen te voorkomen? pour prévenir les crises ?

c. Ouderen. Welke is de aanbevolen aanpak
Personnes âgées. Quelle est la prise en charge recommandée

vii. van migraineaanvallen? / des crises de migraine ?

viii. om aanvallen te voorkomen? pour prévenir les crises ?

d. Menstruatiegebonden migraine. Welke is de aanbevolen aanpak
Migraine menstruelle. Quelle est la prise en charge recommandée

ix. van menstruele migraineaanvallen? / des crises de migraine menstruelles ?

x. om menstruele aanvallen te voorkomen? / pour prévenir les crises menstruelles ?

xi. wat met hormonale contraceptie? / quid de la contraception hormonale ?

e. Zwangerschap en lactatie. Welke is de aanbevolen aanpak
Grossesse et allaitement. Quelle est la prise en charge recommandée

xii. van migraineaanvallen? / des crises de migraine ?

xiii. om aanvallen te voorkomen? / pour prévenir les crises ?

- Question 3a:
  - The literature group will discuss the selected **guidelines**. This discussion can be found in chapter 5.1 and 5.2.
  - The literature group will perform a literature search of **RCTs or systematic reviews/meta-analyses** of RCTs. The results of the literature search can be found in chapters 6 and 7 and details in appendices 12 and 13.
- Question 3b:
  - The literature group will discuss the selected **guidelines**. This discussion can be found in chapter 5.7.
  - The literature group will perform a (limited, see 2.3.3 for the specific search criteria) literature search of **RCTs or systematic reviews/meta-analyses** of RCTs. The results of the literature search can be found in chapters 8 and 9 and details in appendices 14 and 15.
- Question 3c:
  - The literature group will discuss the selected **guidelines**. This discussion can be found in chapter 5.4.
  - The literature group will provide additional information from **observational studies** for cardiovascular adverse events in older people with migraine in chapter 10 (and appendix 16).

- Question 3d and 3e:
  - will be answered by an expert-speaker.
  - The task of the literature group is limited to discussion of the selected **guidelines**. This discussion can be found in chapter 5.5 and 5.6.

- An expert speaker will provide comments and additional information.
- **Additional sources** (see 2.3.2) will also be consulted for safety outcomes. The results of additional sources can be found in chapter 11.

Question 4

Hoe patiënten met migraine optimaal opvolgen?
Comment suivre de manière optimale les patients souffrant de migraine ?

a. qua effect van de behandeling(en) (incl. juiste moment van evaluatie, duur, afbouw en stopzetting van de behandeling, tools om de effectiviteit te evalueren, …)?
en termes d'effet du ou des traitement(s) (y compris le bon moment pour évaluer le traitement : sa durée, sa réduction posologique, son arrêt, les outils pour évaluer son efficacité, etc.) ?

b. qua mogelijke ongewenste effecten (rekening houdend met eventuele comorbiditeiten)? en termes d'effets indésirables éventuels (en tenant compte d'éventuelles comorbidités) ? c. Rolverdeling/samenwerking 1e, 2e en 3e lijn? Répartition des rôles/coopération 1e, 2e et 3e ligne ?
• The task of the literature group is limited to discussion of the selected **guidelines**. This discussion can be found in chapter 5.8. • An expert speaker will provide comments and additional information.
Question 5 Welke kan de rol zijn van andere gezondheidszorgberoepen (andere artsen dan huisartsen en neurologen, apothekers, psychologen, verpleegkundigen, kinesitherapeuten, …) bij de hulp aan migrainepatiënten? Quel pourrait être le rôle des autres professionnels de la santé (médecins autres que généralistes et neurologues, pharmaciens, psychologues, infirmiers, kinésithérapeutes, …) dans l'accompagnement des patients migraineux
• The task of the literature group is limited to discussion of the selected **guidelines**. This discussion can be found in chapter 5.9 and 5.10. • An expert speaker will provide comments and additional information.
Question 6 Zijn de huidige terugbetalingsregels van de specialiteiten ter behandeling van migraine up-to-date? Les règles actuelles de remboursement des spécialités dans le traitement de la migraine sont-elles à jour ?
• This question will be answered by an expert-speaker.

2.3.1 Guidelines

Guidelines will be selected and agreed upon through discussion with the organising committee, based on relevance for the Belgian situation and certain quality criteria:

- Publication date: only guidelines from 2017 onwards are to be selected. Exceptions can be made when only older guidelines regarding a certain topic are available.
- Quality assessment: Only guidelines that report levels of evidence/recommendation are to be selected.
- Systematic review: the guideline needs to be based on a good systematic search and review of the literature.

In order to make an assessment on the rigour of development of the guidelines, guidelines will be scored according to Agree II score, for the domain “Rigour of development”. More information can be found on http://www.agreetrust.org/. [1]

This table gives an overview of the items assessed in this domain according to the Agree II score.[1]

No.	**Description of the item**
7	Systematic methods were used to search for evidence
8	The criteria for selecting the evidence are clearly described
9	The strengths and limitations of the body of evidence are clearly described
10	The methods for formulating the recommendations are clearly described
11	Health benefits, side effects, and risks have been considered in formulating the recommendations.
12	There is an explicit link between the recommendations and the supporting evidence.
13	The guideline has been externally reviewed by experts prior to its publication
14	A procedure for updating the guideline is provided

Table: Items assessed by the domain "Rigour of development" in Agree II score.

Domain scores are calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain. The domain score "Rigour of development" can be used to assess the process used to gather and synthesize the evidence, the methods to formulate the recommendations, and to update them, though be careful with the interpretation because this scoring is also subjective and the resulting scores can thus be disputable.
In the chapter about the guidelines, the Domain scores as assessed by the literature group, are given for each guideline.
The literature group will also report whether the guideline was developed together with other stakeholders (other healthcare professionals: pharmacists, nurses,… or patient representatives) and whether these guidelines are also targeting these groups.
Similarities and discrepancies between guidelines are to be reported.

2.3.2 Study types

We will look at meta-analyses, systematic reviews, RCTs and observational (cohort) studies.
To be included in our review, the selected studies need to meet certain criteria.

Meta-analyses and systematic reviews

- Research question matches research question for this literature review
- Systematic search in multiple databases
- Systematic reporting of results
- Inclusion of randomised controlled trials
- Reporting of clinically relevant outcomes (that match our selected outcomes)
- Only direct comparisons (no network meta-analyses)

If some of the included studies in a meta-analysis do not match all the inclusion criteria for our Consensus Conference literature review (for example: it may include some studies with a small sample size, or studies with drugs that are not on the Belgian market), this meta-analysis may be included in our review if judged to be sufficiently relevant. In this case, the discrepancies with our inclusion criteria will be discussed clearly.

RCT's

- Research question matches research question for this literature review
- Minimum number of participants: 40 per study-arm. For studies with multiple treatment arms, we will look at the number of participants in comparisons relevant to our search.
- Phase III trials (no phase II trials)
- Post hoc (subgroup) analyses are excluded.

Observational studies

- prospective or retrospective cohort studies with a control arm
- minimum sample size of 1000
- observational studies will only be searched for cardiovascular safety aspects in older people with migraine

Other sources for safety, contra-indications, specific subgroups, precautions and monitoring

- Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI) / Centre Belge d'Information Pharmacothérapeutique (CBIP)
    - *Gecommentarieerd geneesmiddelenrepertorium/ Répertoire Commenté des Médicaments*
    - *Folia Pharmacotherapeutica*
- Martindale: The complete drug reference, 40th edition

Some publications will be excluded for practical reasons:

- Publications unavailable in Belgian libraries
- Publications in languages other than Dutch, French, German and English
- Unpublished studies

2.3.3 Specific search criteria

2.3.3.1 Acute treatment of episodic migraine in adults

Population	Adults with episodic migraine (with or without aura) <u>Excluded:</u> Chronic migraine Vestibular migraine Pregnancy Menstrual migraine Emergency department setting
Interventions	Paracetamol Acetylsalicylic acid NSAID: diclofenac, naproxen, ibuprofen Associations: paracetamol + caffeine, acetylsalicylic acid + caffeine, paracetamol +acetylsalicylic acid + caffeine, paracetamol + NSAID Metoclopramide, domperidone, alizipride Triptans: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan Combination of triptans and NSAID Rimegepant, ubrogepant, atogepant Placebo/ no treatment <u>Excluded:</u> Intravenous medication, except anti-emetics Opioids Corticoids Ketamine Propofol Ergotamine
Comparisons	Intervention vs placebo or no treatment Intervention vs intervention

Outcomes	● Pain freedom (2 hours after start of treatment)
	● Pain relief (after 2 hrs)
	● Sustained pain freedom (24 hrs)
	● Sustained pain relief (24 hrs)
	● Improved function
	● Restored function
	● Associated symptoms (photophobia, phonophobia, nausea, vomiting, vertigo)
	● Chronification (development of medication overuse headache)
	● Use of rescue medication
	● Adverse events
	  ○ Total adverse events
	  ○ Severe adverse events
	  ○ Specific cardiovascular adverse events

Study design	RCTs or meta-analyses of RCTs only No post hoc analyses No minimum treatment period Minimum 40 participants per treatment arm

2.3.3.2 Prophylactic treatment of episodic migraine in adults

Population	Adults with episodic migraine (with or without aura) <u>Excluded:</u> Chronic migraine Vestibular migraine Pregnancy Menstrual migraine
Interventions	Beta-blockers: propranolol, metoprolol, bisoprolol, atenolol Candesartan, telmisartan Calcium-antagonists: flunarizine, verapamil Anticonvulsants: topiramate, valproate, lamotrigine Antidepressants: amitriptyline, venlafaxine Rimegepant, atogepant, ubrogepant Supplements: magnesium, coenzyme Q10, melatonin, riboflavin (vitamin B2), folic acid (vitamin B9) <u>Excluded:</u> Botulinum toxin Monoclonal antibodies
Comparisons	Intervention vs placebo or no treatment Intervention vs intervention
Outcomes	● Change in headache frequency (defined as the reduction in number of migraine days per month, reduction of number of headache days per month, or 50% reduction in these frequencies) ● Change in headache severity (defined by visual analog scale or numerical rating scale) ● Response rate ● Quality of life (headache-specific) ● Use of acute pharmacological treatment ● Functional health status and quality of life ● Associated disability ● Adverse events ○ Total adverse events ○ Severe adverse events ○ Specific cardiovascular adverse events
Study design	RCTs or meta-analyses of RCTs only No post hoc analyses Minimum treatment period 3 months Minimum 40 participants per treatment arm

2.3.3.3 Acute treatment of migraine in children and adolescents

Population	Children (younger than 12 years of age) with episodic migraine Adolescents (12- 18 years of age) with episodic migraine Excluded: Chronic migraine
Interventions	Paracetamol NSAID Placebo/ no treatment
Comparisons	Intervention vs placebo or no treatment Intervention vs intervention
Outcomes	● Pain freedom (2 hours after start of treatment) ● Pain relief (after 2 hrs) ● Sustained pain freedom (24 hrs) ● Sustained pain relief (24 hrs) ● Improved function ● Restored function ● Associated symptoms (photophobia, phonophobia, nausea, vomiting, vertigo) ● Chronification (development of medication overuse headache) ● Use of rescue medication ● Adverse events ○ Total adverse events ○ Severe adverse events ○ Specific cardiovascular adverse events
Study design	RCT No post hoc analyses No minimum treatment/ follow-up period Minimum 40 participants per treatment arm

2.3.3.4 Prophylactic treatment of migraine in children and adolescents

Population	Children (younger than 12 years of age) with episodic migraine Adolescents (12- 18 years of age) with episodic migraine Excluded: Chronic migraine
Interventions	Riboflavin (vitamin B2) Magnesium
Comparisons	Intervention vs placebo or no treatment Intervention vs intervention
Outcomes	● Change in headache frequency (defined as the reduction in number of migraine days per month, reduction of number of headache days per month, or 50% reduction in these frequencies) ● Change in headache severity (defined by visual analog scale or numerical rating scale) ● Response rate

	● Quality of life (headache-specific)
	● Use of acute pharmacological treatment
	● Functional health status and quality of life
	● Associated disability
	● Adverse events
	  o Total adverse events
	  o Severe adverse events
	  o Specific cardiovascular adverse events

Study design	RCT No post hoc analyses Minimum treatment period 3 months Minimum 40 participants per treatment arm

2.3.3.5 *Safety aspects in older people*

Population	Older people (65+) with migraine
Interventions	All acute and preventive treatments defined for adults
Comparisons	Intervention vs placebo or no treatment Intervention vs intervention
Outcomes	Cardiovascular adverse events
Study design	RCT – No post hoc analyses – Minimum 40 participants per treatment arm Observational studies – Cohort studies-more than 1000 patients)

2.4 Search strategy

2.4.1 Principles of systematic search

*Relevant RCTs, meta-analyses and systematic review*s were searched in a stepwise approach.

As a start we have searched for large systematic reviews from reliable EBM-producers (NICE, AHRQ, the Cochrane library, systematic reviews for included guidelines) that answer some or all of our research questions. One or more systematic reviews were selected as our basic source. From these sources, all references of relevant publications were screened manually.

In a second step, we conducted a systematic search in the Medline (PubMed) electronic database for randomised controlled trials (RCTs), meta-analyses, systematic reviews that were published after the search date of our selected systematic reviews.

Guidelines were searched on the website of CEBAM Digital Library for Health (www.cdlh.be), which contains links to the national and most frequently consulted international guidelines. Guideline search engines, like G-I-N, TRIP-database and Dynamed were also searched.

2.4.2 Source documents

The following systematic reviews were selected as source documents and starting points to find relevant publications for our literature review:

Topic	Source document
Acute treatment of migraine in adults	VanderPluym JH, Halker Singh RB, Urtecho M, et al. **Acute Treatments for Episodic Migraine in Adults: A Systematic Review and Meta-analysis**. JAMA. 2021;325(23):2357–2369. doi:10.1001/jama.2021.7939
Prophylactic treatment of migraine in adults	Shamliyan TA, Choi JY, Ramakrishnan R, Miller JB, Wang SY, Taylor FR, Kane RL. **Preventive pharmacologic treatments for episodic**

	migraine in adults. J Gen Intern Med. 2013 Sep;28(9):1225-37. doi: 10.1007/s11606-013-2433-1. Epub 2013 Apr 17. PMID: 23592242; PMCID: PMC3744311.
Acute treatment of migraine in children and adolescents	Richer L, Billinghurst L, Linsdell MA, Russell K, Vandermeer B, Crumley ET, Durec T, Klassen TP, Hartling L. **Drugs for the acute treatment of migraine in children and adolescents.** Cochrane Database of Systematic Reviews 2016, Issue 4. Art. No.: CD005220. DOI: 10.1002/14651858.CD005220.pub2
Prophylactic treatment of migraine in children and adolescents	Locher C, Kossowsky J, Koechlin H, et al. **Efficacy, Safety, and Acceptability of Pharmacologic Treatments for Pediatric Migraine Prophylaxis: A Systematic Review and Network Meta-analysis.** JAMA Pediatr. 2020;174(4):341–349. doi:10.1001/jamapediatrics.2019.5856

For all these research questions, a search string was developed to search Medline via Pubmed from the research date of the selected source document up until 1st January 2023.
For all other topics no source document was found, and a search of Medline without a starting date was performed.

2.4.3 Search strategy details

The full search strategy can be found in chapter 17 (appendix).

2.5 Selection procedure

Selection of relevant references was conducted by two researchers independently. Differences of opinion were resolved through discussion. A first selection of references was done based on title and abstract. When title and abstract were insufficient to reach a decision, the full article was read to decide on inclusion or exclusion.
In - and exclusion criteria of the different types of studies are found in “2.3.3. Specific search criteria” with relevant populations, interventions, endpoints and study criteria.
The selection of the studied drugs and supplements was based on discussions with experts of the organisation committee.
The list of articles excluded after reading of the full text can be found in chapter 18 (appendix).

2.6 Assessing the quality of available evidence

To evaluate the quality of the available evidence, the GRADE system was used. In other systems that use ‘levels of evidence’, a meta-analysis is often regarded as the highest level of evidence. In the GRADE

system, however, only the quality of the original studies is assessed. Whether the results of original studies were pooled in a meta-analysis is of no influence to the quality of the evidence.
The GRADE-system is outcome-centric. This means that quality of evidence is assessed for each endpoint, across studies.
The GRADE system assesses the following items:

Study design		+ 4	RCT
		+ 2	Observational
		+ 1	Expert opinion
Study quality		- 1	Serious limitation to study quality
		- 2	Very serious limitation to study quality
Consistency		- 1	Important inconsistency
Directness		- 1	Some uncertainty about directness
		- 2	Major uncertainty about directness
Imprecision		- 1	Imprecise or sparse data
Publication bias		- 1	High probability of publication bias
For observational studies	Evidence of association	+ 1	Strong evidence of association (RR of >2 or <0.5)
		+ 2	Very strong evidence of association (RR of >5 or <0.2)
	Dose response gradient	+ 1	Evidence of a dose response gradient (+1)
	Confounders	+ 1	All plausible confounders would have reduced the effect
SUM		4	HIGH quality of evidence
		3	MODERATE quality of evidence
		2	LOW quality of evidence
		1	VERY LOW quality of evidence

Table. Items assessed by the GRADE system

In this literature review the criteria 'publication bias' has not been assessed.

In assessing the different criteria, we have applied the following rules:

Study design

In this literature review, RCTs and observational studies are included. RCTs start out as high quality of evidence (4 points), observational studies start out as low quality of evidence (2 points). Points can be deducted for items that are assessed as having a high risk of bias.

Study quality

To assess the methodological quality of RCTs, we considered the following criteria:

- **Randomization**: If the method of generating the randomization sequence was described, was it adequate (table of random numbers, computer-generated, coin tossing, etc.) or inadequate (alternating, date of birth, hospital number, etc.)?
- **Allocation concealment:** If the method of allocation was described, was it adequately concealed (central allocation, …) or inadequate (open schedule, unsealed envelopes, etc.)?
- **Blinding**: Who was blinded? Participants/personnel/assessors. If the method of blinding was described, was it adequate (identical placebo, active placebo, etc.) or inadequate (comparison of tablet vs injection with no double dummy)?
- **Missing outcome data:** Follow-up, description of exclusions and drop-outs, ITT
- **Selective outcome reporting**

If a meta-analysis or a systematic review is used, quality of included studies was assessed. It is not the quality of the meta-analysis or systematic review that is considered in GRADE assessment, but only the quality of RCTs that were included in the meta-analysis/systematic review.

Application in GRADE:

Points were deducted if one of the above criteria was considered to generate a high risk of bias for a specific endpoint.

For example:

> Not blinding participants will not decrease validity of the results when considering the endpoint 'mortality', but will decrease validity when considering a subjective endpoint such as pain, so for the endpoint pain, one point will be deducted.
>
> A low follow-up when no ITT analysis is done, will increase risk of bias, so one point will be deducted in this case.

Consistency

Good "consistency" means that several studies have a comparable or consistent result. If only one study is available, consistency cannot be judged. This will be mentioned in the synthesis report as "NA" (not applicable).

Consistency is judged by the literature group and the reading committee based on the total of available studies, whilst taking into account:

- Statistical significance
- Direction of the effect if no statistical significance is reached. E.g. if a statistically significant effect was reached in 3 studies and not reached in 2 others, but with a non-significant result in the same direction as the other studies, these results are considered consistent.
- Clinical relevance: if 3 studies find a non-significant result, whilst a 4th study does find a statistically significant result, that has no clinical relevance, these results are considered consistent.
- For meta-analyses: Statistical heterogeneity.

Directness

Directness addresses the extent in which we can generalise the data from a study to the real population (external validity). If the study population, the studied intervention and the control group or studied endpoint are not relevant, points can be deducted here. When indirect comparisons are made, a point is also deducted.

Imprecision

A point can be deducted for imprecision if the 95%-confidence interval crosses both the point of appreciable harm AND the point of appreciable benefit (e.g. RR 95%CI ≤0.5 to ≥1.5).

Additional considerations for observational studies

For observational studies, when no points are deducted for risk of bias in one of the above categories, a point can be added if there is a large magnitude of effect (high odds ratio), if there is evidence of a dose-response gradient or (very rarely) when all plausible confounders or other biases increase our confidence in the estimated effect.

Application of GRADE when there are many studies for 1 endpoint:

Points are only deducted if the methodological problems have an important impact on the result. If 1 smaller study of poor quality confirms the results of 2 large good quality studies, no points are deducted.

More information on the GRADE Working Group website: http://www.gradeworkinggroup.org

2.7 Synopsis of the study results

The complete report contains:

- (Comprehensive) summary of selected guidelines.
- Evidence tables (English) of systematic reviews or RCTs on which the answers to the study questions are based.
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system (English).

The synopsis report contains:

- (Brief) summary of selected guidelines.
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system.

The conclusions of this report have been discussed and adjusted through discussions between the authors of the literature search and the reading committee of the literature group.

3 Critical reflections of the literature group

3.1 Review scope

In consultation with the Organizing Committee, we determined the specific populations, interventions, comparisons, and outcomes to be reported and for which a search of the literature was to be conducted. The studied populations and interventions are discussed here in short. More details on the studied populations, interventions, comparisons and outcomes can be found in 2.3.3. “Specific search criteria”.

Both the acute treatment and prophylaxis of episodic migraine were the subject of our liteature search. Chronic migraine as well as other particular types of migraine such as ophthalmic migraine, vestibular migraine, and tension headache were not included in the literature search. However, information from the included guidelines about the treatment of chronic migraine was included in this report, given that general practitioners are involved in the care of patients with patients with chronic migraine.

3.1.1 Populations

The questions to the jury include the management of migraine (acute treament and migraine prophylaxis) in different populations:

- adults
- children and/ or adolescents
- older individuals

Other jury questions also concern the management of migraine during pregnancy and breastfeeding and the management of menstrual migraine. Given the specialist care setting, we did not perform a literature search for these populations. Similarly, no guidelines specifically about migraine during pregnancy were selected due to their specialized nature. However, information about these topics were collected from the (more general) guidelines that were selected.

3.1.2 Interventions

We performed an exhaustive search of different therapeutic approaches to migraine that fall under two broad categories: acute treatments and prevention. Only registered drugs available in Belgium were included in the literature search, with the exception of the “gepants”; a recently approved new class of CGRP receptor antagonists for the treatment of acute migraine attacks and for prophylaxis. Only rimegepant is presently marketed in Belgium. However, two additional gepants are possibly expected to be approved in Belgium and have therefore been included in the literature review: ubrogepant and atogepant. Among the investigated gepants, rimegepant is marketed both for the

treatment of migraine attacks and for prophylaxis, while ubrogeptant is indicated for the acute treatment of migraine headache and atogepant is indicated for the prevention of episodic migraine in adults.

Similarly, a literature search was performed for comparisons using associations of triptans with NSAID, even though no fixed association is available in Belgium. According to the opinion of the experts of the Organizing Committee, this is an emergent treatment in the surrounding countries of Belgium and such a combination is possible using mono-compound preparations.

For most of the comparisons, data were found and analysed separately for a series of doses. In order to limit the scope of this report, only the dosages available/recommended in Belgium according to the approved indication were included in this document.

Given the high amount of therapeutic classes used in the management of migraine, we had to somewhat limit the included interventions for our literature search.

With regards to acute treatment:

- Specific drugs for migraine attacks were sought (triptans and gepants), with the exception of the combination of ergotamine and caffeine which according to the experts from the Organizing Committee is a useless and dangerous treatment that has no place in first line treatment of migraine attacks.
- In addition to specific treatments for migraine attacks, a number of other drugs are also frequently used, with a broader indication than migraine attacks, many of which are available as OTC drugs. A search was made for all available OTC interventions, including combinations, used by patients (sometimes on simple demand) in the context of headache: acetylsalicylic acid, paracetamol and ibuprofen. Other NSAIDs are also frequently used. Only diclofenac and naproxen, whose indications include migraine attacks with or without aura, were investigated.
- Opioids (and combinations with opioids, including codeine), corticosteroids, ketamine and propofol were not searched because they are considered “to be avoided” and/or are not intended for general practitioners (GP’s) as discussed with the Organizing Committee. Haloperidol and droperidol are also not used in BE by GP’s for acute migraine treatment.

Regarding migraine prophylaxis :

- Numerous classes of pharmacological interventions exist aimed to reduce frequency, severity, and duration of attacks. Most are not treatments specifically intended for migraine prophylaxis and are used “off label”.
- The selection of individual interventions to be investigated was made on the basis of the opinion of the experts from the Organizing Committee and according to their clinical expertise.
- We have not searched for lisinopril, clonidine, carbamazepine, pregabaline, gabapentine, SSRI’s, nimodipine and nifedipine as, according to the Organizing Committee, these drugs are either not intended for GP’s or not used in Belgium in the context of migraine.
- The novel class of antibodies targeting CGRP receptor have not been searched either as they are not intended for primary care, however GP’s care for these patients as well. Therefore,

information about CGRP monoclonal antibodies from the selected guidelines were included in the report.

3.2 General remarks

Given the scope of the subject, a considerable number of studies have been found and are reported, particularly in comparison to placebo.

For acute treatment, the majority of studies were found for triptans, essentially versus placebo. Very few studies, including a limited number of patients, have been found for paracetamol and ibuprofen. In all these studies, several acute treatments for migraine were associated with improvements in pain, associated symptoms and function, but also with increased risk of adverse effects, with varying strengths of evidence to support their use.

Nevertheless, a limited number of studies, relative to the number of placebo-controlled studies, were found that compared triptans with other triptans, and only a few scattered studies were identified comparing triptans to other active treatments. Similarly, studies with active comparators for drug classes other than triptans are almost non-existent. More head-to-head trials of active therapies and trials of combinations of therapies are needed in order to better evaluate their comparative efficacy.

It is generally considered that triptans are the most frequently used drugs for the acute management of migraine, but it is also assumed that a number of patients who receive triptans develop cardiovascular symptoms.Due to their potent vasoconstrictor effects, triptans are contraindicated for patients with cardiovascular diseases. Additionally, NSAID use may be limited if patients have certain gastrointestinal, renal, or cardiac comorbidities. It sometimes emerged from the literature that rimegepant, as well as other substances of this new pharmacological class not yet marketed in Belgium, represents a good alternative for these patients. However, there are some limitations in the found studies with this new therapeutic class that need to be considered. There was no evaluation in patients with more than 8 migraine attacks per month, nor specifically in patients whose migraine attacks are resistant to triptans or in whom triptans are contraindicated. Most of the patients with uncontrolled, unstable or recently diagnosed cardiovascular disease as well as with uncontrolled hypertension (high blood pressure) were excluded from the different studies on rimegepant. To date, few RCTs have compared CGRP receptor antagonists with triptans, and no studies that directly compared rimegepant or ubrogepant with any of the triptans were identified.

3.2.1 Search strategy

In line with our methodology, a search was performed beginning from the search date of our selected source documents.

One of our source documents (VanderPluym 2021, Acute treatment of migraine in adults(1)), was a

systematic review of abortive pharmacologic or noninvasive nonpharmacologic therapy compared with placebo, usual care, another pharmacologic therapy, noninvasive nonpharmacologic therapy, wait list, no treatment, or attention control in adults with migraine. Given the number of studies and the numerous systematic reviews that already summarised the evidence concerning the use of triptans and NSAIDs (including acetylsalicylic acid) in acute treatment of migraine, this review did not conduct a new systematic search for these topics but rather gave an overview of previously published systematic reviews (approach also called umbrella systematic review). For the other comparisons a systematic review with MA was performed.

Authors of the source document reported that many systematic reviews had updates or recent evaluations that suggested stability of the evidence base and that future trials on the existing triptans and NSAIDs are less likely to be conducted. Furthermore a yearly update of their search stream has been performed from the search date of the source document that has not revealed additional studies meeting our inclusion criteria. Therefore, and in order to be as exhaustive as possible, for the topics triptans and AINS, we have decided to report each of these systematic reviews included in VanderPluym seperately. Of note, one of the reviews comparing rizatriptan to placebo was not a systematic review in the strict sense of the term, but we have included it in this report because most of the reviews were judged to have “high credibility” according to our source document.

In addition, rather than using our source document for comparisons with rimegepant, we selected another systematic review with a slightly earlier publication date. The latter included an additional unpublished study (with slightly inferior results) that had been excluded from the source document for the same reason. Overall, the results of these two MAs are quite similar.

3.2.2 Meta-analyses

We reported many **meta-analyses.** Although a meta-analysis allows for a more robust point estimate than an individual RCT, one should be cautious when interpreting the results. Results from clinically heterogenous studies are often combined. RCTs including different populations, different trial durations, different handling of drop-outs and missing values as well as RCTs of differing methodological quality will be pooled. It can be misleading to generalize these pooled results to the entire population.

Some network-MAs were also found and used to report comparison data with active comparators. As stated in our methodology, where this is the case, only the direct comparisons were reported.

Although it is tempting to try to establish a hierarchy between treatments due to the number of comparisons reported, we would like to reiterate that it is inappropriate to compare different point estimates or data from active arms issued from separate controlled trials.

3.2.3 Statistically significant versus clinically relevant

A study may show a benefit of a certain drug, when compared to another treatment. A point estimate and a confidence interval around this estimate are usually provided. The confidence interval

gives us an idea of the (im) precision of the estimate and of the range in which the true effect plausibly lies. It is important to realize that the true effect can be anywhere within this confidence interval.

The GRADE score reflects how certain we are that this estimate is close to the true effect. This is how the results in this document are reported.

Whether a difference found in a study is also clinically relevant (i.e. will make a noticeable difference to the patient), is another matter.

For certain outcomes, such as Health-related Quality of Life, validated functional scales are used. Clinical relevance in these scales is often defined by the "minimal clinically important difference" (MCID). In the following table, some Migraine-specific Health Related Quality of Life scales are defined, together with their between-group MCIDs.

Scale	Explanation	Between-group MCID
MSQ Migraine-Specific Quality of Life Questionnaire v2.1	14-item questionnaire designed to measure migraine-specific Health-related QoL over the past 4 weeks, with 3 domains: • RFR domain (Role-function restrictive) measures the degree to which migraine limits the performance of daily social and work-related activities • RFP domain (Role-function preventive) measures the degree to which migraine interrupts or prevents the performance of daily social and work-related activities. • EF domain (emotional function) assesses emotions associated with migraine Higher scores mean better daily functioning	MSQ-RFR: 3.2 points MSQ-RFP : 4.6 points MSQ-EF : 7.5 points (2)
HIT-6 Headache Impact Test–6	measures the impact of headaches on normal daily life and ability to function on the job, at school, at home, and in social situations in the past 4 weeks Lower scores mean less impact of headache	-1.5 points (2)
MIDAS Migraine Disability Assessment Questionnaire	measures headache-related disability in the past 3 months Higher scores mean more disability	-5 points (3)

3.3 Guidelines

We searched for guidelines, published in the past 5 years, regarding acute pharmacological treatment and pharmacological prophylaxis of migraine. We selected guidelines that report levels of

evidence in their recommendations and that were based on a good systematic search and review of the literature.

Exceptions were made for these guidelines that are commonly in use in practice, such as Eigenbrodt 2021(4) which did not meet our selection criteria in all areas and is actually a consensus statement. However, this consensus statement proposes a useful stepped care approach in 10 steps. Statements in Eigenbrodt 2021 are endorsed by the European Headache Federation and the European Academy of Neurology.

A total of 9 guidelines were selected. Five guidelines (SIGN 2022(5), NICE 2021(6), NHG 2021(7), Eigenbrodt 2021(4), FR 2021(8)) focus on the management of migraine (acute treatment and prevention). A separate guideline (FR_non-med 2021(9)) from the French headache society was included for the non-pharmacological treatment of migraine in adults.

One guideline (EUR 2019(10)) is specifically about monoclonal antibodies acting on CGRP or its receptor for migraine prevention.

Concerning treatment of migraine in children, two American guidelines (US_treatment 2019(11), US_prevention 2019(12)) from the same group were included. Practices in the management of migraine may differ between the US and Europe, but we found no European guidelines for children that met our inclusion criteria.

No guidelines were found specifically for the elderly population.

No guidelines specifically about migraine during pregnancy were selected due to their specialized nature. However, information about this topic was collected from the (more general) guidelines that were selected.

3.4 Acute treatment in adults

3.4.1 Population

The majority of publications examined a general migraine population (unspecified/multiple types). Episodic migraine is not a commonly used term especially at the time for many publications. Nevertheless numerous publications would likely have been classified as “episodic migraine” judged against the current <15 monthly headache days standardly defined by International Headache Society (IHS), as the majority of studies recruited participants suffering around one to eight attacks per month and with a history of attacks for at least six months, and usually for at least one year. The use of prophylactic medication during the study period was variable, with some studies requiring participants to discontinue any prophylactic medication, while others allowed stable prophylactic medications, and others failed to comment on it.

Overall there did not appear to be a particular bias towards a certain type of migraine patients. It is important to note that:

- Many studies recruited participants through headache clinics, which may have indirectly over-selected people with more severe or difficult-to-treat pain compared to the average population of migraine patients.
- Some studies excluded participants who experienced headaches that were usually severely disabling or incapacitating, and/or accompanied at least 20% of the time by vomiting, while other specifically did not exclude such participants. These studies have been pooled in the different meta-analyses.
- Population with certain conditions, particularly cardio- or cerebrovascular disease or participants with any contraindication to a study medication or resistant to certain medications were excluded from most of the studies. This may mean that the study population is not a reflection of general population. This may be of particular concern regarding OTC medications as for these drugs, patients may choose to self-administer the medication, independently of the condition. Consequently a lack of efficacy and safety data in the more general populations is also a limitation.

Several MAs conducted by the same group of authors have analysed studies using a single dose of medication in established pain of at least moderate intensity separately from studies in which medication was taken before pain was well established (mild pain intensity) or in which a second dose of medication was permitted. Each time that this distinction was explicitly mentioned, we also reported the category of migraine attack to which the comparison relates. We merely refer to migraine attack in adults when a separation was not explicitly intended in the MA, when the study or the MA refer to a mixed population in regard to the baseline pain intensity or when it was not specified. Nevertheless in the vast majority of studies treated attacks had to be established, with moderate or severe pain intensity, before medication could be taken.

This point may somewhat differ from what is generally done by patients since in clinical practice many people treat their headache earlier when the pain is still mild and do not wait until the pain becomes moderate to severe. In this exhaustive report, we found little evidence concerning the benefit of diverse medications when treating attacks in the early stages.

More studies reporting consistently on early treatment and on the difference of efficacy depending on the stage of pain intensity would be required to better inform on the best clinical use.

3.4.2 Single-dose studies

Some MAs have specifically investigated studies in which a second dose of the intervention was given in case of an ineffective first dose. This was considered as a different dose regimen and therefore we decided to exclude those specific analyses.

Most studies evaluated the effectiveness of a *single* dose of medication for a *single* migraine attack, but this was not always clearly reported. Most of the reviewed meta-analyses extracted and pooled data of only the *first* attack.

Information about the consistency of the effect of the medication when used for repeated attacks within a longer period are not provided by this type of analysis. Such information has not been identified in this report.

Further studies are needed to evaluate outcomes such as the preservation or decrease of response over time.

3.4.3 Adverse events

Special caution is needed when interpreting data on adverse events:

- Single-dose studies provide only limited information about adverse events and are certainly unlikely to reveal rare, but potentially serious, adverse events. Furthermore some studies reported data for adverse events only if they occurred at a specified rate, which differed across studies, and inevitably means that some events occurring at lower frequencies were not reported.
- In many studies rescue medication, or a second dose of study medication, was permitted if study medication failed to provide adequate relief, or in the event of recurrence, and this may disproportionately increase rates of adverse events in the placebo group.
- Further studies would be needed to evaluate the outcomes of these medications such as long term adverse events and adverse events with repeated use.
- Individual RCT are typically not designed to assess adverse events and generally underpowered to detect differences in safety outcomes. Pooling adverse event data from similar studies may allow more robust estimates but for uncommon events even pooling studies may not provide adequate numbers of events to demonstrate differences or allow confidence in the size of the effect.
- Some studies did not specify the time period over which data were collected, and if specified most used different time periods, preventing pooling of data.

In this report we have only documented total adverse events and serious adverse events. Given the controversy regarding the potential cardiovascular AEs of triptans and the existing contra-indication in respect to this, we have also mentioned the cardiovascular-related AEs for all the medication classes included in our search.

It should be noted however, that many MAs on triptans have classified specific adverse effects by categories, some of which are tightness, heat sensation or chest pain. While these categories may be related to certain cardiovascular effects this was not explicitly described and could also refer to other types of AEs. Therefore we have only reported the categories that explicitly concern cardiovascular AEs.

3.4.4 Medication overuse headache

Medication overuse headache is defined according to headache frequency (15 or more days per month for more than 3 months) and days of use of specific medications per month. In the literature it is widely acknowledged that frequent use of triptans and analgesics may lead to medication overuse

headaches. Up until now outcomes such as the development of medication overuse headaches have not been evaluated for the recently approved “gepant” class of medication.

No included studies in our literature search evaluated this risk for any class of medication. Relevant information from the selected guidelines and from our “other sources” about medication overuse headache was included in this report.

3.4.5 Endpoints

While the International Headache Society (IHS) and organizations and agencies published guidelines to help improve the quality of acute migraine clinical trials, these trials exhibit a large amount of variability in outcomes used, as well as a variability in how outcomes are measured and in the timing of assessment for these different outcomes.

The IHS guidelines address subject selection (migraine definition, attack frequency, duration of migraine, age of onset), trial design (blinding, randomization, placebo-control, number of treated attacks, rescue medication), evaluation of results (headache diaries, (co)primary endpoints, secondary endpoints, adverse events), and statistical analyses (hierarchy of endpoints, power analyses, alpha corrections, statistical analysis plans).

These guidelines were updated in 2000 (second edition), 2012 (third edition), and 2019 (fourth edition). Other related guidance documents have been published, including by the The US Food and Drug Administration (FDA), American Headache Society (AHS), the European Medicines Agency (EMA), and the US National Institute for Neurologic Diseases (NINDS) to help improve treatment research and clinical practice. We have generally reported the reference to which the MA refers.

According to the latest IHS (2019) for controlled trials of acute treatment of migraine attacks in adults, the primary end point to determine effectiveness should be either pain freedom at 2 hours or the absence of the most bothersome migraine associated symptom at 2 hours as a coprimary end point.

As far as possible, we have tried to report common outcomes across trials that align with guidance from the International Headache Society, the Food and Drug Administration and other regulatory agencies. Pain (freedom or relief) and associated symptoms at 1 h and 2-h post-treatment where the most frequently reported and have been mentioned in this document each time data were available. Given the diversity of outcomes reported in the studies, other time points have not been systematically included. The use of most bothersome symptom and headache-related patient reported outcome measures (PROMs) in acute migraine trials was much less frequent. We reported it when available.

Although most of these endpoints are based on a continuous quantification system, they are reported as dichotomous variables. Most of the time, when we mentioned an increase or a decrease for one of these outcomes (pain freedon, pain relief, associated symptoms or function) this implies

that there are more or fewer events relative to the number of patients or migraine attacks. In the different studies, it was not always clear whether the denominator was the number of patients or the number of attacks. When it was explicitly mentioned that this referred to the number of attacks, we also reported it. Otherwise no further details are given. Sometimes (mainly in the French translation of this document) we simply use the generic terms: “% patients”, or “a larger/smaller number of patients”.

3.5 Preventive treatment in adults

The latest version of the *International Headache Society guidelines for controlled trials of preventive treatment of migraine attacks in episodic migraine in adults(13)* recommends the “change from baseline in migraine days per unit time” as the primary endpoint for the evaluation of efficacy in trials of preventive migraine treatment.

However, this outcome was not always used or well defined in studies, especially in older studies predating the development of these trial guidelines. The outcome “migraine frequency” could mean number of migraine attacks per time period as well as number of migraine days per time period. These outcomes are not the same and often the number of days with migraine is higher than the number of migraine attacks. In meta-analyses, these results are sometimes pooled.

These problems make it difficult to accurately compare results across the body of evidence, especially when it concerns older drugs.

3.6 Acute and preventive treatment in children and adolescents

Given the differences that may exist between different dose ranges, the differences in indications that may exist between children and adolescents, and the fact that adolescents may be considered adults, during the discussions with the Organizing Committee, we were specifically asked to consider children and adolescents separately.

One meta-analysis was found that defined children as under 12 years of age and adolescents as 12-17 years of age and analysed paracetamol and ibuprofen versus placebo separately in these two age groups. Another meta-analysis that used the same RCTs but rather pooled all age categories also reported data for the comparison between paracetamol and ibuprofen and was used for this comparison (without age distinction). Only three small RCTs including a very limited number of participants were found evaluating the efficacy and safety of ibuprofen and paracetamol.

In spite of this, ibuprofen and paracetamol are recommended analgesics for the treatment of acute migraine attacks in children by the WHO.

Similarly, there is almost no data on the use of magnesium or riboflavin for migraine prophylaxis in children and adolescents. 1 and 3 RCTs were found respectively for these comparisons with a tiny number of participants.

The level of evidence of the effect estimate for all the included comparisons is therefore limited by the inclusion of such underpowered RCTs as well as by a elevated risk of bias of the included studies.

In order to achieve a relevant analysis of the available evidence in the context of studies of migraine in children, it is also valuable to consider some of the comments formulated by the authors of the systematic reviews reported in this document:

- Results are unavailable for more than half of the studies involving children, revealing a substantial publication bias.
- The optimal duration of preventive treatment and sustained benefits and harms with preventive drugs in children with migraine remain unclear.
- Because specific effects of drugs are associated with the size of the placebo effect […] there is indirect evidence that the placebo effect is more pronounced in children and adolescents than in adults. The quantification of the placebo effect would therefore require comparison with a nontreated group, which is rarely included in clinical trials.

Future studies should separate the childhood and adolescent age groups to enable separate meta-analyses of these groups. More studies of simple analgesics commonly used in the treatment of migraine like paracetamol and ibuprofen, other NSAIDs, preventive treatment, as well as head to head comparisons are warranted.

3.7 Cardiovascular safety in older people

People over 65 are poorly represented in migraine studies. Persons at cardiovascular risk also often excluded.

Contra-indications to certain treatments, such as NSAID and triptans, often exist. Newer medications, such as gepants, are suggested as potentially safer alternatives, but even in those studies there is very little data on older people and not much is yet known about the (cardiovascular) long-term effects.

We performed a search for cardiovascular adverse effects of migraine medications in older people. We found very limited observational data with high risk of bias in a small number of interventions.

Data from studies cannot as of yet determine which pharmacological interventions can be safely used in older people with cardiovascular risk factors.

4 General information on selected guidelines

4.1 Selected guidelines

The selected guidelines and their abbreviations as used in this report can be found in Table 1.

Pharmacological treatment for acute migraine and pharmacological prevention

Abbreviation	Guideline
SIGN 2022(5)	Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of migraine. Edinburgh: SIGN; 2022. (SIGN publication no. 155). [February 2022]. Available from URL: http://www.sign.ac.uk
NICE 2021(6)	Headaches Diagnosis and management of headaches in young people and adults. Clinical Guideline 150. September 2012/update december 2021
NHG 2021(7)	NHG-Standaard Hoofdpijn (M19) versie 5.0, September 2021
Eigenbrodt 2021(4)	Eigenbrodt AK, Ashina H, Khan S, et al. Diagnosis and management of migraine in ten steps. Nat Rev Neurol. 2021;17(8):501-514. doi:10.1038/s41582-021-00509-5
FR 2021(8)	Ducros A, de Gaalon S, Roos C, et al. Revised guidelines of the French headache society for the diagnosis and management of migraine in adults. Part 2: Pharmacological treatment. Rev Neurol (Paris). 2021;177(7):734-752. doi:10.1016/j.neurol.2021.07.006

Table 1a: Selected guidelines and their abbreviations as used in this report.

Specific guideline about monoclonal antibodies targeting the CGRP pathway (prevention)

EUR 2022(10)	Simona Sacco S, Amin FM, Ashina M, et al. European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention – 2022 update, Journal of Headache and Pain, 2022 ;23 (1): 67. doi: 10.1186/s10194-022-01431-x.

Table 2b: Selected guidelines and their abbreviations as used in this report.

Specific guidelines for children

Abbreviation	Guideline
US_prevention 2019(12)	Oskoui M, Pringsheim T, Billinghurst L, et al. Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society [published correction appears in Neurology. 2020 Jan 7;94(1):50]. Neurology. 2019;93(11):500-509. doi:10.1212/WNL.0000000000008105
US_treatment 2019(11)	Practice guideline update summary: Acute treatment of migraine in children and adolescents: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2020;94(1):50. doi:10.1212/WNL.0000000000008728

Table 3c: Selected guidelines and their abbreviations as used in this report.

Specific guideline for non-pharmacological treatment

Abbreviation	Guideline
FR_non-med_2021(9)	Demarquay G, Mawet J, Guégan-Massardier E, et al. Revised guidelines of the French headache society for the diagnosis and management of migraine in adults. Part 3: Non-pharmacological treatment. Rev Neurol (Paris). 2021;177(7):753-759. doi:10.1016/j.neurol.2021.07.009

Table 4d: Selected guidelines and their abbreviations as used in this report.

4.2 Grades of recommendation

Grades of recommendation and levels of evidence as defined in each guideline, can be found in table 2 to 10.

SIGN 2022		
Grades of recommendation:	Strong recommendation	For 'strong' recommendations on interventions that 'should' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do

		more good than harm. For 'strong' recommendations on interventions that 'should not' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more harm than good.
	Conditional recommendation	For 'conditional' recommendations on interventions that should be 'considered', the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.
	Good-practice points	Recommended best practice based on the clinical experience of the guideline development group.
Levels of evidence	1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
	1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
	1–	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
	2++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
	2+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
	2–	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
	3	Non-analytic studies, eg case reports, case series
	4	Expert opinion

Table 2: Grades of recommendation and Level of evidence of the SIGN 2022 guideline.

NICE 2021		
Grades of recommendation:	Interventions that must (or must not) be used worded as such in the text.	Generally used if there is a legal duty to apply the recommendation. But used as well if the consequences of not following the recommendation could be extremely serious or potentially life threatening.
	Intervention that should (or should not) be used are	There is clear evidence of benefit. We are confident that, for the vast majority of

	worded in the text using the term “offer”, “refer”, “advise” or similar…	patients, an intervention will do more good than harm, and be cost effective.
	Intervention that could (or could not) be used are worded in the text using the term “consider”	Reflects a recommendation for which the evidence of benefit is less certain. We are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient’s values.
Levels of evidence	While levels of evidence have been evaluated using described procedures (GRADE, CASP RCT, cohort study, case-control checklists, CERQual) NICE does not explicitly attribute strength levels to each particular recommendation.	

Table 3: Grades of recommendation and Level of evidence of the NICE 2021 guideline.

NHG 2021		
Grades of recommendation:	Strong: expressed in the wording of the recommendation	/
	Weak: expressed in the wording of the recommendation	This often means there is not enough evidence to recommend a specific option and that medical professionals, together with their patient, make a choice from different options.
Levels of evidence	While levels of evidence have been evaluated using described procedures (GRADE), NHG does not explicitly attribute levels of evidence to each particular recommendation.	

Table 4: Grades of recommendation and Level of evidence of the NHG 2021 guideline.

Eigenbrodt 2021
Eigenbrodt 2021 is a Consensus Statement established by experts, supported by current literature, and endorsed by the European Headache Federation and the European Academy of Neurology. No information was given regarding the method of evidence selection and appraisal and no levels of evidence were reported. The panel of experts also provided recommendations for evaluating treatment response and managing treatment failure without defining grades of recommendation. This Consensus Statement was included as a guideline as adviced by one of the experts of the organization committee since it is often used in clinical practice.

Table 5: Grades of recommendation and Level of evidence of Eignbrodt 2021.

FR 2021		
Grades of recommendation:	Strong	Benefits clearly outweigh risks and burdens for most patients = Can apply to most patients in most circumstances.
	Moderate	Benefits clearly outweigh risks and burdens for most patients = Can apply to most patients, but there is a chance the recommendation may change with more research.
	Weak	Benefits clearly outweigh risks and burdens for most patients = Can apply to most patients, but there is a good chance the recommendation could change with more research.
	Not recommended	Not recommended.
Levels of evidence	High	We are confident that the true effect lies close to the estimate given by the evidence available.
	Moderate	We are moderately confident in the effect estimate, but there is a possibility it is substantially different.
	Low	Our confidence in the effect estimate is limited. The true effect may be substantially different.

Table 6: Grades of recommendation and Level of evidence of the FR 2021 guideline.

EUR 2022		
Grades of recommendation: according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system.	**Evidence-based recommendations:**	
	Strong (↑ ↑)	The panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects.
	Weak (↑)	The panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but is not confident.
	Expert consensus statements :	
	Expert consensus	GRADE approach was not applicable, recommendations were developed as expert statements.
Levels of evidence According to according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system (study design, study limitations, inconsistency, indirectness, imprecision, publication bias, effect size, dose response, and confounding factors).	High	We are very confident that the true effect lies close to that of the estimate of the effect.
	Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
	Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
	Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Table 7: Grades of recommendation and Level of evidence of the EUR 2022 guideline.

US_prevention 2019		
Grades of recommendation:	A: worded as “must (not) prescribe/offer (Rx), must (not) test/counsel/monitor (Scrn, Dx, Px), must avoid (causation)”.	Adherence expected to affect: Nearly all Variation in patient preferences: Minimal Cost: Minimal Availability: Universal Value of benefit relative to risk: Large Confidence in evidence: High Strength of principle-based inferences: Compelling
	B: worded as “should (not) offer/prescribe, should (not) test/ counsel/monitor, should avoid”.	Adherence expected to affect: Most Variation in patient preferences: / Cost: / Availability: / Value of benefit relative to risk: Moderate Confidence in evidence: Moderate

		Strength of principle-based inferences: Convincing
	C: worded as “may offer/prescribe, may test/counsel/ monitor/educate, may avoid, may choose not to offer/ prescribe, may choose not to test/ counsel/monitor”.	Adherence expected to affect: Some Variation in patient preferences: / Cost: / Availability: / Value of benefit relative to risk: Small Confidence in evidence: Low Strength of principle-based inferences: Plausible
	U: No recommendation can be made because of insufficient evidence.	Adherence expected to affect: Few Variation in patient preferences: Large Cost: Prohibitive Availability: Limited Value of benefit relative to risk: Too close to call Confidence in evidence: Very Low Strength of principle-based inferences: Not plausible
Levels of evidence	Strong: worded as “highly likely (highly probable) that”.	Multiple class I evidence: • Randomized, controlled clinical trial (RCT) in a representative population. • Masked or objective outcome assessment. • Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences. • Also required: a. Concealed allocation b. Primary outcome(s) clearly defined c. Exclusion/inclusion criteria clearly defined d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required: 1. The authors explicitly state the clinically meaningful difference to be

		excluded by defining the threshold for equivalence or noninferiority. 2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective). 3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment. 4. The interpretation of the study results is based on a per-protocol analysis that accounts for dropouts or crossovers
	Moderately strong: worded as "likely (probable) that".	Multiple class II evidence: • Cohort study meeting criteria a–e (see Class I) or an RCT that lacks one or two criteria b–e (see Class I). • All relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. • Masked or objective outcome assessment. Or a single class I study.
	Weak: worded as "possible that".	Multiple Class III evidence: • Controlled studies (including well-defined natural history controls or patients serving as their own controls) • A description of major confounding differences between treatment groups that could affect outcome. • Outcome assessment masked, objective or performed by someone who is not a member of the treatment team. Or a single class II study.

	Insufficient: worded as “insufficient evidence to support or refute that”.	Multiple class IV evidence: • Did not include patients with the disease. • Did not include patients receiving different interventions. • Undefined or unaccepted interventions or outcome measures. • No measures of effectiveness or statistical precision presented or calculable. Or a single class III study.

Table 8: Grades of recommendation and Level of evidence of the US_prevention 2019 guideline.

US_treatment 2019		
Grades of recommendation:	A: worded as “must (not) prescribe/offer (Rx), must (not) test/counsel/monitor (Scrn, Dx, Px), must avoid (causation)”.	Adherence expected to affect: Nearly all Variation in patient preferences: Minimal Cost: Minimal Availability: Universal Value of benefit relative to risk: Large Confidence in evidence: High Strength of principle-based inferences: Compelling
	B: worded as “should (not) offer/prescribe, should (not) test/ counsel/monitor, should avoid”.	Adherence expected to affect: Most Variation in patient preferences: / Cost: / Availability: / Value of benefit relative to risk: Moderate Confidence in evidence: Moderate Strength of principle-based inferences: Convincing
	C: worded as “may offer/prescribe, may test/counsel/ monitor/educate, may avoid, may choose not to offer/ prescribe, may choose not to test/ counsel/monitor”.	Adherence expected to affect: Some Variation in patient preferences: / Cost: / Availability: / Value of benefit relative to risk: Small Confidence in evidence: Low Strength of principle-based inferences: Plausible
	U: No recommendation can be made because of insufficient evidence.	Adherence expected to affect: Few Variation in patient preferences: Large Cost: Prohibitive Availability: Limited Value of benefit relative to risk: Too close to call Confidence in evidence: Very Low

		Strength of principle-based inferences: Not plausible
Levels of evidence	Strong: worded as "highly likely (highly probable) that".	Multiple class I evidence: • Randomized, controlled clinical trial (RCT) in a representative population. • Masked or objective outcome assessment. • Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences. • Also required: f. Concealed allocation g. Primary outcome(s) clearly defined h. Exclusion/inclusion criteria clearly defined i. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias j. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required: 1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority. 2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective). 3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment. 4. The interpretation of the study results is based on a per-protocol

		analysis that accounts for dropouts or crossovers
	Moderately strong: worded as “likely (probable) that”.	Multiple class II evidence: • Cohort study meeting criteria a–e (see Class I) or an RCT that lacks one or two criteria b–e (see Class I). • All relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. • Masked or objective outcome assessment. Or a single class I study.
	Weak: worded as “possible that”.	Multiple Class III evidence: • Controlled studies (including well-defined natural history controls or patients serving as their own controls) • A description of major confounding differences between treatment groups that could affect outcome. • Outcome assessment masked, objective or performed by someone who is not a member of the treatment team. Or a single class II study.
	Insufficient: worded as “insufficient evidence to support or refute that”.	Multiple class IV evidence: • Did not include patients with the disease. • Did not include patients receiving different interventions. • Undefined or unaccepted interventions or outcome measures. • No measures of effectiveness or statistical precision presented or calculable. Or a single class III study.

Table 9: Grades of recommendation and Level of evidence of the US_treatment 2019 guideline.

FR_non-med 2021

Grades of recommendation:	Strong	Benefits clearly outweigh risks and burdens for most patients = Can apply to most patients in most circumstances.
	Moderate	Benefits clearly outweigh risks and burdens for most patients = Can apply to most patients, but there is a chance the recommendation may change with more research.
	Weak	Benefits clearly outweigh risks and burdens for most patients = Can apply to most patients, but there is a good chance the recommendation could change with more research.
	Not recommended	Not recommended.
Levels of evidence	High	We are confident that the true effect lies close to the estimate given by the evidence available.
	Moderate	We are moderately confident in the effect estimate, but there is a possibility it is substantially different.
	Low	Our confidence in the effect estimate is limited. The true effect may be substantially different.

Table 10: Grades of recommendation and Level of evidence of the FR non-med guideline.

4.3 Agree II score

Information about the Agree II score can be found in the section “Methodology”.
A summary of the assessment by the literature group of the individual items of the domain score for each guideline can be found in Table 11. The total domain score is also reported in this table.

Rigour of development item	7	8	9	10	11	12	13	14	Total	Domain score
SIGN 2022	7	6	6	6	5	6	5	6	**47**	**84**
NICE 2021	7	7	7	4	7	7	4	5	**48**	**86**
NHG 2021	7	5	4	5	6	7	5	5	**44**	**79**
Eigenbrodt 2021	1	3	2	3	3	5	2	1	**20**	**36**
FR 2021	2	1	3	3	4	4	2	2	**21**	**38**
EUR 2012	5	5	7	4	5	6	1	2	**35**	**63**
US_prevention 2019	7	7	6	7	6	7	6	7	**53**	**95**
US_treatment 2019	7	6	6	7	6	7	6	7	**52**	**93**
FR_non-med 2021	2	1	3	3	4	4	2	2	**21**	**38**

Table 11: AGREE score of selected guidelines on item “Rigour of development”, see methodology for a description of the items.

4.4 Included populations – interventions – main outcomes

In the following tables, the populations, interventions and main outcomes considered in the selected guidelines are represented.

SIGN 2022	
Population	This guideline provides recommendations based on current evidence for best practice in the acute and prophylactic management of adults with migraine using pharmacological therapies or devices. The focus is on adults with acute migraine and preventative treatment in patients with episodic or chronic migraine and medication-overuse headache. Studies of children with migraine were not included, however the recommendations could be considered for treating adolescents with migraine.
Interventions	The guideline excludes complementary, physical and psychological therapies, and specialist surgical interventions. <u>Treatment acute migraine:</u> • Aspirin • NSAID • Paracetamol • Antiemetics • Triptans • Combined therapies • Steroids <u>Pharmacological prevention of migraine:</u> • Beta blockers • Topiramate • TCA • Candesartan • Sodium Valproate • Calcium channel blockers • Pizotifen • Gabapentin and pregabalin • Angiotensin-converting enzyme inhibitors • SSRI • Other antiepileptics • Botulinum toxin A • Calcitonine gene-related peptide monoclonal antibodies • Occipital nerve block <u>Devices for migraine therapy:</u> • Vagus nerve stimulation (VNS) • Transcutaneous supraorbital nerve stimulation (TSNS) • Transcranial magnetic stimulation (TMS)

Outcomes	<u>Treatment for adults with acute migraine</u> • Pain free • Pain free within two hours • Sustained pain relief at 24 hours • Adverse effects • QALYs • Incremental cost-effectiveness ratio (ICER) <u>Treatment with devices for adults with acute migraine</u> • Pain free within two hours • Adverse effects • QALYs • ICER <u>Preventative treatment for adults with episodic or chronic migraine</u> • 30% or 50% reduction in number of headache days per cycle • Reduction in number of migraine episodes • Days or headache days • Reduction in migraine disability assessment questionnaire (MIDAS, HIT6) scores • Adverse effects • QALYs • ICER

Table 12: Included population, intervention and main outcomes of the SIGN 2022 guideline.

NICE 2021	
Population	Young people (12 years and older) and adults in all settings in which NHS healthcare is provided. The following clinical issues are covered: • Diagnosis of the following primary headaches: migraine with or without aura, menstrual related migraine, chronic migraine, tension-type headache and cluster headache. Consideration will also be given to people whose headaches have characteristics of more than one primary headache disorder. • … • Acute pharmacological management of the specified primary headaches with: … • Prophylactic pharmacological treatment for specified primary headaches with: … • … • Prevention and treatment of medication overuse headache. • Management during pregnancy. … This guideline does not cover: • Children aged under 12. • Management of primary headaches other than those specified in 2.3.

	• Investigation and management of secondary headache other than medication overuse headache. • Diagnosis and management of cranial neuralgias and facial pain. • Management of comorbidities.
Interventions	<u>Acute pharmacological treatment: migraine with or without aura</u> • Antiemetics, • Aspirin, • NSAIDs, • Opioids, • Paracetamol, • Triptans, • Ergots • Corticosteroids <u>Prophylactic pharmacological treatment of migraine</u> • ACE inhibitors and angiotensin II receptor antagonists (ARBs) • Antidepressants (SNRIs, SSRIs, tricyclics) • Beta blockers • Calcium channel blockers • Antiepileptics • Other serotonergic modulators <u>Prophylactic pharmacological treatment of menstrual migraine</u> • ACE inhibitors and angiotensin II receptor antagonists • Antidepressants (SNRIs, SSRIs, tricyclics) • Beta blockers • Calcium channel blockers • Antiepileptics • Triptans • Other serotonergic modulators • NSAIDs • Hormonal therapy (contraceptives) <u>Prophylaxis with herbal remedies and dietarty supplements</u> • Dietary supplements: e.g. magnesium, vitamin B12, coenzyme Q10 and riboflavin (vitamin B2)) <u>Diaries for the management of primary headaches and medication overuse headache</u> <u>Prophylactic non-pharmacological treatment with Acupuncture</u> Acupuncture
Outcomes	<u>Acute pharmacological treatment: migraine with or without aura</u>

	• Time to freedom from pain • Headache response at up to 2 hours • Freedom from pain at up to 2 hours • Sustained headache response at 24 hours • Sustained freedom from pain at 24 hours • Headache specific quality of life • Functional health status and health related quality of life • Incidence of serious adverse events <u>Prophylactic pharmacological treatment of migraine</u> • Change in patient-reported headache days, frequency and intensity • Responder rate • Functional health status and health-related quality of life Headache specific quality of life • Resource use • Use of acute pharmacological treatment • Incidence of serious adverse events. <u>Prophylactic pharmacological treatment of menstrual migraine</u> • Change in patient-reported headache days, frequency and intensity • Responder rate • Functional health status and health-related quality of life Headache specific quality of life • Resource use • Use of acute pharmacological treatment • Incidence of serious adverse events. <u>Prophylactic non-pharmacological management of primary headaches with herbal remedies</u> • Change in patient-reported headache days, frequency and intensity • Responder rate • Functional health status and health-related quality of life • Headache specific quality of life • Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care • Use of acute pharmacological treatment • Incidence of serious adverse events. <u>Prophylactic non-pharmacological management of primary headaches with dietary supplements</u> • Change in patient-reported headache days, frequency and intensity • Responder rate • Functional health status and health-related quality of life • Headache specific quality of life • Resource use • Use of acute pharmacological treatment • Incidence of serious adverse events.

	Diaries for the management of primary headaches and medication overuse headache • Clinical headache outcomes (for RCTs) • Patients' and practitioners' experience of using diaries. Prophylactic non-pharmacological treatment with Acupuncture • Change in patient-reported headache days, frequency and intensity • Responder rate • Functional health status and health-related quality of life • Headache specific quality of life • Resource use, including GP consultation, A&E attendance, investigations and referral to secondary care • Use of acute pharmacological treatment • Incidence of serious adverse events.

Table 13: Included population, intervention and main outcomes of the NICE 2021 guideline.

NHG 2021	
Population	Diagnostiek, behandeling en begeleiding van kinderen en volwassenen met migraine. Exclusie: Zeldzame vormen van migraine, zoals aura zonder hoofdpijn, retinale migraine, familiaire hemiplegische migraine en hersenstammigraine
Interventions	Gedragspsychologische interventie (cognitieve gedragstherapie) bij kinderen Gedragspsychologische interventie (cognitieve gedragstherapie) Acute behandeling (met misselijkheid) • Paracetamol, NSAID, Triptanen • Paracetamol + NSAID • Triptanen + NSAID of paracetamol Met misselijkheid tijdens migraineaanvral Anti-emetica (domperidon, metoclopramide, ondansetron, granisetron) (oraal of rectaal) Preventieve behandeling • RAS-remmer (ACE-remmers, ARB) • Tricyclische antidepressiva • Bètablokkers • Anti-epileptica

	Preventieve behandeling met acupunctuur Acupunctuur Preventieve behandeling bij menstruele migraine Anticonceptiva met alleen progestagenen (desogestrel, levonorgestrel IUD, prikpil, implantatiestaafje) Acuut staken van analgetica bij medicatieovergebruikshoofdpijn Acuut staken van alle analgetica (paracetamol, NSAID's, opiaten) en triptanen
Outcomes	Gedragspsychologische interventie (cognitieve gedragstherapie) bij kinderen - Aantal dagen hoofdpijn per maand - Ernst van de hoofdpijn - Aantal dagen analgeticagebruik (per maand) - Functioneren – Aanvalsfrequentie Acute behandeling Pijnvrij na 2 uur - Blijvend pijnvrij na 24 uur - Tijdsduur tot weer kunnen functioneren - Afname misselijkheid en braken – Bijwerkingen Met misselijkheid tijdens migraineaanvral - Ernst van de hoofdpijn - Ernst van de misselijkheid, braken - Tijdsduur tot weer kunnen functioneren - Bijwerkingen Preventieve behandeling - Aantal dagen hoofdpijn per maand - Aanvalsfrequentie - Ernst van de hoofdpijn - Aantal dagen analgeticagebruik (per maand) - Functioneren – Bijwerkingen Preventieve behandeling met acupunctuur - Aanvalsfrequentie migraine - Aantal dagen met migraine - Hoofdpijnintensiteit Preventieve behandeling bij menstruele migraine - Aantal dagen hoofdpijn per maand - Aanvalsfrequentie - Ernst van de hoofdpijn - Aantal dagen analgeticagebruik (per maand) - Functioneren - Bijwerkingen - Cardiovasculaire gebeurtenissen/eindpunten Acuut staken van analgetica bij medicatieovergebruikshoofdpijn - Aantal dagen hoofdpijn per maand - Ernst van de hoofdpijn - Aantal dagen analgetica-/triptaangebruik - Functioneren - Percentage patiënten met MOH - Relapse/terugval

Table 14: Included population, intervention and main outcomes of the NHG 2021 guideline.

Eigenbrodt 2021	
Population	We outline best practices for acute and preventive treatment of migraine in various patient populations, including: • Adults • Children and adolescents • Pregnant and breastfeeding women • Older people
Interventions	Acute and preventive treatment of migraine.
Outcomes	• We introduce typical clinical features, diagnostic criteria and differential diagnoses of migraine. • We then emphasize the value of patient centricity and patient education to ensure treatment adherence and satisfaction with care provision. • We outline best practices for acute and preventive treatment. • We provide recommendations for evaluating treatment response and managing treatment failure. • Lastly, we discuss the management of complications and comorbidities as well as the importance of planning long- term follow-up.

Table 15: Included population, intervention and main outcomes of the Eigenbrodt 2021 guideline.

FR 2021	
Population	Adult patients with migraine: • Episodic migraine • Chronic migraine with and without medication overuse The specific situations that can be encountered in women with migraine are also discussed, including: • Pregnancy • Menstrual migraine • Contraception and hormonal replacement therapy

Interventions	• Acute treatments
	• Prophylactic treatments
	• Non-pharmacological treatment of migraine, including:
	  ○ Physical exercise
	  ○ Dietary supplements and plants
	  ○ Diets
	  ○ Neuromodulation therapies
	  ○ Acupuncture
	  ○ Behavioral interventions and mindfulness therapy
	  ○ Patent foramen ovale closure
	  ○ Surgical nerve decompression

Outcomes	/

Table 16: Included population, intervention and main outcomes of the FR 2021 guideline.

EUR 2022	
Population	• Individuals with episodic migraine • Individuals with chronic migraine
Interventions	CGRP-mAbs (eptinezumab, erenumab, fremanezumab, Galcanezumab)
Outcomes	• Reduction in migraine days • Responder rate (individuals with migraine with at least 50% reduction in migraine days) • Reduction in the use of acute attack medicatio • Safety (serious adverse events or mortality)

Table 17: Included population, intervention and main outcomes of the EUR 2022 guideline.

US_prevention 2019	
Population	Migraine prevention in children aged 3 to 18 20 years. The subject's headache disorders in these studies were classified according to either the *International Classification of Headache Disorders*, 2nd edition or the *International Classification of Headache Disorders*, 3rd 1 edition (beta version). Special populations included sexually active adolescents who were of childbearing age. Patients with episodic syndromes that may be associated with migraine, including cyclic vomiting, abdominal migraine, benign paroxysmal vertigo, and benign paroxysmal torticollis were excluded.
Interventions	All pharmacologic interventions for the preventive treatment of migraine as well as the use of CBT in combination with pharmacologic therapy. Nonpharmacologic interventions, such as behavioral interventions alone or nutraceuticals, are not addressed by this guideline.
Outcomes	• Change in headache frequency (defined as the reduction in number of migraine days per month, reduction of number of headache days per month, or 50% reduction in these frequencies) • Headache severity (defined by visual analog scale or numerical rating scale) • Associated disability (PedMIDAS)

Table 18: Included population, intervention and main outcomes of the US_prevention 2109 guideline.

US_treatment 2019	
Population	Children (individuals younger than 12 years) and adolescents (individuals aged 12–17 years) with migraine. Special populations included sexually active adolescents who were of childbearing age.

	Patients with episodic syndromes that may be associated with migraine, including cyclic vomiting, abdominal migraine, benign paroxysmal vertigo, and benign paroxysmal torticollis were excluded.
Interventions	All pharmacologic interventions for the acute treatment of nonrefractory migraine, including acute self-administered treatments. Trials of medications administered intravenously in the ED or in an infusion center setting were not included.

Outcomes	Reduction of headache pain and associated symptoms at specific time points:
	• For headache pain, the most commonly reported outcomes were:
	  ○ Headache pain improvement, usually termed "headache pain response" and typically quantified as an improvement in intensity from moderate-to-severe pain to mild or no pain
	  ○ Headache pain freedom, usually termed "free of headache pain,"
	
	… at specific time points after intervention (typically from 30 minutes to 2 hours).
	• The most commonly reported associated symptoms were:
	  ○ Freedom from photophobia,
	  ○ Phonophobia
	  ○ Nausea
	  ○ Vomiting
	
	… at specific time points after intervention.

Table 19: Included population, intervention and main outcomes of the US_treatment 2019 guideline.

FR_non-med 2021	
Population	Adults with migraine
Interventions	Non pharmacological treatment of migraine including: • Physical exercise • Dietary supplements and plants • Diets • Neuromodulation therapies • Acupuncture • Behavioral interventions and mindfulness therapy • Patent foramen ovale closure • Surgical nerve decompression.
Outcomes	/

Table 20: Included population, intervention and main outcomes of the WOREL 2018 guideline.

4.5 Members of development group – target audience

Members of the development group that produced the guidelines, and the target audience for whom the guidelines are intended, can be found in the following tables.

SIGN 2022	
Development group	SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising healthcare professionals using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in 'SIGN 50: A Guideline Developer's Handbook', available at www.sign.ac.uk The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest. A register of interests is available in the supporting material section for this guideline at www.sign.ac.uk
Target audience	This guideline will be of interest to healthcare professionals in primary and secondary care, including general practitioners (GPs), headache nurses, neurologists, out-of-hours clinicians, pharmacists, and patients with migraine.

Table 21: Members of the development group and target audience of the SIGN 2022 guideline.

NICE 2021	
Development group	A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see section on Guideline Development Group Membership and acknowledgements).
Target audience	• Healthcare professionals who provide care for young people and adults with headaches • Young people (12 years and older) and adults with headaches, and their families and carers. Particular consideration is given to the needs of girls and women of reproductive age

Table 22: Members of the development group and target audience of the NICE 2021 guideline.

NHG	
Development group	Dr. Alexandra Bensdorp Aios huisartsgeneeskunde; Dr. Frans Dekker Huisarts; Hans van Krimpen Huisarts; Rob van der Spruit Huisarts; Ellinore Tellegen Huisarts; Dr. Annemiek Schep-Akkerman Wetenschappelijk medewerker NHG, epidemioloog; Dr. Margriet Bouma Senior wetenschappelijk medewerker NHG, huisarts n.p.; Arianne Verburg-Oorthuizen Senior wetenschappelijk medewerker NHG, huisarts Dr. Gisela Terwindt en dr. Wim Mulleners, neurologen, hebben namens de Nederlandse Vereniging voor Neurologie (NVN) gedurende het proces de conceptaanbevelingen becommentarieerd.
Target audience	De richtlijn is primair ontwikkeld voor huisartsen die bij de diagnostiek en behandeling van patiënten met hoofdpijn betrokken zijn.

Table 23: Members of the development group and target audience of the NICE 2018 guideline.

Eigenbrodt 2021	
Development group	The Danish Headache Society and its representatives (A.K.E., H.A., H.W.S. and M.Ashina) conceived a European Consensus Statement on the diagnosis and clinical management of migraine. A formal proposal, including a suggested list of authors, was prepared and submitted to the Board of Directors of the EHF, the Chairs of the EAN Headache Panel and the Chair of the EAN Scientific Committee. The proposal was approved by unanimous decision and a European expert panel was convened to develop this Consensus Statement. Three authors (H.A., T.J.S. and M.Ashina) identified the ten most important steps in diagnosis and management of migraine through email correspondence. Once these steps were agreed, seven authors (A.K.E., H.A., S.K., H.- C.D., H.W.S., T.J.S. and M.Ashina) wrote the initial draft.
Target audience	The aim of the approach is to support care and clinical decision-making by primary care practitioners, neurologists and headache specialists alike.

Table 24: Members of the development group and target audience of the Eigenbrodt 2021 guideline.

FR 2021	
Development group	During the first stage, an expert writing group (CL, CR, ADo, ADu, GD, SDG, EGM, JM, XM MLM, PG, DV) and 14 invited experts were assembled. A group of 24 interprofessional external reviewers and patients who were not involved in any aspects of the guideline development, was convened to conduct a final review of the guidelines.
Target audience	… with the aim of assisting all health care professionals supporting patients with migraine in selecting the best management strategies.

Table 25: Members of the development group and target audience of the FR 2021 guideline.

EUR 2022	
Development group	The EHF identified a Panel of Experts consisting of the members of the working group contributing to the first guideline plus members of the EHF council; one junior member who did not participate in voting provided support for data extraction and statistical analyses. All but one member are physicians with expertise in migraine treatment; one member (AMVDB) is a pharmacologist with expertise in migraine treatment.
Target audience	The guideline was published to provide a first guidance on the use of CGRP-mAbs to clinicians.

Table 26: Members of the development group and target audience of the EUR 2022 guideline.

US_prevention 2019	
Development group	These guidelines were jointly developed by the American Academy of Neurology Institute and American Headache Society. A multidisciplinary author panel, consisting of headache experts, child neurologists, clinical psychologists, methodologists and patients, was assembled by the Guideline Development, Dissemination, and Implementation Subcommittee of the AAN to write this guideline. Multidisciplinary author panel consisted of headache experts, child neurologists, clinical psychologists, methodologists and patients. The patient representatives (E.G., E.L., H.Z) included 2 adolescents and 1 adult who had experienced migraine in childhood.
Target audience	The goal is to provide patients and providers with a synthesis of available evidence…

Table 27: Members of the development group and target audience of the US_prevention 2019 guideline.

US_treatment 2019	
Development group	These guidelines were jointly developed by the American Academy of Neurology Institute and American Headache Society. A multidisciplinary author panel, consisting of headache experts, child neurologists, clinical psychologists, methodologists and patients, was assembled by the Guideline Development,

	Dissemination, and Implementation Subcommittee of the AAN to write this guideline. In January 2015, the Guideline Development, Dissemination, and Implementation Subcommittee 7 (GDDI) of the American Academy of Neurology (AAN) convened a multidisciplinary panel consisting of 9 AAN physician members and 3 patient representative members to develop this guideline. In September 2017, 3 more AAN GDDI Subcommittee physician members were added to the panel to assist with evidence rating and recommendation drafting.
Target audience	

Table 28: Members of the development group and target audience of the US_treatment 2019 guideline.

FR_non-med_2021	
Development group	During the first stage, an expert writing group (CL, CR, ADo, ADu, GD, SDG, EGM, JM, XM MLM, PG, DV) and 14 invited experts were assembled. A group of 24 interprofessional external reviewers and patients who were not involved in any aspects of the guideline development, was convened to conduct a final review of the guidelines.
Target audience	... with the aim of assisting all health care professionals supporting patients with migraine in selecting the best management strategies.

Table 29: Members of the development group and target audience of the FR_non-med_2021 guideline.

5 Information and recommendations from guidelines

Not considering the summary section, formal and concise recommendations are written in bold. In contrast, all information from the NHG 2021 guideline are shown in plain text due to the nature of NHG guidelines. For FR 2021, formal recommendations are mainly included in the tables.

Supplemental information are shown in plain text.

Comments from the bibliography group (besides the summary section) start with [Bib. group].

FR 2021, FR_non-med 2021 and EUR 2022 provide the strength (for example strong or weak) of their recommendations while other guidelines do not explicitly categorize their recommendations. The wording used in the recommendations of the other guidelines (for example “offer”, “consider”, “must”, “should”) denotes the certainty with which the recommendations were made.

Overview of the selected guidelines

A total of 9 guidelines were selected.

Five guidelines (SIGN 2022, NICE 2021, NHG 2021, Eigenbrodt 2021, FR 2021) focus on the management of migraine: acute treatment and prevention. Some of which also focus on other types of headache than migraine.

The French guideline (FR 2021) has an separate publication (FR_non-med 2021) for guidelines regarding the non-pharmacological treatment of migraine.

One guideline (EUR 2019) is specifically about monoclonal antibodies acting on CGRP or its receptor for migraine prevention.

Two American guidelines (US_treatment 2019, US_prevention 2019) from the same group focus specically on the treatment of migraine in children. One guideline is about the acute pharmacological treatment and the other guideline about pharmacological prevention.

No guidelines specifically about migraine during pregnancy were selected due to its specialized nature. However, information about this topic was collected from the (more general) guidelines that were selected.

5.1 Acute pharmacological treatment

5.1.1 Summary

Summary

The goal of acute treatment is complete relief of headache two hours after medication intake with 24 hours sustained response without adverse events (FR 2021).

All guidelines discuss a stepped approach for the acute treatment of episodic migraine. Two guidelines also (SIGN 2022, FR 2021) mention a stratified treatment approach where treatment depends on the intensity of the headache. Most guidelines provide treatment algorithms. Differences between guidelines exist in how they recommend paracetamol, NSAID, and triptans. Differences also exist in the recommendations regarding the use of antiemetics.

Guidelines recommend to use acute medications as soon as the patient knows they are developing a migraine attack (SIGN 2022, NHG 2021, Eigenbrodt 2021, FR 2021).
Guidelines recommend to evaluate the effectiveness of treatment after 2-3 attacks.
All guidelines point out that frequent, repeated use of acute medication risks development of medication-overuse headache.

Only NHG 2021 clearly recommends paracetamol as the first treatment step and NSAID as a second treatment step. SIGN 2022 recommends aspirin or ibuprofen as a first choice and paracetamol can be considered for patients who are unable to take other acute therapies. NICE 2021 generally prefers an oral triptan in combination with a NSAID or paracetamol. The guideline group makes the consideration that people may prefer to take one drug rather than two, but that it is likely however that most people consulting a healthcare professional for migraine will have tried over the counter preparations such as paracetamol or NSAIDs before they consult. For patients who prefer monotherapy, an oral triptan, NSAID, aspirin or paracetamol are to be considered taking into account the person's preference, comorbidities and risk of adverse events.
Eigenbrodt 2021 recommends NSAID as first-line medications and paracetamol only in those who are intolerant of NSAID.
The recommendations from FR 2021 depend on the intensity of the headache. NSAID are recommended for a mild headache and the addition of a triptan is recommended in case of insufficient response after one hour. For moderate or severe headache a triptan is recommended and the addition of an NSAID is recommended in case of insufficient response after one hour.

Among the NSAID, SIGN 2022 recommends ibuprofen. They also separately recommend aspirin. NICE 2021 does not mention a preference among the NSAID, but they separately recommend aspirin next to the NSAID. NHG 2021 has a preference for ibuprofen or naproxen. Eigenbrodt 2021 recommends aspirin, ibuprofen and diclofenac potassium. FR 2021 do not mention a preference.

SIGN 2022 recommends sumatriptan as the first choice among the triptans based on efficacy, safety profile and cost. NICE 2021 and NHG 2021 (sumatriptan, rizatriptan, zolmitriptan) recommend to start with a triptan with the lowest cost. Eigenbrodt 2021 and FR 2021 do not select a first choice among the triptans in their recommendations.

Guidelines recommend several strategies to optimize efficacy and/or tolerability. These include dose increases of NSAID and/or triptans when applicable, combination therapies, switching to a non-oral formulation, switching the NSAID to another NSAID, and switching the triptan with another triptan.

The guidelines do not recommend opioids and ergots for the acute treatment of migraine.

Eigenbrodt 2021 include the recent ditans and gepants in their recommendations. These drugs could be used after failure of all available triptans. They state that indirect comparison of data from randomized controlled trials suggests that the efficacy of the ditan lasmiditan (not available in Belgium) is comparable to that of triptans, but its use is associated with temporary driving impairment, which is likely to discourage widespread use.
FR 2021 describes the available evidence for ditans and gepants but does not formulate any recommendations.

Some guidelines provide specific recommendations for patients with migraine with aura. Several guidelines (SIGN 2022, NHG 2021, Eigenbrodt 2021, FR 2021) do not recommend triptans at the start of the aura, triptans should be started at onset of the headache. FR 2021 recommends a NSAID at the beginning of the aura and a triptan at the onset of the headache. However, they also state that currently there is no pharmacological treatment proved effective in stopping aura.

For migraine with nausea and/or vomiting, all guidelines recommend metoclopramide. SIGN 2022 and NICE 2021 also recommend prochlorperazine (not available in Belgium). NHG 2021 and Eigenbrodt 2021 also recommend domperidone. SIGN 2022, NICE 2021, FR 2021 also consider antiemetics for the treatment of migraine in absence of nausea and/or vomiting.

SIGN 2022 recommends aspirin (900 mg) and ibuprofen (400-600 mg) as first-line treatment for patients with acute migraine. Paracetamol can be considered for patients who are unable to take other acute therapies. If not successful over three headaches, treatment is stepped up to triptans. The first choice among the triptans is sumatriptan (50–100 mg), but other triptans should be offered if sumatriptan fails. Try triptan and NSAID combinations. Combination therapy using sumatriptan (50–85 mg) and naproxen (500 mg) should be considered.
Metoclopramide (10 mg) or prochlorperazine (10 mg) can be considered in the treatment of headache in patients with acute migraine. They can be used either as an oral or parenteral formulation depending on presentation and setting.
Metoclopramide (10 mg) or prochlorperazine (10 mg) should be considered for patients presenting with migraine-associated symptoms of nausea or vomiting. They can be used either as an oral or parenteral formulation depending on presentation and setting.

NICE 2021 recommends to offer combination therapy with an oral triptan and an NSAID or paracetamol, taking into account the person's preference, comorbidities and risk of adverse events. For people who prefer monotherapy, consider an oral triptan, NSAID, aspirin (900 mg) or paracetamol, taking into account the person's preference, comorbidities and risk of adverse events.
When prescribing a triptan start with the one that has the lowest acquisition cost; if this is consistently ineffective, try one or more alternative triptans. Consider an antiemetic in addition to other acute treatment for migraine even in the absence of nausea and vomiting.
For people in whom oral preparations (or nasal preparations in young people aged 12 to 17 years) for the acute treatment of migraine are ineffective or not tolerated:
• consider a non-oral preparation of metoclopramide or prochlorperazine and
• if non-oral metoclopramide or prochlorperazine is used, consider adding a non-oral NSAID or triptan if they have not been tried.

NHG 2021 recommends paracetamol as a first step at the onset of the headache. Rectal administration of paracetamol in only recommended in case of severe nausea.
After failure of paracetamol at a sufficient dose (evaluate effectiveness after 2-3 attacks), NSAID are recommended as a second step. Ibuprofen and naproxen are preferred. In case of severe

nausea and/or vomiting rectal administration of NSAID (naproxen or diclofenac) is recommended. A sufficiently high dose is required and treatment is recommended at the onset of the headache. If necessary, repeat ibuprofen for persistent or recurrent pain after 6 hours and naproxen after 12 hours.

After failure of NSAID (evaluate effectiveness after 2-3 attacks), oral triptans are recommended as a third step. The selection of the triptan is based on the cost: sumatriptan, rizatriptan, zolmitriptan. Only the dose of sumatriptan and zolmitriptan can be increased. If the triptan is effective but the headache returns, another tablet can be administered after two hours or opt for a combination therapy (see forth step). After failure (insufficient effect, intolerance) of the triptan at a maximum dose following 2-3 attacks, switch to other triptans. Re-evaluate after 2-3 attacks. Prescribe sumatriptan injection or nasal spray in case of severe nausea with or without vomiting in whom oral triptans are inadequate as a result despite the use of anti-emetics.

Combination therapy is recommended as a forth step. In case of insufficient efficacy with only paracetamol, NSAID, and triptans, consider combination therapy: paracetamol + NSAID or if this provides insufficient pain relief consider triptan + paracetamol or NSAID. Consider combination therapy (triptan + NSAID) as initial treatment in patients in who a triptan initially was effective but the migraine returned within 24 hours.

Domperidone (max. 7 days) or metoclopramide (max. 5 days) are to be considered for migraine with nausea and/or vomiting. Evaluate effectiveness after 2-3 attacks and discontinue the antiemetic in case of insufficient effectiveness.

Eigenbrodt 2021 recommends a stepped care approach with first-line, second-line, third-line treatments. Move to a next line of treatment (or when switching between triptans) after three consecutive attacks without treatment success.

First-line medication are NSAID (acetylsalicylic acid, ibuprofen or diclofenac potassium). Paracetamol has less efficacy and should be used only in those who are intolerant of NSAID.

Second-line medications are triptans. When triptans provide insufficient pain relief, combine with fast-acting NSAID. Consider combining triptans with fast-acting NSAIDs to avert recurrent relapse. Sumatriptan by subcutaneous injection can be useful when all other triptans have failed or in patients who rapidly reach peak headache intensity or cannot take oral triptans because of vomiting. After treatment failure of all available triptans, the third-line medications ditans or gepants are to be considered.

For patients who experience nausea and/or vomiting during migraine attacks, prokinetic antiemetics such as domperidone and metoclopramide are useful oral adjuncts.

FR 2021 recommends NSAID for a mild headache and the addition of a triptan is recommeded in case of insufficient response after one hour. For moderate or severe headache a triptan is recommended and the addition of a NSAID is recommended in case of insufficient response after one hour. In patients with contraindications or intolerance to NSAIDs, aspirin and triptans, a combination of paracetamol and metoclopramide is recommended. For attacks with severe nausea or vomiting, oral or parenteral metoclopramide (suppository or intravenous) is recommended.
The authors recommend different strategies to optimize efficacy and/or tolerability. They recommend to increase the dose of NSAID and/or triptan when applicable, to combine a triptan and an NSAID simultaneously when attacks are resistant to a triptan alone and/or when relapses are troublesome, to switch to a non-oral formulation (NSAID suppository; sumatriptan nasal spray or subcutaneous) and/or add metoclopramide in case of bothersome digestive symptoms, to switch the NSAID to another NSAID, and to combine a triptan.

5.1.2 SIGN 2022

Acute treatment should be taken as early as possible in the headache phase with the aim of aborting an attack. It is given once, with the option of repeating after two hours (with the same or different treatment) if there is an inadequate response. Preventative treatment is taken continuously in order to reduce the frequency and severity of migraine attacks. Often a combination of acute and preventative treatment is needed.

For treatment to be effective, it is crucial that the correct diagnosis has been made. Diagnostic criteria for migraine and MOH are listed in Annex 2. Choice of treatment should take account of severity and frequency of attacks, other symptoms, patient preference, history of treatment and comorbid conditions.

Patients have a variable response to triptans and it is worth sequencing through the triptans to find the most effective treatment. When starting a preventative treatment a low dose should be used and treatment dose gradually increased. The minimum effective dose should be used and this may vary between patients. The need for ongoing prophylaxis should be considered after six to 12 months.

INTRODUCTION
Acute treatment is used either to abort an attack of migraine or to significantly reduce the severity of the headache and other symptoms. Acute treatment should be taken as soon as the patient knows they are developing a migraine headache. In patients who have aura, it is recommended that triptans are taken at the start of the headache and not at the start of the aura (unless the aura and headache

start at the same time). It is given once, with the option of repeating after two hours (with the same or different treatment) if there is an inadequate response.

Treatment response is measured as pain free at two hours and sustained pain free at 24 hours. In addition, pain relief or headache relief (from severe/moderate to mild or no pain) is reported in some studies. A table of numbers needed to treat (NNTs) to achieve pain free at two hours for some acute therapies can be found in section 3.9.

Treatment can either be stepped or stratified. In stepped treatment high-dose aspirin or ibuprofen is given first and, if not successful over three headaches, treatment is stepped up to triptans. In stratified treatment patients might, for example, use high dose aspirin for a milder headache and a triptan for a more severe headache. The strategy used should be tailored to patient preference. Patients have a variable response to individual triptans and it is worth sequencing through different triptans to find the most effective one. Acute treatment will not always work for every migraine. Patients should be offered appropriate rescue medication for this situation, for example subcutaneous sumatriptan may be appropriate in some patients who don't respond to oral or nasal triptan. The risk of MOH should be discussed with every patient started on acute treatment.

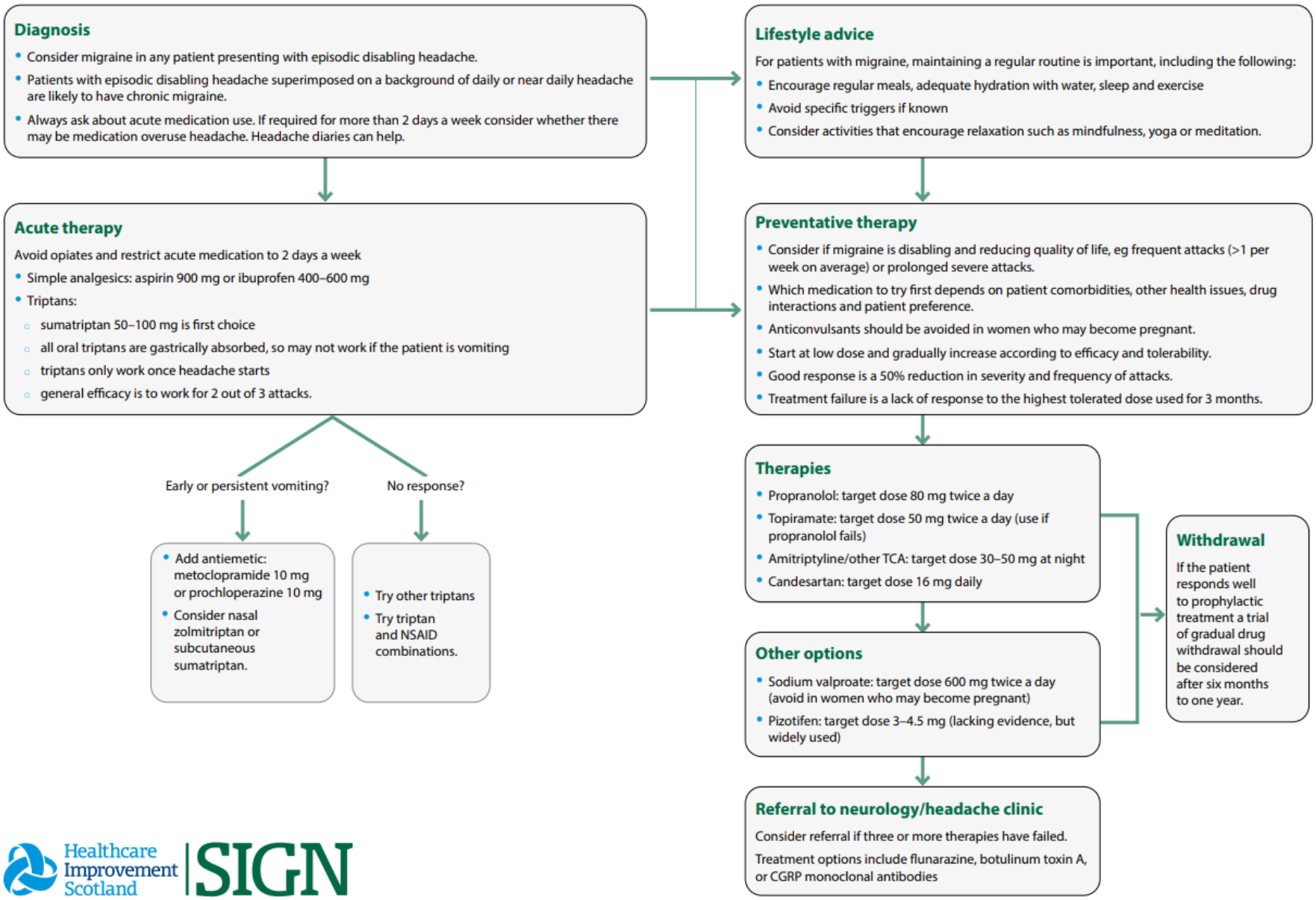
It should be noted that all orodispersible (dissolve in the mouth) triptans are gastrically absorbed. In patients who vomit early in a migraine attack, nasal and subcutaneous triptans should be considered. A significant proportion of the nasal dose is still gastrically absorbed. Antiemetics should be considered in patients with nausea or vomiting.

In patients with moderate to severe attacks combining a triptan with aspirin or a non-steroidal anti-inflammatory drug (NSAID) may be beneficial. Nasal or subcutaneous triptans should also be considered.

A treatment algorithm outlining good practice in acute treatment can be found in Annex 3 ([Bib. group]. see next page).

When starting acute treatment, healthcare professionals should warn patients about the risk of developing medication-overuse headache.

SIGN 155: Pharmacological management of patients with migraine. Treatment pathway



Healthcare Improvement Scotland | SIGN

Aspirin

Aspirin (900 mg) is recommended as first-line treatment for patients with acute migraine.

NSAID

Ibuprofen (400 mg) is recommended as first-line treatment for patients with acute migraine. If ineffective, the dose should be increased to 600 mg.

Paracetamol

Paracetamol (1,000 mg) can be considered for treatment of patients with acute migraine who are unable to take other acute therapies.

Antiemetics

Metoclopramide (10 mg) or prochlorperazine (10 mg) can be considered in the treatment of headache in patients with acute migraine. They can be used either as an oral or parenteral formulation depending on presentation and setting.

Metoclopramide (10 mg) or prochlorperazine (10 mg) should be considered for patients presenting with migraine-associated symptoms of nausea or vomiting. They can be used either as an oral or parenteral formulation depending on presentation and setting.

Metoclopramide should not be used regularly due to the risk of extrapyramidal side effects.

Triptans

Sumatriptran is the preferred triptan based on efficacy, safety profile and cost. For patients with early vomiting, a nasal or subcutaneous triptan may be more effective. Nasal zolmitriptan 5 mg and sumatriptan 6 mg subcutaneous are effective (see Table 1, section 3.9). Where treatment with paracetamol (all trimesters) or ibuprofen (first and second trimester only) fail, the use of triptans, in particular sumatriptan, in all stages of pregnancy can be considered. None of the triptans are classed as non-teratogenic.

Triptans are recommended as first-line treatment for patients with acute migraine. The first choice is sumatriptan (50–100 mg), but others should be offered if sumatriptan fails.

In patients with severe acute migraine or early vomiting, nasal zolmitriptan or subcutaneous sumatriptan should be considered.

Combined therapies

Combination therapy using sumatriptan (50–85 mg) and naproxen (500 mg) should be considered for the treatment of patients with acute migraine.

Steroids

No evidence was identified on the use of prednisolone as a tapered treatment in patients with prolonged migraine (>3 days).

5.1.3 NICE 2021

Migraine with or without aura

1.3.10 Offer combination therapy with an oral triptan and an NSAID, or an oral triptan and paracetamol, for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of adverse events. For young people aged 12 to 17 years consider a nasal triptan in preference to an oral triptan. [2012]

Trade off between clinical benefits and harms
The risk of medication overuse headache with the use of triptans should be considered. However the evidence shows good efficacy of these treatments used in combination.
The potential side-effects of non-steroidal drugs, especially gastric ulceration and bleeding and cardiovascular risks should be balanced against the more rapid and prolonged benefit when used in combination with a triptan for treating an acute migraine episode.

Quality of evidence
The evidence from the network meta-analysis (based on low and very low quality direct comparison evidence) showed good efficacy of these combinations when compared to singly administered treatments. The evidence suggested that triptan and NSAID was a more effective combination.
All evidence is based on oral administered drugs. Only one study of triptan use included people less than 18 years old.

Other considerations
The GDG considered that people may prefer to take one drug rather than two. It is likely however that most people consulting a healthcare professional for migraine will take tried over the counter preparations such as paracetamol or NSAIDs before they consult. The GDG considered it important that patients and health professionals are informed of the added efficacy of taking these drugs in combination although patient preference and experience should inform the decision of which treatment to prescribe. The GDG considered the use of triptans for the 12-17 age groups and agreed that triptans were an appropriate option for younger people. Oral triptans are not licensed for use in people aged under 18, sumatriptan is licensed to use as a nasal spray in the under 18 age group and the GDG agreed to indicate this in the recommendation.

1.3.11 For people who prefer to take only one drug, consider monotherapy with an oral triptan, NSAID, aspirin (900 mg) or paracetamol for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of adverse events. [2012]

Because of the association with Reye's syndrome, preparations containing aspirin should not be offered to under 16s.

Trade off between clinical benefits and harms
The risk of medication overuse headache with acute treatments should be considered. NSAIDs can cause gastric ulceration, reduce renal function and may trigger an anaphylactic reaction in

susceptible individuals. Aspirin should not be given to children under 16 years because of potential risk of Reye's syndrome.

Quality of evidence

The direct evidence is of moderate to very low quality. Only one study of triptan use included people less than 18 years. Network meta-analysis of the evidence shows moderate efficacy for these treatments. All evidence is from oral administered drugs and is for the NSAIDs at 400mg minimum, aspirin at 900mg minimum and paracetamol at 1000mg.

Other considerations

The GDG agreed that there is evidence that compliance may be better with single administrations than dual administration of treatment. Patient preference and experience should inform the decision of which treatment to prescribe. The GDG considered the use of triptans for the 12-17 age groups and agreed that triptans were an appropriate option for younger people. Oral triptans are not licensed for use in people aged under 18 but sumatriptan is licensed to use as a nasal spray in the under 18 age group. GDG consensus opinion was that failure to respond to a particular triptan may not be indicative that another triptan will also not work, therefore it may be worth considering an alternative triptan if there's no response to the first one. Studies for aspirin were either 500mg or 1000mg, these were pooled for analysis. GDG consensus opinion was that the higher doses are more effective, therefore agreed to recommend 900mg.

1.3.12 When prescribing a triptan start with the one that has the lowest acquisition cost; if this is consistently ineffective, try one or more alternative triptans. [2012]

Trade off between clinical benefits and harms

The risk of medication overuse headache with acute treatments should be considered. The GDG considered that efficacy of triptans can vary between individuals.

Quality of evidence

The direct evidence is of moderate to very low quality. Network meta-analysis of the evidence shows moderate efficacy for triptans. The GDG agreed that triptans should be reviewed as a class (as detailed in the protocol), and therefore no evidence was reviewed comparing different triptans to each other. GDG consensus opinion was that failure to respond to a particular triptan may not be indicative that another triptan will also not work, so this recommendation was formed on informal consensus.

Other considerations

GDG consensus opinion was that failure to respond to a particular triptan may not be indicative that another triptan will also not work, therefore it may be worth considering an alternative triptan if there's no response to the first one. Response should not be judged on one migraine attack alone- the GDG considered that people should be encouraged to use triptan for at least three attacks before considering an alternative triptan. Sumatriptan is licensed to use as a nasal spray in the under 18 age group but other triptans are unlicensed in this age group.

1.3.13 Consider an anti-emetic in addition to other acute treatment for migraine even in the absence of nausea and vomiting. [2012]

Trade off between clinical benefits and harms

There is a small risk that anti-emetic drugs can trigger extra pyramidal side effects; the GDG agreed the risk is higher in those under the age of 20. These reactions which include dystonic reactions can be frightening but are rare and reversible. The GDG also considered the practical difficulty of ingesting three medications together and whether this could trigger more nausea and vomiting.

Quality of evidence

The addition of an antiemetic is based on GDG informal consensus. However there was very low quality evidence from one study suggesting paracetamol + anti emetic to be more effective than triptans in producing headache response at 2 hours and indirect evidence from non-oral administration of antiemetics showing efficacy at producing freedom from pain at 2 and 24 hours (moderate to very low quality evidence).

Other considerations

The decision to add an antiemetic is likely to depend on patient preference and experience of benefit without anti-emetic. Many people will find it easier and preferable to use fewer drugs, at least initially. The GDG considered it useful for the generalist to be made aware that anti-emetics may have an effect on migraine itself and can be a useful adjunct even if the patient does not have significant nausea and vomiting. The GDG were aware that anti-emetic has historically been included in treatment for effect on nausea and vomiting alone and that for patients with significant nausea and vomiting anti-emetic might be required for those symptoms as well.

1.3.14 Do not offer ergots or opioids for the acute treatment of migraine. [2012]

Trade off between clinical benefits and harms

The other treatments reviewed in the network meta-analysis were superior to ergots in producing headache response or freedom from pain at up 2 or at 24 hours, with the exception of paracetamol where there is no difference in efficacy.

The GDG agreed that the high risk of adverse events associated with the use of ergots, together with the evidence for superiority of comparator treatments, supported this negative recommendation for ergots in the treatment of acute migraine.

There was little evidence for effectiveness of opioids in the analyses, but they are known to have addictive properties and the potential to lead to medication overuse headache.

Quality of evidence

The direct evidence for ergots was of very low quality and was in favour of the comparator (triptan). Network meta-analysis of the available evidence did not favour ergots.

The GDG agreed that this evidence together with their informal consensus opinion on the high risk of adverse events was sufficient quality evidence for this recommendation. No evidence was identified for opioids and these were therefore not included in the network meta-analysis.

Other considerations

The recommendation against the use of ergots was based on evidence for oral, nasal, subcutaneous and intravenous preparations of ergot derivatives. Opioids may exacerbate nausea and will also increase the risk of medication overuse headache.

1.3.15 For people in whom oral preparations (or nasal preparations in young people aged 12 to 17 years) for the acute treatment of migraine are ineffective or not tolerated:
• consider a non-oral preparation of metoclopramide or prochlorperazine and
• if non-oral metoclopramide or prochlorperazine is used, consider adding a non-oral NSAID or triptan if they have not been tried. [2012, amended 2021]

Note the special warnings and precautions for use in the summaries of product characteristics for metoclopramide and prochlorperazine, and discuss the benefits and risks with the person (or their parents or carers, as appropriate).

Trade off between clinical benefits and harms
There is a small risk that anti-emetic drugs can trigger extra pyramidal side effects; the GDG agreed the risk is higher in those under the age of 20. These reactions which include dystonic reactions can be frightening but are rare and reversible.
The GDG agreed that the benefits of dopamine receptor antagonists (metoclopramide or prochlorperazine) justify their use with consideration of the side-effects in at risk groups. The GDG agreed by informal consensus that additional benefits may be achieved by co-administering an NSAID or triptan.

Quality of evidence
There is evidence from this systematic review that antiemetics are effective for pain relief, regardless of whether the person has either nausea or vomiting. The evidence review included chlorpromazine, metoclopramide and prochlorpromazine (moderate, low and very low quality evidence). However, parenteral chlorpromazine is not widely used in the UK in the non-palliative setting, therefore the GDG agreed not to make a recommendation for or against its use for migraine treatment.
Intravenous or rectal preparations of prochlorperazine are not available the UK and therefore their use by intramuscular administration should be considered. This was agreed by GDG informal consensus. The evidence for prochlorperazine included children in the study population. Although none of the evidence for metoclopramide included in this review was for children and young people aged under 18, the GDG agreed that there were no other considerations for the use of this drug in the 12-17 year old age group (except those stated above in trade offs between clinical benefits and harms) and it could be recommended. There is evidence for good effectiveness of subcutaneous triptans and intravenous NSAIDs given in isolation (low and very low quality). GDG consensus (informal methods) agreed that their use in addition to the antiemetic should be recommended. Intramuscular or rectal administration was based on GDG informal consensus if intravenous administration not available or appropriate.

Other considerations
This recommendation would mainly apply in accident and emergency settings and for out-of-hours GPs. Reasons for oral treatment not being appropriate could include vomiting, previous attempt at oral treatment which has been ineffective and patient choice. The GDG noted that hypotension is

more likely when prochlorperazine is given intramuscularly, than by oral administration. If the individual has already taken an NSAID or triptan with unsatisfactory response, do not re-administer the same drug parenterally in addition to the antiemetic.

5.1.4 NHG 2021

Medicamenteuze behandeling
Algemeen

- Ga vóór het starten van een medicamenteuze behandeling na of de patiënt al eerder medicatie heeft gebruikt en zo ja, welke en in welke dosering.
- Ga na of de patiënt geneesmiddelen in een te lage dosering of frequentie gebruikt heeft, waardoor deze mogelijk niet of onvoldoende effectief zijn geweest.
- Behandel MOH als eerste wanneer deze aanwezig is; spanningshoofdpijn en migraine zijn in dat geval namelijk niet te herkennen.
- Een proefbehandeling met medicatie met als doel de diagnose te stellen wordt afgeraden.
- Gebruik eventueel het hoofdpijndagboek (versie behandeling) om het effect van de medicatie te evalueren.

De medicamenteuze behandeling (zie ook tabel 17) bestaat uit:

- aanvalsbehandeling met paracetamol, NSAID of triptaan
- preventieve behandeling met een bètablokker, candesartan of amitriptyline

Aanvalsbehandeling

- De effectiviteit van paracetamol, NSAID's en triptanen is waarschijnlijk vergelijkbaar. Het bijwerkingenprofiel is echter verschillend. Op grond hiervan is paracetamol eerste keus, zijn NSAID's tweede keus en triptanen derde keus.
- De werkzaamheid van de verschillende medicijnen verschilt per individu. Beoordeel na 2-3 aanvallen de effectiviteit van het voorgeschreven middel en wissel zo nodig bij onvoldoende effectiviteit tussen de verschillende triptanen en NSAID's.
- Voeg zo nodig bij hevige misselijkheid en/of braken een anti-emeticum toe (zie Anti-emetica).
- Schrijf geen opioïden voor.
- Patiënten kunnen verschillend reageren op een middel; het hoofdpijndagboek (versie behandeling) kan inzicht bieden in de effectiviteit van de behandeling.
- Waarschuw de patiënt dat veelvuldig gebruik, ongeacht de dosering, MOH kan veroorzaken:
    - paracetamol of NSAID's ≥ 15 dagen per maand gedurende 3 maanden
    - triptanen of opioïden ≥ 10 dagen per maand gedurende 3 maanden
    - combinaties van analgetica ≥ 10 dagen per maand gedurende 3 maanden

Medicamenteus stappenplan aanvalsbehandeling

Stap 1 Paracetamol

- Adviseer paracetamol in te nemen bij het begin van de hoofdpijn.
- Kies alleen bij hevige misselijkheid voor rectale toediening van paracetamol. Een zetpil geeft een onvoorspelbaar wisselende en vertraagde absorptie.

- Evalueer na 2-3 aanvallen de effectiviteit en stop paracetamol bij onvoldoende effectiviteit.

Stap 2 NSAID's

- Kies bij onvoldoende effect van voldoende hoog gedoseerde paracetamol een NSAID.
- NSAID's (voorkeur voor ibuprofen of naproxen) zijn ongeveer even effectief. Het werkings- en bijwerkingenpatroon verschilt enigszins per middel en per patiënt. Houd rekening met patiëntkenmerken (zoals comorbiditeit, voorgeschiedenis van cardiovasculaire of gastrointestinale aandoeningen en respons op eerder voorgeschreven NSAID's).
- Controleer of er geen contra-indicaties zijn (zie NHG-Standaard Pijn).
- Beoordeel of er een indicatie is voor maagbescherming (zie NHG-Behandelrichtlijn Preventie van maagcomplicaties door medicatiegebruik).
- Kies bij hevige misselijkheid en/of braken voor rectale toediening (naproxen of diclofenac). De snelheid van absorptie van NSAID-zetpillen is vergelijkbaar met die van NSAID-tabletten.
- Zorg voor een voldoende hoge dosering en adviseer het middel in te nemen bij het begin van de hoofdpijn.
- Herhaal ibuprofen zo nodig bij aanhoudende of terugkerende pijn na 6 uur en naproxen na 12 uur.
- Evalueer na 2-3 aanvallen de effectiviteit en stop de NSAID bij onvoldoende effectiviteit.

Stap 3 Triptanen

- Alle triptranen zijn ongeveer even effectief; het werkings- en bijwerkingenpatroon verschilt enigszins per middel en per patiënt.
- Schrijf een oraal triptaan voor (gewone tabletten werken even snel als smelttabletten). Op grond van de kosten hebben de volgende triptanen de voorkeur:
    - sumatriptan
    - rizatriptan
    - zolmitriptan
- Alleen sumatriptan en zolmitriptan kunnen bij een volgende aanval in hogere dosering worden voorgeschreven, bijvoorbeeld bij het terugkeren van de hoofdpijn, of bij onvoldoende verbetering van de hoofdpijn.
- Adviseer het triptaan in te nemen bij het begin van de hoofdpijn (en de patiënt de hoofdpijn herkent als migraine). Het is niet zinvol om een triptaan in te nemen bij het begin van een eventueel aura of in de prodromale fase.
- Neem zo nodig, als het middel effect heeft maar de hoofdpijn terugkeert, na minimaal 2 uur nog een tablet in of kies voor een combinatiebehandeling (zie stap 4).
- Indien een triptaan in de maximale dosering na 2-3 aanvallen geen of onvoldoende effect heeft of als er te veel bijwerkingen optreden, probeer dan de andere triptanen uit tabel 17. Beoordeel het effect na 2-3 aanvallen.
- Schrijf aan patiënten die ondanks gebruik van een anti-emeticum last hebben van hevige misselijkheid, al dan niet met braken, en bij wie orale geneesmiddelen hierdoor onvoldoende werkzaam zijn, sumatriptaninjectie of neusspray voor. Deze middelen zijn aanzienlijk duurder en waarschijnlijk niet effectiever dan de orale middelen.

Stap 4 Combinatiebehandeling

- Overweeg bij migraine waarbij onvoldoende effect wordt ervaren van alleen paracetamol, NSAID's en triptanen een combinatiebehandeling (paracetamol en NSAID en bij onvoldoende effect paracetamol of NSAID en triptaan).
- Overweeg bij patiënten bij wie de aanval in eerste instantie onderdrukt is met een triptaan, maar binnen 24 uur weer terugkomt, een combinatiebehandeling (NSAID in combinatie met een triptaan) als initiële aanvalsbehandeling.

Anti-emetica

Overweeg bij migraine met misselijkheid en/of braken een anti-emeticum voor te schrijven naast de aanvalsbehandeling; maak een keuze tussen domperidon (maximaal 7 dagen) en metoclopramide (maximaal 5 dagen) op basis van patiëntkenmerken, comorbiditeit, comedicatie, contra-indicaties en mogelijke bijwerkingen. Evalueer na 2-3 aanvallen de effectiviteit en stop het anti-emeticum bij onvoldoende effectiviteit.

Tabel 17. Overzicht geneesmiddelen aanvalsbehandeling migraine bij volwassenen

Middel	Startdosering	Maximale dosering per 24 uur bij incidenteel gebruik	Contra-indicaties	Bijwerkingen
Paracetamol (tablet of zetpil)	1000 mg	4000 mg	Zie NHG-Standaard Pijn	Zie NHG-Standaard Pijn
NSAID's				
Ibuprofen (tablet)	400 mg	1200mg	Zie NHG-Standaard Pijn	Zie NHG-Standaard Pijn
Naproxen (off-label) (tablet of zetpil)	500 mg	1000 mg		
Acetylsalicylzuur (off-label) (tablet)	1000 mg	4000 mg		
Diclofenac (off-label) (tablet of zetpil)	25-50-75 mg	150 mg		

Triptanen				
Sumatriptan • tablet • injectie sc • neusspray	• 50 mg • 6 mg • 20 mg	• 300 mg • 12 mg • 40 mg	• coronair vaatlijden • doorgemaakt herseninfarct of TIA • ernstige of ongecontroleerde hypertensie • ernstige leverfunctiestoornis	• misselijkheid • braken • moeheid • sufheid/slaperigheid • duizeligheid • drukkend gevoel op de borst • tintelingen, paresthesieën en warmte-sensaties
Rizatriptan (smelt)tablet	10 mg (5 mg bij propranololgebruik /leverfunctiestoornis)	20 mg (10 mg bij propranololgebruik /leverfunctiestoornis)		
Zolmitriptan smelttablet	2,5 mg	10 mg (5 mg bij matige of ernstige leverfunctiestoornis)		
Anti-emetica				
Domperidon (off-label) tablet	10 mg (max. 7 dagen)	30 mg	• verlengde QT-tijd • hartritmestoornissen • leverfunctiestoornissen • bekende elektrolytstoornissen (hyperkaliëmie, hypomagnesiëmie)	• droge mond • hartritmestoornissen (zelden) • extrapiramidale verschijnselen (soms)
Metoclopramide tablet of zetpil	10 mg (max. 5 dagen) eGFR 10-50 ml/min/1,73 m^2: 50% van de dosering eGFR < 10 ml/min/1,73 m^2: 25% van de dosering	30 mg	• gebruik van levodopa en andere dopamine-agonisten • ziekte van Parkinson • epilepsie • verlengde QT-tijd	extrapiramidale stoornissen (vaak)

5.1.5 Eigenbrodt 2021

Step 4: Acute treatment

Acute treatments can be classified as first- line, second- line, third- line and adjunct (Table 3), and should be used in a stepped care approach (Fig. 2). Our recommendations for each line of treatment are outlined below. The medications at each stage were selected on the basis of efficacy, tolerability, safety, cost and availability.

First-line medication.

Over-the-counter analgesics are used worldwide for acute migraine treatment. Those with proven efficacy include non-steroidal anti-inflammatory drugs (NSAIDs), and the strongest evidence supports use of acetylsalicylic acid, ibuprofen and diclofenac potassium as first-line medications. Paracetamol has less efficacy and should be used only in those who are intolerant of NSAIDs.

Second-line medication.
Patients for whom over-the-counter analgesics provide inadequate headache relief should be offered a triptan. All triptans have well documented effectiveness, but availability of and acces to each vary between countries. Triptans are most effective when taken early in an attack, when the headache is still mild. However, no evidence supports the use of triptans during the aura phase of a migraine attack. If one triptan is ineffective, others might still provide relief. When all other triptans have failed or in patients who rapidly reach peak headache intensity or cannot take oral triptans because of vomiting, sumatriptan by subcutaneous injection can be useful.
Some patients can experience relapses, which are defined as a return of symptoms within 48 h after apparently successful treatment. Upon relapse, patients can repeat their triptan treatment or combine the triptan with simultaneous intake of fast-acting formulations of naproxen sodium, ibuprofen lysine or diclofenac potassium. However, patients should be informed that repeating the treatment does not preclude further relapses and ultimately increases the risk of developing MOH.

Third-line medication.
If all available triptans fail after an adequate trial period (no or insufficient therapeutic response in at least three consecutive attacks) or their use is contraindicated, alternatives are currently limited. Ditans or gepants could be used, but their availability is currently very limited. Lasmiditan is the only ditan approved for acute treatment of migraine, and ubrogepant and rimegepant are the only gepants approved. Indirect comparison of data from randomized controlled trials suggests that the efficacy of lasmiditan is comparable to that of triptans, but its use is associated with temporary driving impairment, which is likely to discourage widespread use. Individuals who take lasmiditan might be unable to self-assess their driving competence and should not operate machinery for at least 8 h after intake.

Adjunct medication.
For patients who experience nausea and/or vomiting during migraine attacks, prokinetic antiemetics such as domperidone and metoclopramide are useful oral adjuncts.

Medications to avoid.
Oral ergot alkaloids are poorly effective and potentially toxic, and should not be used as a substitute for triptans. The efficacy of opioids and barbiturates is questionable, and both are associated with considerable adverse effects and the risk of dependency. All of these medications should, therefore, be avoided for the acute treatment of migraine.

Recommendations.
- **Offer acute medication to everyone who experiences migraine attacks.**
- **Advise use of acute medications early in the headache phase of the attack, as effectiveness depends on timely use with the correct dose.**
- **Advise patients that frequent, repeated use of acute medication risks development of MOH.**

• Use NSAIDs (acetylsalicylic acid, ibuprofen or diclofenac potassium) as first-line medication.
• Use triptans as second-line medication.
• Consider combining triptans with fast-acting NSAIDs to avert recurrent relapse.
• Consider ditans and gepants as third-line medications.
• Use prokinetic antiemetics (domperidone or metoclopramide) as adjunct oral medications for nausea and/or vomiting.
• Avoid oral ergot alkaloids, opioids and barbiturates

4 Acute treatment

First-line medication
- NSAIDs (acetylsalicylic acid, ibuprofen or diclofenac potassium)

Second-line medication
- Triptans
- When triptans provide insufficient pain relief, combine with fast-acting NSAIDs

Third-line medication
- Ditans
- Gepants

Adjunct medications for nausea and/or vomiting
- Prokinetic antiemetics (domperidone or metoclopramide)

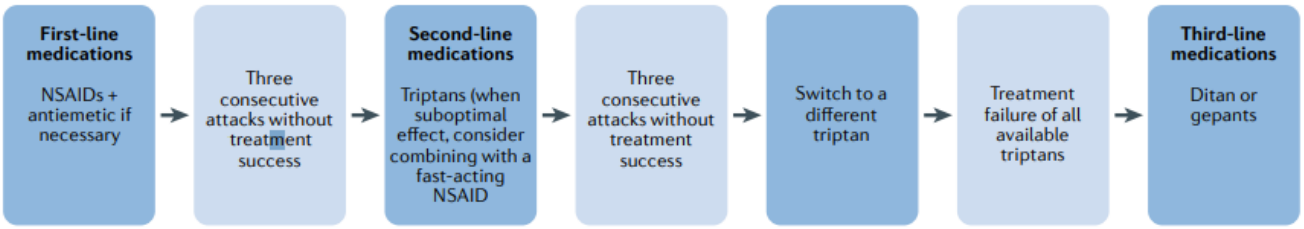


Fig. 2 | **Stepped care across migraine attacks.** Preventive therapy, in addition, may be indicated at any stage. In general, initiation of preventive therapy is indicated in patients who are adversely affected on ≥2 days per month despite acute treatment optimized according to the stepped care approach. NSAID, non-steroidal anti-inflammatory drug.

Table 3 | **Acute migraine treatment**

Drug class	Drug	Dosage and route	Contraindications
First-line medication			
NSAIDs	Acetylsalicylic acid	900–1,000 mg oral	Gastrointestinal bleeding, heart failure
	Ibuprofen	400–600 mg oral	
	Diclofenac potassium	50 mg oral (soluble)	
Other simple analgesics (if NSAIDs are contraindicated)	Paracetamol	1,000 mg oral	Hepatic disease, renal failure
Antiemetics (when necessary)	Domperidone	10 mg oral or suppository	Gastrointestinal bleeding, epilepsy, renal failure, cardiac arrhythmia
	Metoclopramide	10 mg oral	Parkinson disease, epilepsy, mechanical ileus
Second-line medication			
Triptans	Sumatriptan	50 or 100 mg oral or 6 mg subcutaneous or 10 or 20 mg intranasal	Cardiovascular or cerebrovascular disease, uncontrolled hypertension, hemiplegic migraine, migraine with brainstem aura
	Zolmitriptan	2.5 or 5 mg oral or 5 mg intranasal	
	Almotriptan	12.5 mg oral	
	Eletriptan	20, 40 or 80 mg oral	
	Frovatriptan	2.5 mg oral	
	Naratriptan	2.5 mg oral	
	Rizatriptan	10 mg oral tablet (5 mg if treated with propranolol) or 10 mg mouth-dispersible wafers	
Third-line medication			
Gepants	Ubrogepant	50, 100 mg oral	Co-administration with strong CYP3A4 inhibitors
	Rimegepant	75 mg oral	Hypersensitivity, hepatic impairment
Ditans	Lasmiditan	50, 100 or 200 mg oral	Pregnancy, concomitant use with drugs that are P-glycoprotein substrates

5.1.6 FR 2021

Table 1 – Non-specific acute migraine treatments (MA: specific French Market Approval for the acute treatment of migraine headache).

Analgesics	Level of evidence for efficacy	Strength of recommendation by the French Headache Society	Dose, route	Main side effects	Main contraindications[a]
Acetylsalicylate acid, aspirin	High	Strong	1000 mg (tablet, powder, disintegrating tablet) Maximum 3000 mg/day	Acetylsalicylate: digestive disorder hemorrhage, allergy, Reye syndrome	Acetylsalicylate: active gastroduodenal ulcer, hemorrhagic risk, pregnancy, asthma, severe hepatic, cardiac or renal insufficiency, hypersensitivity, pregnancy
Acetylsalicylate + metoclopramide (MA)	High	Strong	900 mg + 10 mg (powder) Maximum 3/day	Metoclopramide: dyskinetic syndrome, restlessness psychiatric disorder, endocrine disorder	Metoclopramide: gastrointestinal hemorrhage, digestive perforation, history of dyskinesia, extrapyramidal syndrome, children
Paracetamol	High (in mild-to-moderate attacks)	High in mild attacks, moderate in moderate attacks, not recommended in severe attacks	500, 1000 mg (tablet) Maximum 4 g/day	Paracetamol: hepatic and hematologic toxicity	Severe hepatic insufficiency
Paracetamol + caffeine	High	Low	500 mg + 50 mg (tablet) Maximum 6 tablets/day	Caffeine: palpitation insomnia	

NSAIDs	Level of evidence	Strength of recommendation	Dose, route	Main side effects	Main contraindications[a]
Diclofenac	High	Strong	25, 50, 100 mg (tablet) Maximum 150 mg/day	Hemorrhagic syndrome	Active gastroduodenal ulcer Hypersensitivity to NSAIDs Hemorrhagic risk (cerebral, digestive other), severe hepatic or renal insufficiency, pregnancy (after the 5th month)
Flurbiprofen	High	Strong	8.75 mg (tablet) Maximum 5 tablets/day	Digestive disorder, dyspepsia, nausea, diarrhea, constipation Dizziness, asthenia	
Ibuprofen (MA)	High	Strong	200, 400 mg (tablet) Maximum 1200 mg/day		
Indomethacin	Medium	Moderate	25, 75 mg (tablet) 100 mg (suppository) Maximum 300 mg/day		
Ketoprofen (MA)	High	Strong	100, 150 mg (tablet) 100 mg (suppository) Maximum 200 mg/day		
Naproxen	High	Strong	550, 1000 mg (tablet) Maximum 1100 mg/day		

NSAIDs: nonsteroidal anti-inflammatory drugs.
[a] Contraindications and side effects are not exhaustive, but listed according to frequency occurrence. Interactions are not given. Refer to Vidal.

Table 2 – Specific acute migraine treatments (MA: specific French Market Approval for the acute treatment of migraine headache).

Triptans	Level of evidence for efficacy	Strength of recommendation by the French Headache Society	Dose (route)	Main side effects	Main contraindications[a]
Almotriptan (MA)	High	Strong	12.5 mg (tablet) Maximum 25 mg/day	Paresthesia of extremities, nausea, feeling of cold, dizziness, asthenia, "chest syndrome" (feeling of constriction in the chest and neck), flushing, somnolence Rare cases of coronary spasms, severe hypertension, serotonin syndrome	Coronary heart disease Wolff Parkinson White syndrome Myocardial infarction Peripheral arterial disease Raynaud TIA and stroke Uncontrolled hypertension Serious hepatic or renal insufficiency Concurrent treatment with a MAO inhibitor Cross allergy with sulfonamides (except for rizatriptan and zolmitriptan)
Eletriptan (MA)	High	Strong	20 or 40 mg (tablet) Maximum 80 mg/day		
Frovatriptan (MA)	High	Strong	2.5 mg (tablet) Maximum 5 mg/day		
Naratriptan (MA)	High	Strong	2.5 mg (tablet) Maximum 5 mg/day		
Rizatriptan (MA)	High	Strong	5, 10 mg (tablets), 10 mg (disintegrating tablet) Maximum 20 mg/day		
Sumatriptan (MA)	High	Strong	50 mg (tablets) Maximum 300 mg/day 10/20 mg (nasal spray) Maximum 40 mg/day 6 mg (subcutaneous injection) Maximum 12 mg/day		
Zolmitriptan (MA)	High	Strong	2.5 mg (tablet/disintegrating tablet) Maximum 10 mg/day Nasal spray 5 mg (not available in France)		

Gepants	Level of evidence	Strength of recommendation	Dose, route	Main side effects	Main contraindications[a]
Rimegepant (not available in France in 2021)	High	Strong	75 mg (tablet) Maximum 75 mg/day	Nausea Rare severe allergic reaction	History of hypersensitivity reaction to rimegepant
Ubrogepant (not available in France in 2021)	High	Strong	50 mg, 100 mg (tablets) Maximum 200 mg/day	Nausea, drowsiness Rare severe allergic reaction	History of hypersensitivity reaction to ubrogepant
Ditans	Level of evidence	Strength of recommendation	Dose, route	Main side effects	Main contraindications[a]
Lasmiditan (not available in France in 2021)	High	Moderate	50 mg, 100 mg (tablets) Maximum 200 mg/day No more than one dose should be taken in 24 hours (FDA)	Common (> 2%): dizziness, fatigue, paresthesia, sedation, nausea and/or vomiting, muscle weakness Significant driving impairment Central nervous system depression (dizziness, sedation) Rare (1%): hallucinations, euphoria Risk of misuse or abuse Rare cases of serotonin syndrome	Should be used with caution if used in combination with alcohol, cannabis or other CNS depressants No driving within the first 8 hours after intake (FDA)

NSAIDs: nonsteroidal anti-inflammatory drugs; FDA: Food and Drug Administration.

[a] Contraindications and side effects are not exhaustive, but listed according to frequency occurrence. Interactions are not given. Refer to Vidal.

Table 3 – Recommendations on acute migraine treatment.

Concerning education and initial strategy of acute treatment, we recommend to		Strength of the recommendation
Rt1	Explain the goals of acute treatment, namely complete relief of headache two hours after medication intake with 24 hours sustained response and without adverse events	Strong
Rt2	Explain to patients with migraine with aura that there is currently no pharmacological treatment proved effective in stopping aura	Strong
Rt3	Explain that acute treatments must be taken early (within one hour of headache onset), with an adequate dosage and a route adapted to the severity of digestive symptoms	Strong
Rt4	Explain that the use of acute treatments should be limited to a maximum of eight days per month, because overusing medication carries the risk of medication overuse headache	Strong
Rt5	Encourage patients to use a headache calendar (headache frequency, intensity and acute medication), which will be reviewed at each visit	Strong
Rt6	Prescribe an acute treatment with an NSAID and a triptan, both chosen according to previous treatments and patient's preference	Strong
Rt7	Provide an education about the strategy for acute migraine treatment: a. When headache is mild, the patient should take an NSAID, and add a triptan in case of insufficient response after one hour b. When headache is moderate or severe, the patient should take a triptan, and add an NSAID in case of insufficient response after one hour c. In migraine with aura, the patient should take an NSAID at the beginning of the aura and a triptan at the onset of headache	Strong
Rt8	Avoid prescribing opiates to treat migraine due to the risks of misuse, abuse, and of medication overuse headache	Strong
Rt9	Prescribe a combination of paracetamol and metoclopramide in patients with contraindications or intolerance to NSAIDs, aspirin and triptans	Moderate
Rt10	Prescribe oral or parenteral metoclopramide (suppository or intravenous) to treat attacks with severe nausea or vomiting	Strong
Rt11	Explain that the efficacy and tolerability of the acute treatment is evaluated after three attacks, and plan a follow-up visit	Strong
Concerning the evaluation and optimization of acute treatment, we recommend to		**Strength of the recommendation**
Rt12	Use the Migraine Treatment Optimization Questionnaire (M-TOQ) at each visit and optimize the acute treatment in any patient responding "No" to one or more items	Strong
Rt13	Choose one or several strategies to optimize efficacy and/or tolerability of acute treatment and educate the patient a. To treat as early as possible into the headache phase b. To increase the dose of NSAID and/or triptan when applicable c. To combine a triptan and an NSAID simultaneously when attacks are resistant to a triptan alone and/or when relapses are troublesome d. To switch to a non-oral formulation (NSAID suppository; sumatriptan nasal spray or subcutaneous) and/or add metoclopramide in case of bothersome digestive symptoms e. To switch the NSAID to another NSAID f. To combine a triptan	Strong
Rt14	Diagnose resistance to a. NSAIDs only after complete inefficacy of at least two NSAIDs, used with adequate dose and route, each tested on at least three distinct attacks b. Triptans only after complete inefficacy of at least two triptans, used with adequate dose and route, each tested on at least three distinct attacks	Strong

NSAIDs: nonsteroidal anti-inflammatory drugs.

3.2.3. Ergots

Ergotamine (combined with caffeine) is an older acute migraine treatment that is still occasionally used. Ergots are associated with an increased risk of serious adverse effects (level of evidence high) and are contraindicated in patients with increased cardiovascular risk. Dihydroergotamine (DHE) is the best tolerated of this class, but still has more adverse effects than NSAIDs and triptans.

5.2 Pharmacological prevention

5.2.1 Summary

Summary

The goal of prophylactic treatment according to FR 2021 is to reduce monthly migraine days by 50% in episodic migraine and by 30% in chronic migraine. Prophylaxis also aims at reducing consumption of acute treatments, intensity and duration of attacks, and improving quality of life. Similarly, NHG 2021 states that preventive treatment is expected to reduce migraine attacks with 20-50%.

The decision about when to start migraine prophylaxis is best guided by establishing the impact of migraine on each patient, rather than just focusing on the absolute number of headaches or migraines per month (SIGN 2022). Though some guidelines also mention to consider preventive treatment after at least 2 migraine days per month (NHG 2021, Eigenbrodt 2021).

SIGN 2022 recommends propranolol (80–160 mg daily) as a first-line prophylactic treatment for patients with episodic or chronic migraine. Topiramate (50–100 mg daily) is also recommended. Amitriptyline (25–150 mg at night) should be considered and in patients who cannot tolerate amitriptyline a less sedating tricyclic antidepressant should be considered.
Candesartan (16 mg daily) and Sodium valproate (400–1,500 mg daily) can be considered. Flunarizine (10 mg daily) should be considered. There is insufficient evidence to support a recommendation for pizotifen, but it is a well-established therapy which is widely used.
Botulinum toxin A and the CGRP monoclonal antibodies are only recommended when medication overuse has been addressed and patients have been appropriately treated with three or more oral migraine prophylactic treatments. Botulinum toxin A is only recommended for chronic migraine. Fremanezumab and galcenezumab are recommended for episodic migraine and are to be considered for chronic migraine. Erenumab is only recommended for episodic migraine. Prophylactic treatment should be used for at least three months at the maximum tolerated dose before deciding if it is effective or not.

NICE 2021 recommends to offer topiramate or propranolol taken into account the benefits and risks of each option. They warn for example for the risks of topiramate: fetal malformations, reduced effectiveness of hormonal contraceptives. They recommend to consider amitriptyline.

Furthermore they recommend to advise people that riboflavin (400 mg once a day) may be effective in reducing migraine frequency and intensity for some people. Review the need for continuing migraine prophylaxis 6 months after the start of prophylactic treatment.

NHG 2021 recommends beta blockers (metoprolol, propranolol) or candesartan as a first step for the prophylactic treatment of episodic migraine. Based on the safety profile, there is a preference among the beta blockers for metoprolol (selective) over propranolol (non-selective). In case of insufficient efficacy, taper beta blockers or candesartan at maximum dose after 3 months. In case of efficacy, taper beta blockers or candesartan after 6-12 months.
NHG 2021 recommends as a second step to switch between beta blockers and candesartan in case of insufficient efficacy.
Amitriptyline is recommended as a third step after failure (or contraindication) with beta blockers and candesartan. Patients should not drive a car in the first week of treatment up to doses of 75 mg. Consider an ECG before start of amitriptyline in patients with known cardiovascular disease and in older patients (>65 years). In case of insufficient efficacy, taper amitriptyline after 3 months. In case of efficacy, taper the treatment after 6-12 months.
For all prophylactic treatments, the guideline recommends to evaluate efficacy after at least 3 months of use. In case of good efficacy, continue treatment for 6 to 12 months. After this, taper treatment on a trial basis and restart treatment if symptoms increase.
For chronic migraine, follow the prophylactic treatment as recommended for episodic migraine after excluding medication-overuse headache or after persistent symptoms despite the discontinuation of all analgesics and triptans.
In secondary care, topiramate and valproate are also options besides candesartan, beta blockers and amitriptyline. Botulinum toxin A has a limited place in the treatment of chronic migraine.

For Eigenbrodt 2021, as for acute medications, preventive treatments can be classified as first-line, second-line and third-line options. However, choice of medication and the order of use depend on local practice guidelines and local availability, costs and reimbursement policies. Eigenbrodt 2021 recommends beta blockers (atenolol, bisoprolol, metoprolol or propranolol), topiramate or candesartan as first-line medications. Flunarizine, amitriptyline or (in men) sodium valproate are recommended as second-line medications. CGRP monoclonal antibodies are to be considered as third-line medications.

No recommendations are provided for other therapeutic options, such as melatonin, magnesium and riboflavin, as limited evidence for their efficacy is available and their use in clinical practice is limited.
If a therapeutic dose of an oral preventive medication is ineffective after 2–3 months, an alternative should be tried. For CGRP monoclonal antibodies, efficacy should be assessed only after 3–6 months. For onabotulinumtoxinA, efficacy should be assessed after 6–9 months.

FR 2021 recommends propranolol or metoprolol as first-line medication for episodic migraine. If beta blockers are not suitable, amitriptyline, candesartan or topiramate are recommended as first-line medication depending on the patient's preferences and comorbidities. After failure of the first prophylaxis, switch to a second recommended drug. After failure of 2 prophylactic medications and less than 8 migraine days/month, switch to another recommended drug depending on the patient's preferences and comorbidities. After failure of at least 2 prophylactic medications and at least 8 migraine days/month, CGRP monoclonal antibodies (erenumab, fremanezumab and galcanezumab) are recommended. After failure of a CGRP monoclonal antibody in a patient with refractory migraine, switch to another CGRP monoclonal antibody with or without an oral prophylactic medication.
For chronic migraine, topiramate is recommended as first-line medication. If topiramate is not suitable, prescribe another recommended prophylaxis depending on the patient's preferences and comorbidities. After failure of the first oral prophylaxis, switch to a second recommended oral drug. After failure of at least 2 prophylactic oral treatments including topiramate, onabotulinumtoxin A or a CGRP monoclonal antibody (erenumab, fremanezumab and galcanezumab) is recommended. After failure of a CGRP monoclonal antibody in a patient with refractory migraine, switch to another CGRP monoclonal antibody or to onabotulinumtoxin A, both with or without an oral prophylactic medication.
For chronic migraine with medication overuse headache, first-line prophylactic medication is recommended and the ambulatory withdrawal of the overused acute medication is advised.
It is recommended to continue the prophylaxis for 6–12 months, in case of efficacy and good tolerability, then decrease slowly before considering cessation.

EUR 2022 is a guideline about CGRP monoclonal antibodies for migraine prevention.
For episodic and chronic migraine, eptinezumab (not available in Belgium), erenumab, fremanezumab and galcanezumab are recommended. Furthermore, EUR 2022 recommends erenumab over topiramate as preventive treatment.

The guideline also provides several expert consensus statements. The authors suggest CGRP monoclonal antibodies to be included as a first line treatment option. It is suggested to evaluate efficacy after a minimum of 3 consecutive months treatment. It is suggested considering a pause in the treatment with CGRP monoclonal antibodies after 12-18 months of continuous treatment and to restart treatment if migraine worsens. If deemed necessary treatment should be continued as long as needed. There is insufficient evidence to make suggestions for the combination with other prophylactic medication. There is insufficient evidence on the potential benefits of switching between CGRP monoclonal antibodies, but it may be an option.
The authors suggests caution and decision on a case-by-case basis when considering CGRP monoclonal antibodies in the presence of vascular disease or risk factors and Raynaud phenomenon. They suggest caution in erenumab use in patients with a history of severe constipation.

5.2.2 SIGN 2022

Acute treatment should be taken as early as possible in the headache phase with the aim of aborting an attack. It is given once, with the option of repeating after two hours (with the same or different treatment) if there is an inadequate response. Preventative treatment is taken continuously in order to reduce the frequency and severity of migraine attacks. Often a combination of acute and preventative treatment is needed.

[Bib. group]: see also the treatment algorithm in section “acute pharmacological treatment”.

INTRODUCTION
This section considers the preventative treatment options for patients with episodic and chronic migraine. Most of the available evidence is based on studies of a patient population with episodic migraine rather than chronic migraine (for definitions, see section 1.2.3). There is limited data to make specific treatment recommendations for patients with chronic migraine. Recommendations are therefore based on the premise that chronic migraine and episodic migraine are on a spectrum of the same condition and patients with chronic migraine may benefit from the therapies found to be effective for prophylaxis of episodic migraine.

Migraine can have considerable impact on quality of life and daily function. Modest improvements in the frequency or severity of migraine headaches may provide considerable benefits to an individual. Within trials, a reduction in migraine headache severity and/or frequency of 30–50% is regarded as a successful outcome. The decision about when to start migraine prophylaxis is best guided by establishing the impact of migraine on each patient, rather than just focusing on the absolute number of headaches or migraines per month. For example, a few severe incapacitating migraines per month may warrant prophylactic treatment whereas more frequent but milder migraines that

have little impact on daily function may not warrant treatment. Overusing acute medication can limit the effectiveness of preventative medication and medication overuse should also be assessed and addressed. Prophylactic treatment should be used for at least three months at the maximum tolerated dose before deciding if it is effective or not. In many patients prophylactic medication can be successfully phased out again and the need for ongoing prophylaxis should be considered after six to 12 months.

An algorithm of a suggested treatment pathway can be found in Annex 3 (see section "acute pharmacological treatment"). The decision regarding which medication to try first is dependent on evidence of effectiveness, patient comorbidities, other risk factors, drug interactions and patient preference. It is important to ensure adequate contraception whilst on preventative therapies as some have risks of teratogenicity and others can potentially cause harm to unborn babies. Given that migraine without aura often improves during pregnancy women should aim to stop migraine prophylactic treatments before pregnancy. Migraine with aura often continues unchanged. Before commencing treatment, potential harmful effects of therapies need to be discussed with women who are, or may become, pregnant. No evidence was identified on which to base recommendations on preventative treatments for women during pregnancy.

Beta Blockers

Propranolol (80–160 mg daily) is recommended as a first-line prophylactic treatment for patients with episodic or chronic migraine.

Topiramate

Topiramate (50–100 mg daily) is recommended as a prophylactic treatment for patients with episodic or chronic migraine.

Before commencing treatment women who may become pregnant should be advised of the associated risks of topiramate during pregnancy, the need to use effective contraception and the need to seek further advice on migraine prophylaxis if pregnant or planning a pregnancy.

Tricyclic antidepressants

Amitriptyline (25–150 mg at night) should be considered as a prophylactic treatment for patients with episodic or chronic migraine.

In patients who cannot tolerate amitriptyline a less sedating tricyclic antidepressant should be considered.

Candesartan

The evidence base for candesartan is small and further trials are unlikely to be conducted. However, candesartan is a widely used and inexpensive drug with a good side-effect profile, and no potential cognitive effects.

Candesartan (16 mg daily) can be considered as a prophylactic treatment for patients with episodic or chronic migraine.

Sodium valproate

Sodium valproate (400–1,500 mg daily) can be considered as a prophylactic treatment for patients with episodic or chronic migraine.

Prescribers should be aware that sodium valproate is associated with an increased risk of foetal malformations and poorer cognitive outcomes in children exposed to valproate in utero. For women who may become pregnant sodium valproate should only be considered as a prophylactic treatment when:

- **other treatment options have been exhausted**
- **patients are using adequate contraception.**

Before commencing treatment women should be informed of:

- **the risks associated with taking valproate during pregnancy**
- **the risk that potentially harmful exposure to valproate may occur before a woman is aware she is pregnant**
- **the need to use effective contraception**
- **the need to seek further advice on migraine prophylaxis if pregnant or planning a pregnancy.**

Good-practice point. When prescribing sodium valproate for women who may become pregnant check the MHRA website for current advice. The MHRA checklist must be used (see Annex 4).

Calcium Channel Blockers

Flunarazine is often well tolerated. Depression is a possible side effect, so it should be used with caution in patients with depression.

Flunarizine (10 mg daily) should be considered as a prophylactic treatment for patients with episodic or chronic migraine.

Pizotifen

There is insufficient evidence to support a recommendation, but it is a well-established therapy which is widely used.

Gapapentin and pregabalin

If migraine is part of a chronic pain syndrome, further advice on the use of pregabalin is available in SIGN 136: Management of chronic pain.

Use of gabapentin or pregabalin is associated with increased risk of addiction.

Gabapentin should not be considered as a prophylactic treatment for patients with episodic or chronic migraine.

[Bib. group]. The SIGN 2022 guideline also describe studies with angiotensin-converting enzyme inhibitors, SSRIs and Other antiepileptics. However, the guidelines does not provide formal recommendations, probably due to the limited and poor quality evidence.

Botulinum toxin A

Botulinum toxin A is not recommended for the prophylactic treatment of patients with episodic migraine.

Botulinum toxin A is recommended for the prophylactic treatment of patients with chronic migraine where medication overuse has been addressed and patients have been appropriately treated with three or more oral migraine prophylactic treatments.

Good-practice point. Botulinum toxin A should only be administered by appropriately trained individuals under the supervision of a headache clinic or the local neurology service.

Calcitonin gene-related peptide monoclonal antibodies

Erenumab, fremanezumab and galcanezumab are recommended for the prophylactic treatment of patients with chronic migraine where medication overuse has been addressed and patients have not benefitted from appropriate trials of three or more oral migraine prophylactic treatments.

Fremanezumab and galcenezumab can be considered for the prophylactic treatment of patients with episodic migraine where medication overuse has been addressed and patients have not benefitted from appropriate trials of three or more oral migraine prophylactic treatments.

Good-practice point. Use of CGRP monoclonal antibodies should only be initiated following consultation with a neurologist or headache specialist.

Good-practice point. There should be careful consideration of potential risks and benefits to patients at high risk of ischaemic cardiovascular disease before prescribing CGRP monoclonal antibodies.

Good-practice point. Medication overuse headache should be addressed before treatment with CGRPs (see section 5). However, in patients where treatment of MOH has been unsuccessful, CGRP monoclonal antibodies should still be considered.

Occipital nerve block

… Although they are used in headache clinics in Scotland further evidence is required before recommendations for use can be made.

5.2.3 NICE 2021

Migraine with or without aura

1.3.16 Discuss the benefits and risks of prophylactic treatment for migraine with the person, taking into account the person's preference, comorbidities, risk of adverse events and the impact of the headache on their quality of life. [2012]

1.3.17 For the prophylaxis of migraine, offer topiramate or propranolol after a full discussion of the benefits and risks of each option. Include in the discussion:
• the potential benefit in reducing migraine recurrence and severity
• the risk of fetal malformations with topiramate
• the risk of reduced effectiveness of hormonal contraceptives with topiramate
• the importance of effective contraception for women and girls of childbearing potential who are taking topiramate (for example, by using medroxyprogesterone acetate depot injection, an intrauterine method or combined hormonal contraception with a barrier method).

Follow the MHRA safety advice on antiepileptic drugs in pregnancy. [2015, amended 2021]

In November 2015, this was an off-label use of topiramate in children and young people. See NICE's information on prescribing medicines.

People with depression and migraine could be at an increased risk of using propranolol for self-harm. Use caution when prescribing propranolol, in line with the Healthcare Safety Investigation Branch's report on the under-recognised risk of harm from propranolol.

1.3.18 Consider amitriptyline for the prophylactic treatment of migraine according to the person's preference, comorbidities and risk of adverse events.

In November 2015, this was an off-label use of amitriptyline. See NICE's information on prescribing medicines. [2015]

For guidance on safe prescribing of antidepressants (such as amitriptyline) and managing withdrawal, see NICE's guideline on medicines associated with dependence or withdrawal symptoms.

1.3.19 Do not offer gabapentin for the prophylactic treatment of migraine. [2015]

1.3.20 If both topiramate and propranolol are unsuitable or ineffective, consider a course of up to 10 sessions of acupuncture over 5 to 8 weeks according to the person's preference, comorbidities and risk of adverse events. [2012, amended 2015]

1.3.21 For people who are already having treatment with another form of prophylaxis and whose migraine is well controlled, continue the current treatment as required. [2012, amended 2015]

Quality of evidence
This recommendation was based on GDG consensus opinion.

Other considerations
The GDG considered that there may be other prophylactic treatments, such as amitriptyline, pizotifen, sodium valproate, lisinopril and losartan which are in regular use and are effective for some people, although no evidence was identified in this review. Pizotifen is particularly used for

prophylaxis in children and young people. This was noted as an absence of evidence, not evidence that such treatments are ineffective.

1.3.22 Review the need for continuing migraine prophylaxis 6 months after the start of prophylactic treatment. [2012]

1.3.23 Advise people with migraine that riboflavin (400 mg once a day) may be effective in reducing migraine frequency and intensity for some people. [2012]

In November 2015, this was an off-label use of riboflavin, but this is available as a food supplement.

Quality of evidence
This recommendation is based on moderate quality evidence from one outcome (responder rate).

Other considerations
All studies had a population of people with migraine with or without aura, there was no evidence for use of dietary or herbal supplements in people with other types of primary headache. In all of the included studies people took acute pharmacological medication throughout the study. The review also demonstrated evidence for trimagnesium dicitrate (low quality) for change in patient reported headache days and reduction in headache frequency and very low quality evidence for improving headache intensity, responder rate and reducing the use of acute pharmacological treatment. However, trimagnesium dicitrate does not ahave a marketing authorisation in the UK for medical use at the time of publication and is not available as a food supplement, although other magnesium salt preparations are available.
Although the evidence review did not identify issues with the safety of butterbur, the MHRA issued a warning in January 2012 about an association between use of butterbur and liver toxicity.
The doses of riboflavin shown to be effective in the review was 400mg per day.

5.2.4 NHG 2021

Preventieve behandeling

- Overweeg preventieve behandeling bij episodische migraine ≥ 2 aanvallen/maand.
- Bespreek het te verwachten effect: medicatie kan tot circa 20- 50% reductie van de aanvallen leiden.
- Betrek bij het maken van de keuze voor een preventieve behandeling de (gemiddelde) aanvalsduur, ernst van de aanvallen en reactie op aanvalsbehandeling. Gebruik hiervoor de keuzetabel Preventieve behandeling migraine bij volwassenen.
- Bespreek welk doel de patiënt wil behalen: afname van de aanvalsfrequentie of een subjectiever behandeldoel (minder werkverzuim).
- Laat frequente gebruikers van paracetamol of NSAID's (≥ 15 dagen per maand) of triptanen (≥ 10 dagen per maand) vooraf stoppen om MOH uit te sluiten. Zie Richtlijnen beleid Medicatieovergebruikshoofdpijn). Mogelijk is preventieve medicatie nadien niet meer nodig.
- Voor alle middelen geldt (zie tabel 18):

- Start met een lage dosering en bouw stapsgewijs op bij onvoldoende effect.
- Bouw de medicatie langzaam op om bijwerkingen te voorkomen. Op geleide van effectiviteit en bijwerkingen kan de dosering eventueel sneller opgebouwd worden.
- Tijdens een preventieve behandeling mag, indien nodig, aanvalsmedicatie gebruikt worden.
- Evalueer het effect na minimaal 3 maanden gebruik:
  - Ga, als de klachten onvoldoende onder controle zijn, de therapietrouw na en kies eventueel voor een ander middel.
  - Zet de behandeling bij een goed effect voort gedurende 6 tot 12 maanden. Bouw daarna de medicatie op proef af. Indien de klachten weer toenemen kan de behandeling weer gestart worden.

- Verwijs bij onvoldoende effectiviteit naar de neuroloog met expertise op het gebied van hoofdpijn; behandelopties in de tweede lijn zijn onder andere valproïnezuur en topiramaat.

Medicamenteus stappenplan preventieve behandeling

Stap 1 Bètablokker of candesartan

- De effectiviteit van bètablokkers en candesartan is waarschijnlijk gelijkwaardig.
- Maak met de patiënt een keuze tussen een bètablokker en candesartan, rekening houdend met comorbiditeit, contra-indicaties, bijwerkingenprofiel en voorkeur van de patiënt (zie tabel 18).

Bètablokker (metoprolol, propranolol)

- Metoprolol en propranolol zijn geregistreerd als migraineprofylaxe. Op grond van het bijwerkingenprofiel heeft metoprolol (selectief) de voorkeur boven propranolol (niet-selectief).
- Eventuele bijwerkingen verminderen of verdwijnen vaak bij langer gebruik. Bijwerkingen kunnen echter optreden voordat de patiënt effect op de migraine ervaart.
- Meet voor het instellen van de behandeling bloeddruk en pols. Bij een systolische bloeddruk < 90 mmHg of een polsslag < 50/minuten is een bètablokker gecontra-indiceerd.
- Bouw de behandeling bij onvoldoende effect na 3 maanden in maximale dosering in 14 dagen af (een week halve dosering, vervolgens een week kwart dosering).
- Bouw de behandeling bij goede effectiviteit na 6-12 maanden gebruik van de onderhoudsdosering op proef in 14 dagen af (een week halve dosering, vervolgens een week kwart dosering).

Candesartan (off-label)

- Bepaal de eGFR na 2 weken gebruik. Zie voor het beleid bij daling van de nierfunctie (eGFR < 60 ml/min/1,73 m2) de Praktische handleiding bij de NHG-Standaard Cardiovasculair risicomanagement.
- Bouw de behandeling bij onvoldoende effect na 3 maanden in 14 dagen af (een week halve dosering, vervolgens een week kwart dosering).
- Bouw de behandeling bij goede effectiviteit na 6-12 maanden gebruik van de onderhoudsdosering op proef in 14 dagen af (een week halve dosering, vervolgens een week kwart dosering).

Stap 2 Wissel tussen bètablokker en candesartan

Wissel bij onvoldoende effect tussen een bètablokker en candesartan (zie stap 1).

Stap 3 Amitriptyline

- Overweeg dit middel bij onvoldoende effect van een bètablokker en candesartan of bij contra-indicaties hiervoor.
- Zie tabel 18 voor dosering, contra-indicaties en bijwerkingen.
- De patiënt mag bij een dosis tot en met 75 mg de eerste week geen autorijden.
- Overweeg een ecg voor start van de behandeling bij bestaande cardiovasculaire aandoeningen of bij ouderen (> 65 jaar). Let hierbij op ritme- en/of geleidingsstoornissen en op (oude) ischemische afwijkingen.
- Bouw de behandeling bij onvoldoende effect na 3 maanden in 2-4 weken af (halveer de dosering elke 1-2 weken).
- Bouw de behandeling bij goede effectiviteit na 6-12 maanden gebruik van de onderhoudsdosering op proef in 2-4 weken af (halveer de dosering elke 1-2 weken).

Chronische migraine

- Bij chronische migraine (≥ 15 dagen hoofdpijn per maand, waarvan ≥ 8 dagen migraine) is het essentieel om eerst te beoordelen of er sprake is van MOH en in dat geval alle analgetica en triptanen te staken (zie Richtlijnen beleid Medicatieovergebruikshoofdpijn).
- Behandel, indien er geen sprake is van MOH, of bij persisterende klachten ondanks het staken van de medicatie, met preventieve medicatie (zie Medicamenteus stappenplan preventieve behandeling). Start deze behandeling zelf (eventueel in samenspraak met de neuroloog) of verwijs hiervoor naar de neuroloog met expertise op het gebied van hoofdpijn.

Chronische migraine (detail nr.37)
Bij chronische migraine is het in eerste instantie essentieel om te beoordelen of sprake is van MOH en alle analgetica en triptanen te staken. Indien de chronische klachten desondanks aanhouden is het advies om 3 verschillende preventieve middelen te proberen, conform het stappenplan bij episodische migraine. Start deze preventieve behandeling zelf (eventueel in samenspraak met de neuroloog) of verwijs hiervoor naar de neuroloog met expertise op het gebied van hoofdpijn.

Behandelopties in de tweede lijn:

- Preventieve behandeling zoals bij episodische migraine, naast ARB's, bètablokkers en amitriptyline ook valproïnezuur en topiramaat.
- Botulinetoxine A. De effectiviteit hiervan is beperkt en er is kans op bijwerkingen. Daarnaast is de behandeling duur. Deze behandeling heeft een beperkte indicatie bij chronische migraine in de NVN-richtlijn Medicamenteuze behandeling migraine en MOH.

Mogelijk toekomstige behandeloptie in de tweede lijn:
Calcitonin gene-related peptide (CGRP)-remmers: deze middelen zijn geregistreerd voor de behandeling van volwassen patiënten met ten minste 4 dagen migraine per maand. Ze zijn echter nog niet op de markt in Nederland anno januari 2021. De middelen zijn duur (kosten per jaar naar verwachting € 5.000 tot € 10.000). Momenteel beoordeelt het Zorginstituut Nederland of er een subgroep patiënten is waarvoor CGRP-remmers een meerwaarde heeft.

(https://www.medicijngebruik.nl/nieuwe-geneesmiddelen/medicijngroep/3958/cgrp-remm ers) De plaatsbepaling ten opzichte van de andere preventieve middelen is nog niet bekend.

Tabel 18. Overzicht geneesmiddelen preventieve behandeling migraine bij volwassenen

Middel	Startdosering	Gebruikelijke dosering	Maximale dosering	Contra-indicaties	Bijwerkingen
Bètablokkers					
Metoprolol (met gereguleerde afgifte)	1 dd 50 mg (opbouw: 50 mg per 2 weken)	1 dd 100-200 mg	200 mg	sick-sinussyndroom, tweede en derdegraads AV-blok, hypotensie of klinisch relevante bradycardie (hartfrequentie < 50 slagen/min), astma en COPD (propranolol; metoprolol bij hoge doseringen) Interactie: adrenaline (propranolol)	afname inspanningstolerantie, vermoeidheid, (orthostatische) hypotensie, duizeligheid, hoofdpijn, bradycardie, palpitaties, evenwichtsstoornissen, dyspneu bij inspanning, koude handen en voeten, fenomeen van Raynaud
Propranolol	2 dd 10 mg (opbouw: 20 mg per 2 weken)	1 dd 80-160 mg (met gereguleerde afgifte)	160 mg		
Angiotensinereceptorblokkers					
Candesartan (offlabel)	1 dd 4 mg (opbouw: 4 mg per 2-4 weken)	8-16 mg	32 mg	ernstige leverfunctiestoornis	luchtweginfecties, duizeligheid, hoofdpijn, hypotensie, verminderde nierfunctie, hyperkaliëmie
Tricyclische antidepressiva					
Amitriptyline	1 dd 10 mg (a.n.) (opbouw: 10-25 mg per 2-4 weken)	40 mg (a.n.)	75 mg (a.n.)	recent hartinfarct, ernstige leverfunctiestoornis, ernstig hartfalen, aangeboren lang QT-syndroom en Brugada	droge mond, obstipatie, urineretentie misselijkheid, gewichtstoename, seksuele disfunctie, slaperigheid, buikpijn, duizeligheid

5.2.5 Eigenbrodt 2021

Initiation and termination

In patients whose migraine continues to impair their quality of life despite optimized acute therapy, additional preventive therapy should be considered (Table 4). In practice, patients who are considered for preventive treatment remain adversely affected on at least 2 days per month, although this should not be regarded as an absolute rule. Aside from migraine frequency, clinicians should always consider factors such as the severity of attacks, the duration of attacks (for example, menstruation-related attacks tend to last longer) and migraine-related disability. A further indication for preventive therapy is overuse of acute medication.

Efficacy of preventive therapy is rarely observed immediately. Only after several weeks or months can efficacy be ascertained, so patients should be discouraged from abandoning the treatment in these early stages on the grounds of apparent inefficacy. If a therapeutic dose of an oral preventive medication is ineffective after 2–3 months, an alternative should be tried. For monoclonal antibody treatments that target calcitonin gene-related peptide (CGRP) or its receptor, efficacy should be assessed only after 3–6 months. For onabotulinumtoxinA, efficacy should be assessed after 6–9 months.

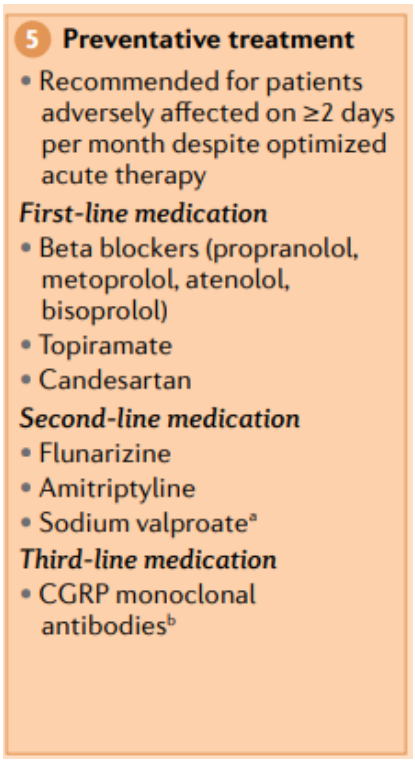
Failure of one preventive treatment does not predict failure of treatment with other drug classes, except when failure is due to poor adherence. Treatment adherence is often very poor but can be improved by simplified dosing schedules (once daily or less). For most preventive medications, clinical experience suggests that pausing can be considered when treatment has been successful for 6–12 months. The purpose of pausing is to ascertain whether preventive treatment can be stopped, which minimizes the risk of unnecessary drug exposure and allows some patients to manage their migraine with acute medications only. A useful measure to quantify the degree of preventive treatment success is to calculate the percentage reduction in monthly migraine days or monthly headache days of moderate-to-severe intensity. However, a pragmatic approach is needed and clinicians should decide to pause preventive therapy on a case-by-case basis.

Current standard of care.
As for acute medications, preventive treatments can be classified as first-line, second-line and third-line options (Table 4). However, choice of medication and the order of use depend on local practice guidelines and local availability, costs and reimbursement policies. First-line medications are beta blockers without intrinsic sympathomimetic activity (atenolol, bisoprolol, metoprolol or propranolol), topiramate and candesartan. If these fail, second-line medications include flunarizine, amitriptyline and sodium valproate, although valproate is strictly contraindicated in women of childbearing potential, which greatly limits its utility in migraine. Third-line medications are the four CGRP monoclonal antibodies erenumab, fremanezumab, galcanezumab and eptinezumab. These antibodies have been approved for the preventive treatment of migraine in the past few years. In Europe, regulatory restrictions limit their use to patients in whom other preventive drugs have failed or are contraindicated.

Non-pharmacological therapies.
A range of non-pharmacological preventive therapies can be used either as adjuncts to acute and preventive medications or instead of them if medication use is contraindicated. Some evidence supports the use of non-invasive neuromodulatory devices, biobehavioural therapy and acupuncture, although a study of acupuncture indicated that it is not superior to sham acupuncture. Contrary to popular belief, little to no evidence exists for physical therapy, spinal manipulation and dietary approaches. We make no recommendations about other therapeutic options, such as melatonin, magnesium and riboflavin, as limited evidence for their efficacy is available and their use in clinical practice is limited.

Recommendations.
• Consider preventive treatment in patients who are adversely affected by migraine on ≥2 days per month despite optimized acute treatment.

• Use beta blockers (atenolol, bisoprolol, metoprolol or propranolol), topiramate or candesartan as first-line medications.
• Use flunarizine, amitriptyline or (in men) sodium valproate as second-line medications.
• Consider CGRP monoclonal antibodies as third-line medications.
• Consider neuromodulatory devices, biobehavioural therapy and acupuncture as adjuncts to acute and preventive medication or as stand-alone preventive treatment when medication is contraindicated.



5 Preventative treatment

- Recommended for patients adversely affected on ≥2 days per month despite optimized acute therapy

First-line medication

- Beta blockers (propranolol, metoprolol, atenolol, bisoprolol)
- Topiramate
- Candesartan

Second-line medication

- Flunarizine
- Amitriptyline
- Sodium valproate[a]

Third-line medication

- CGRP monoclonal antibodies[b]

Table 4 | **Preventive migraine treatment**

Drug class	Drug	Dosage and route	Contraindications
First-line medication			
Beta blockers	Atenolol	25–100 mg oral twice daily	Asthma, cardiac failure, Raynaud disease, atrioventricular block, depression
	Bisoprolol	5–10 mg oral once daily	
	Metoprolol	50–100 mg oral twice daily or 200 mg modified-release oral once daily	
	Propranolol	80–160 mg oral once or twice daily in long-acting formulations	
Angiotensin II-receptor blocker	Candesartan	16–32 mg oral per day	Co-administration of aliskiren
Anticonvulsant	Topiramate	50–100 mg oral daily	Nephrolithiasis, pregnancy, lactation, glaucoma
Second-line medication			
Tricyclic antidepressant	Amitriptyline	10–100 mg oral at night	Age <6 years, heart failure, co-administration with monoamine oxidase inhibitors and SSRIs, glaucoma
Calcium antagonist	Flunarizine	5–10 mg oral once daily	Parkinsonism, depression
Anticonvulsant	Sodium valproate[a]	600–1,500 mg oral once daily	Liver disease, thrombocytopenia, female and of childbearing potential
Third-line medication			
Botulinum toxin	OnabotulinumtoxinA	155–195 units to 31–39 sites every 12 weeks	Infection at injection site
Calcitonin gene-related peptide monoclonal antibodies	Erenumab	70 or 140 mg subcutaneous once monthly	Hypersensitivity Not recommended in patients with a history of stroke, subarachnoid haemorrhage, coronary heart disease, inflammatory bowel disease, chronic obstructive pulmonary disease or impaired wound healing
	Fremanezumab	225 mg subcutaneous once monthly or 675 mg subcutaneous once quarterly	
	Galcanezumab	240 mg subcutaneous, then 120 mg subcutaneous once monthly	
	Eptinezumab	100 or 300 mg intravenous quarterly	

5.2.6 FR 2021

Table 4 – Oral prophylactic treatments: dosage, side effects and contraindications.

Treatment (French Market Approval, yes or no)	Level of evidence for efficacy	Strength of recommendation by the French Headache Society	Daily dosage Minimum–Maximum (mean daily dosage)	Main side effects	Main contraindications
Amitriptyline (yes)	High in EM Fair in CM	Strong in EM Moderate in CM	10–100 mg (25 mg) Once at dinner time	Dry mouth, somnolence, weight gain	Absolute: glaucoma, prostatic adenoma Relative: obesity
Beta-blocker					
Propranolol (yes)	High in EM Fair in CM	Strong in EM Weak in CM	20–240 mg (80 mg) BID or once in the morning (extended release)	Common: asthenia, poor tolerance to effort Rare: depression	Absolute: asthma, heart failure, atrio-ventricular block, bradycardia Relative: depression
Metoprolol (yes)	High in EM Unknown in CM	Strong in EM Not recommended in CM	50–200 mg (100 mg) Once in the morning (extended release)		
Nebivolol (no)	Medium in EM Unknown in CM	Moderate in EM Not recommended in CM	5–10 mg (10 mg) Once in the morning		
Atenolol (no)	High in EM Fair in CM	Moderate in EM Weak in CM	50–200 mg (100 mg) Once in the morning		
Timolol (no)	High in EM Unknown in CM	Moderate in EM Not recommended in CM	10–60 mg (20 mg) BID		
Candesartan (no)	Medium in EM Fair in CM	Strong in EM Weak in CM	8–32 mg (16 mg) BID or once a day	Hypotension	Absolute: heart failure, renal artery stenosis, renal impairment, pregnancy Relative: hypotension
Flunarizine (yes)	High in EM Fair in CM	Moderate in EM Weak in CM	5–10 mg (5 mg) Once in the evening Stop after 6 months	Common: somnolence, weight gain, depression Rare: parkinsonism	Depression, obesity, Parkinson disease, parkinsonism, pregnancy
Lisinopril (no)	Fair in EM Unknown in CM	Moderate in EM Not recommended in CM	5–40 mg (20 mg) Once a day	Hypotension, dry cough, exanthema, impaired renal function	Angio-edema, renal artery stenosis, renal impairment, hyperkaliemia, pregnancy
Lamotrigine (no)	Fair in migraine with aura	Weak in migraine with aura Not recommended in migraine without aura	25–300 mg (100 mg) Once or twice a day	Common: dizziness, insomnia Rare: serious hypersensitivity reactions, depression, suicidal ideation	Absolute: hypersensitivity to lamotrigine, breastfeeding Relative: previous allergy to another antiepileptic
Levetiracetam (no)	Medium in EM Fair in CM	Weak in EM Weak in CM	500–3000 mg Twice a day	Irritability, depression	Relative: renal impairment
Oxetorone (yes)	Fair in EM Unknown in CM	Moderate in EM Not recommended in CM	60–180 mg (120 mg) Once in the evening	Common: somnolence Rare: diarrhea, parkinsonism	Parkinson disease, parkinsonism, pregnancy
Pizotifene (yes)	Medium in EM Unknown in CM	Moderate in EM Not recommended in CM	50–300 mg (150 mg) BID	Common: sedation, weight gain	Obesity, glaucoma, prostatic adenoma, pregnancy
Topiramate (yes)	High in EM High in CM	Strong in EM Strong in CM	50–200 mg (100 mg) Once or twice a day	Common: paresthesia, weight loss, cognitive effects (word-finding difficulties), depression Rare: renal calculi, acute myopia with secondary angle closure glaucoma	Absolute: hypersensitivity to topiramate, pregnancy, glaucoma, severe pulmonary disease, metformin use, hepatic disease, nephrolithiasis, renal failure Relative: depression, suicidal ideation
Valproate (no)	High in EM Medium in CM	Strong in EM Moderate in CM Do never use in women of childbearing potential	250–2000 mg (750 mg) Once in the evening or twice a day	Common: nausea, weight gain, somnolence, tremor, alopecia, ASAT, ALAT increase, hepatitis	Absolute: liver disease, pregnancy, mitochondrial disease Relative: obesity Do never use in women of childbearing potential
Venlafaxine (no)	Fair in EM Unknown in CM	Weak in EM Not recommended in CM	37.5–300 mg (75–150 mg) Once a day	Common: nausea, dry mouth, hyperhydrosis	Hypersensitivity to venlafaxine

Table 5 – Injectable prophylactic treatments: dosage, side effects and contraindications.

Active component (French Market Approval, yes or no)	Level of evidence for efficacy	Strength of recommendation by the French Headache Society	Daily dosage Minimum–Maximum (mean daily dosage)	Side effects	Contraindications
OnabotulinumtoxinA (yes)	High in CM Not efficient in EM	Strong in CM Not recommended in EM	31–39 injections of 155–195 UI (195 UI) in 7 muscular groups, quarterly	Injection site pain	Absolute: myasthenia gravis, amyotrophic lateral sclerosis
Anti-CGRP or CGRP-receptor antibodies					
Erenumab (yes)	High in EM High in CM	Strong in EM Strong in CM	70–140 mg SC monthly	Injection site pain or redness, constipation, allergy	Myocardial infarction, stroke, TIA, uncontrolled vascular risk factor Pregnancy
Eptinezumab (no)	High in EM High in CM	Strong in EM Strong in CM	100–300 mg IV quarterly		
Fremanezumab (yes)	High in EM High in CM	Strong in EM Strong in CM	225 mg SC monthly 675 mg SC quarterly		
Galcanezumab (yes)	High in EM High in CM	Strong in EM Strong in CM	240 mg SC the first month, then 120 mg SC monthly		

4.4. Recommendations for pharmacological prophylaxis of migraine

The recommendations are summarized in the Table 6. These recommendations will be updated after marketing approval of eptinezumab and oral gepants.

Table 6 – Recommendations for pharmacological prophylaxis of migraine.

Regarding the initiation of prophylactic treatment, we recommend to		Strength of the recommendation
Rt15	Determine individual patient's eligibility to prophylaxis based on the patient's preference, headache diary or calendar, criteria for severe migraine and chronic migraine, HIT-6 and HAD scales	Strong
Rt16	Initiate a prophylactic treatment in any patient a. Using acute medications eight days or more per month since at least three months b. With severe migraine according to French criteria c. With chronic migraine according to ICHD-3 criteria d. With a HIT-6 scale of 60 or more e. With debilitating migraine attacks despite optimization of acute treatment	Strong
Regarding patient education and optimal follow-up plan, we recommend to		
Rt17	Explain the goals of prophylactic migraine treatment a. The objective is to reduce monthly migraine days by 50% in episodic migraine and by 30% in chronic migraine b. Efficacy will be judged during the third month of treatment (weeks 8–12) c. Prophylaxis also aims at reducing consumption of acute treatments, intensity and duration of attacks, and improving quality of life d. Failure can be due to insufficient efficacy and/or tolerability	Strong
Rt18	Start an oral prophylaxis as monotherapy and at a low-dose, and increase progressively to achieve optimal daily dose, taking into account possible side effects	Strong
Rt19	Explain that adherence to the prophylaxis is mandatory. When appropriate, prescribe once-daily dosage to improve compliance	Strong
As first-line prophylaxis for episodic migraine, our recommendations are		Strength of the recommendation
Rt20	Prescribe propranolol or metoprolol as first-line medication in any suitable patient with episodic migraine, because of the high level of evidence of efficacy	Strong
Rt21	Prescribe amitriptyline, candesartan or topiramate as first-line medication in patients with episodic migraine not suitable to beta-blockers, depending on the patient's preferences and comorbidities	Strong
As first-line prophylaxis for chronic migraine, our recommendations are		Strength of the recommendation
Rt22	Prescribe topiramate as first-line medication in any suitable patient with chronic migraine, because of the high level of evidence of efficacy	Strong
Rt23	Prescribe another recommended prophylaxis in patients with chronic migraine not suitable to topiramate, depending on the patient's preferences and comorbidities	Strong
Rt24	In patients with chronic migraine and medication overuse headache, prescribe a first-line prophylactic medication and advise an ambulatory withdrawal of the overused acute medication	Strong
To evaluate and adapt the prophylactic treatment, our recommendations are		Strength of the recommendation
Rt25	Assess efficacy, tolerability, compliance, and burden of migraine by interview, review of the calendar, and systematic use of HIT-6 and HAD scales at each visit. The efficacy of the prophylaxis should be evaluated after the third month of treatment except for onabotulinumtoxinA whose efficacy should be evaluated after six months	Strong
Rt26	In case of efficacy and good tolerability, continue the prophylaxis for 6–12 months, then decrease slowly before considering cessation. Restart the same treatment if the frequency of attacks increases again during decrease or after cessation	Strong

Table 6 (*Continued*)		
To evaluate and adapt the prophylactic treatment, our recommendations are		Strength of the recommendation
Rt27	In case of insufficient efficacy and/or tolerability, choose one or several strategies to optimize the prophylaxis, and educate the patient a. Check for compliance b. Check for medication overuse, including analgesics for non-headache pain c. In case of insufficient efficacy and good tolerability, increase daily doses to the maximal recommended dose with an acceptable tolerance d. Switch to another prophylaxis	Strong
Regarding switching prophylaxis in episodic migraine, our recommendations are		Strength of the recommendation
Rt28	After failure of the first prophylaxis in episodic migraine, select a second recommended medication, depending on the patient's preferences and comorbidities	Strong
Rt29	After failure of two prophylactic medications in patients with less than eight migraine days per month, select another recommended medication depending on the patient's preferences and comorbidities	Strong
Rt30	After failure of at least two prophylactic treatments in patients with at least eight monthly migraine days, prescribe a CGRP-MAB selected among erenumab, fremanezumab and galcanezumab, based on the patient's preferences	Strong
Regarding switching prophylaxis in chronic migraine, our recommendations are		Strength of the recommendation
Rt31	After failure of the first oral prophylaxis in chronic migraine, select a second recommended oral medication, based on the patient profile, comorbidities, and the patient's preferences	Strong
Rt32	After failure of at least two oral treatments including topiramate in chronic migraine, prescribe a treatment with onabotulinimtoxin A or a CGRP-MAB selected among erenumab, fremanezumab and galcanezumab, based on the patient's preferences	Strong
For prophylaxis of resistant or refractory migraine, our recommendations are		Strength of the recommendation
Rt33	After failure of a CGRP-MAB in a patient with refractory episodic migraine, consider switching to another CGRP-MAB, with or without combination with an oral prophylactic medication	Moderate
Rt34	After failure of a CGRP-MAB in a patient with refractory chronic migraine, consider switching to another CGRP-MAB, or to treatment with onabotulinimtoxin A, both with or without combination with an oral treatment	Moderate
CGRP-MABs: calcitonin-gene-related peptide-receptor monoclonal antibodies.		

5.2.7 EUR 2022

The landscape of migraine prevention has experienced relevant changes since the introduction of the monoclonal antibodies (mAbs) targeting the calcitonin generelated (CGRP) peptide or the CGRP receptor (together referred to as CGRP-mAbs). CGRP-mAbs entered the market with different prescription and reimbursement regulations for their use across countries.

Evidence-based recommendations

In individuals with episodic migraine, we recommend eptinezumab, erenumab, fremanezumab and galcanezumab as preventive treatment. (Quality of evidence: moderate to high, Strength of the recommendation: strong)

All the considered CGRP-mAbs (eptinezumab, erenumab, galcanezumab and fremanezumab) were associated with significant benefits considering the predefined outcomes as compared to placebo.

No significant safety concerns were found in the different studies.

In individuals with chronic migraine, we recommend eptinezumab, erenumab, fremanezumab and galcanezumab as preventive treatment. (Quality of evidence: moderate to high, Strength of the recommendation: strong)

All the considered CGRP-mAbs (eptinezumab, erenumab, galcanezumab and fremanezumab) were associated with significant benefits considering the pre-defined outcomes as compared to placebo. No significant safety concerns were found in the different studies.

In individuals with episodic or chronic migraine we recommend erenumab over topiramate as preventive treatment. (Quality of evidence: low, Strength of the recommendation: strong)

Based on an intention-to-treat analysis, over the 24-week study period, there was a higher reduction in monthly migraine days with erenumab (− 5.86, SE 0.24) than with topiramate (− 4.02, SE 0.24; $p < 0.001$).

Expert consensus statements

Expert consensus statement 1
In individuals with migraine who require preventive treatment, we suggest monoclonal antibodies targeting the CGRP pathway to be included as a first line treatment option. (Expert consensus statements)

Of note, in phase II and phase III trials on CGRP-mAbs, 46.3% of individuals with migraine were treatment naive or without a previous history of drug failure.

Real-world observational studies confirmed the effectiveness of those drugs outside RCTs. Tolerability and safety profiles were confirmed to be excellent and the adherence to treatment was not reported as a critical issue as it was with oral treatments.

The major added value of CGRP-mAbs, compared to the classical preventatives, seems to be their unprecedented favorable adverse effect profile that is also associated with ease of use and high efficacy.

Additionally, CGRP-mAbs may represent a suitable option for individuals with migraine who have contraindications to other preventive treatments or in whom adverse events may be particularly challenging.

The panel was in favor of offering those drugs within the other available options which are usually considered when choosing a migraine preventive treatment. There are no reasons on clinical grounds to postpone the initiation of this treatment.

Expert consensus statement 2
In individuals with episodic or chronic migraine there is insufficient evidence to make suggestions regarding the combination of monoclonal antibodies targeting the CGRP with other preventatives to improve migraine clinical outcomes. (Expert consensus statements)

So far, there is no robust evidence either to support or discard the combination of different migraine preventatives.

Withdrawal of other preventive drugs can be done early or later in individuals with migraine showing a favorable clinical response after starting the CGRP-mAb.

While as general concept monotherapy is preferrable, some individuals with migraine do not have adequate pain relief with a single drug. In those cases, a combination of different drugs might be considered referring to the previous pharmacological history and comorbidities.

The panel decided not to make an explicit statement either in favor or against combination therapy and to leave this option to individual considerations.

Expert consensus statement 3
In individuals with episodic or chronic migraine who start a new treatment with one monoclonal antibody targeting the CGRP pathway we suggest evaluating efficacy after a minimum of 3 consecutive months on treatment. (Expert consensus statements)

We recognize that some individuals with migraine may take more time to achieve a relevant benefit. In selected cases decision on treatment maintenance can be readdressed after an additional period of 3 months.

Expert consensus statement 4
In individuals with episodic or chronic migraine we suggest considering a pause in the treatment with monoclonal antibodies targeting the CGRP pathway after 12-18 months of continuous treatment. If deemed necessary, treatment should be continued as long as needed. In individuals with migraine who pause treatment, we suggest restarting the treatment if migraine worsens after treatment withdrawal. (Expert consensus statements)

Monthly or quarterly administration of CGRP mAbs is more accepted by individuals with migraine than the daily oral regimen. Moreover, the excellent tolerability profile makes the CGRP-mAbs more suitable for prolonged treatments. So far, there are no studies which provide a clear guidance on the optimal duration of migraine preventive treatments. It is highly probable that a broadly generalizable approach does not exist and that also treatment duration needs to be adapted on a case-by-case strategy or considering homogeneous groups of individuals with migraine.

Expert consensus statement 6
In individuals with migraine with inadequate response to one monoclonal antibody targeting the CGRP pathway, there is insufficient evidence on the potential benefits of antibody switch but switching may be an option. (Expert consensus statements)
Considerations to support the switch from one CGRP-mAb to another, include differences in the mechanism of action (action on the ligand or on the receptor), difference in administration schedule (monthly versus quarterly) and to a lesser extent difference in formulations (subcutaneous versus intravenous). So far, there are no RCTs which addressed whether switching between different CGRP-mAbs may offer benefits to non-responder individuals with migraine.

The panel expressed a consensus statement to recognize the lack of adequate scientific evidence but at the same time we acknowledge that, for some individuals with migraine, a switch may represent the best therapeutic option.

Expert consensus statement 7
We suggest avoiding monoclonal antibodies targeting the CGRP pathway in pregnant or nursing women. We suggest caution and decision on a case-by-case basis in the presence of vascular disease or risk factors and Raynaud phenomenon. We suggest caution in erenumab use in individuals with migraine and history of severe constipation. (Expert consensus statements)

CGRP-mAbs are unlikely to produce drug interactions which may be particularly relevant in individuals with migraine with comorbidities.

Pregnant and nursing women were excluded from RCTs and there is no robust information on the risk for the fetus or the newborn driven by CGRP-mAbs.The limited real-life data available so far have not shown major concerns with the accidental and short-lived exposure to erenumab, galcanezumab, and fremanezumab in pregnancy and lactation. However, caution is needed because experimental data indicate that erenumab crosses the placenta. Concerns in the use of those drugs in women of childbearing potential are related also to the long (around 1 month) half-life of the CGRP-mAbs that implies that these drugs can only be considered as eliminated from the circulation 6 months after stopping.

Concerns regarding vascular safety of these drugs were raised considering that CGRP is among the most potent vasodilators in animals and humans and that CGRPmediated vasodilation is a rescue mechanism in brain as well as cardiac ischemia. A case-by-case evaluation is needed when considering the use of CGRP-mAbs in individuals with migraine considered at high vascular risk of with overt history of vascular events.

The Expert panel also decided to suggest caution in the use in individuals with migraine with a history of Raynaud phenomenon as some reports have linked the use of CGRP-mAbs to this phenomenon.

Constipation could be related to CGRP-mAb use due to potential inhibition of gastrointestinal motility, which is regulated by CGRP. Constipation emerged as a frequent adverse event of treatment with galcanezumab and mostly with erenumab, as reported in realworld studies.

5.3 Medication-overuse headache

5.3.1 Summary

Summary

Not considering opioids, most guidelines prefer abrupt withdrawal rather than slow withdrawal of analgesics and triptans (NICE 2021, NHG 2021, Eigenbrodt 2021). SIGN 2022 recommends to tailor the strategy to the individual patient.

There are differences between the guidelines regarding preventive therapy and whether it is appropriate during withdrawal. Eigenbrodt 2021 mentions that this topic remains a subject of debate. For SIGN 2022, it should be tailored to the individual patient. For NICE 2021 and Eigenbrodt 2021, it can be considered in addition to withdrawal. Eigenbrodt 2021 mentions that recent evidence suggests that the best therapeutic strategy is withdrawal combined with preventive treatment from the start. For NHG 2021, the usefulness of preventative treatment can only be assessed after triptans have been stopped for 2 months and analgesics for 3 months taken into account any remaining symptoms after this period.

SIGN 2022 states that the choice of strategy to address medication overuse should be tailored to the individual patient and may be influenced by comorbidities. Strategies include abrupt withdrawal alone and preventative treatment may then be considered after a delay; abrupt withdrawal and immediately starting preventative treatment; starting a preventative treatment without withdrawal. Prednisolone should not be used routinely in the management of patients with medication overuse headache.

NICE 2021 recommends to advise people to stop taking all overused acute headache medications for at least 1 month and to stop abruptly rather than gradually. It is recommended to consider prophylactic treatment in addition to withdrawal of overused medication. The guideline recommends to not routinely offer inpatient withdrawal for medication overuse headache. Specialist referral and/or inpatient withdrawal of overused medication is to be considered for people who are using strong opioids, or have relevant comorbidities, or in whom previous repeated attempts at withdrawal of overused medication have been unsuccessful. Review the diagnosis of medication

overuse headache and further management 4–8 weeks after the start of withdrawal of overused medication.

NHG 2021 recommends abrupt withdrawal of analgesics and triptans. Stop triptans for 2 months and analgesics for 3 months. Only after this period can any remaining symptoms be assessed and is it possible to assess whether preventative treatment is useful. When discontinuing triptans, improvement occurs faster (after 7-10 days) than when discontinuing analgesics (after 2-3 weeks). Prednisone is not recommended as supportive drug during withdrawal of analgesics and/or triptans. Frequent check-ups after withdrawal are important to prevent relapse. Referral for inpatient withdrawal of analgesics and triptans is not recommended.
It is recommended to consider referral to a neurologist specialized in headache/headache center for outpatient counselling after a previously unsuccessful attempt to discontinue medication or if the GP and/or patient assesses that discontinuation of the medication is difficult, based on factors such as patient insight, extent of patient's ability to solve problems (motivation and cooperation) and comorbidity.

Eigenbrordt 2021 prefers the abrupt withdrawal of overused medication (not opioids). This can be managed in primary care unless addictive drugs (e.g. opioids) are involved. The guidelines states that preventive therapy can be started in parallel with withdrawal or upon re-emergence of the headache disorder, although this topic remains a subject of debate.
Patients with chronic migraine are recommended to be referred to specialist care.

FR 2021 recommends for chronic migraine with medication overuse headache, first-line prophylactic medication and advises the ambulatory withdrawal of the overused acute medication.

EUR 2022 suggests offering CGRP monoclonal antibodies in patients with migraine and medication overuse.

5.3.2 SIGN 2022

Always ask about acute medication use. If required for more than 2 days a week consider whether there may be medication overuse headache. Headache diaries can help.

Risk factors for the development of MOH include frequent headache, frequent acute medication use, another painful condition and psychiatric comorbidity. Use of triptans, ergots, combination

analgesics and/or opioids 10 or more days per month and simple analgesics 15 or more days per month is accepted to cause MOH. Importantly, not all patients overusing acute treatments have MOH and some just have poorly-treated migraine.

Naproxen is often used in clinical practice as a transitional treatment. No evidence was identified for this use in patients with MOH.

No studies were identified on the use of greater occipital nerve blocks, or combinations of triptans, analgesics, NSAIDs or opioids for the management of patients with MOH

In patients overusing acute treatment, medication overuse should be addressed.

The choice of strategy to address medication overuse should be tailored to the individual patient and may be influenced by comorbidities. Strategies include:

- **abrupt withdrawal alone and preventative treatment may then be considered after a delay**
- **abrupt withdrawal and immediately starting preventative treatment**
- **starting a preventative treatment without withdrawal.**

Good-practice point. Consider withdrawing regular opioids gradually.

Prednisolone should not be used routinely in the management of patients with medication-overuse headache.

5.3.3 NICE 2021

1.2.7. Be alert to the possibility of medication overuse headache in people whose headache developed or worsened while they were taking the following drugs for 3 months or more:
-triptans, opioids, ergots or combination analgesic medications on 10 days per month or more or
-paracetamol, aspirin or an NSAID, either alone or any combination, on 15 days per month or more. [2012]

1.3.34 Explain to people with medication overuse headache that it is treated by withdrawing overused medication.

1.3.35 Advise people to stop taking all overused acute headache medications for at least 1 month and to stop abruptly rather than gradually.

1.3.36 Advise people that headache symptoms are likely to get worse in the short term before they improve and that there may be associated withdrawal symptoms, and provide them with close follow-up and support according to their needs.

1.3.37 Consider prophylactic treatment for the underlying primary headache disorder in addition to withdrawal of overused medication for people with medication overuse headache.

Trade off between clinical benefits and harms (1.3.34 – 1.3.37)
Headache symptoms typically get worse for up to two weeks before improvement. Other withdrawal symptoms depend on drug being used Relapse rate is very high.

Quality of evidence (1.3.34 – 1.3.37)
The recommendations were based on very low quality evidence from one study and the consensus opinion of the GDG.
Other considerations (1.3.34 – 1.3.37)
The GDG recommended a minimum period of withdrawal of one month, and acknowledged that although this was different from the IHS criteria, which state a minimum of 8 weeks as the period of withdrawal, it is a more practical approach.
The GDG experience was that the majority of people could manage withdrawal without the addition of adjunctive treatments such as steroids, anxiolytics and antiemetics. These have been used to assist withdrawal and manage associated symptoms. There is evidence that the majority of people can withdraw from overused treatment without further medication. However, the GDG acknowledged that some people will benefit from introduction of prophylactic treatment for their primary headache disorder. This can be instituted at the time of withdrawal of acute medication but the GDG did not consider this was always necessary. Withdrawal of medication may result in significant reduction of headache so prophylaxis might not be required.
The GDG also discussed the issues with abrupt and gradual withdrawal and acknowledged that in the first week or two after stopping medications, most people experience a worsening of symptoms, before improvement. Patient experience suggested that gradual withdrawal is preferred. The GDG concluded that this may differ was according to the individual concerned and was best decided on a case by case basis and following discussion between practitioner and patient. The GDG also felt that gradual withdrawal could be managed in the community by those experienced in managing withdrawal.

1.3.38 Do not routinely offer inpatient withdrawal for medication overuse headache.

1.3.39 Consider specialist referral and/or inpatient withdrawal of overused medication for people who are using strong opioids, or have relevant comorbidities, or in whom previous repeated attempts at withdrawal of overused medication have been unsuccessful.

Quality of evidence (1.3.38 – 1.3.39)
The recommendation is based on the consensus opinion of the GDG as the evidence reviewed was of very low quality. This evidence suggested that community or outpatient treatment was better than inpatient treatment with respect to reducing the number of headache days and relapse back to medication overuse headache, but the GDG informal consensus decision was that in some specific cases, inpatient withdrawal may be appropriate.

Other considerations
The GDG also discussed the practical aspects of implementation of this recommendation. The majority of cases can be managed in a primary care setting. It was discussed that inpatient

withdrawal should take place in centres with specialist expertise in this area and that those services may differ by areas e.g. they may be within a drug dependency service or a specialist headache service.
The GDG discussed the practical aspects of referral and agreed that specialist referral could be to a community drugs team if available and deemed appropriate.

1.3.40 Review the diagnosis of medication overuse headache and further management 4–8 weeks after the start of withdrawal of overused medication.

Trade off between clinical benefits and harms
There is a high relapse rate associated with management of medication overuse headache which may occur within the period of withdrawal. There is often a worsening of symptoms before any improvement is seen. However, the benefits of subsequent successful withdrawal greatly outweigh this.

Quality of evidence
These recommendations were based on the consensus opinion of the GDG.

5.3.4 NHG 2021

Medicatieovergebruikshoofdpijn

Voorlichting
Algemeen

- Leg bij een vermoeden van MOH uit dat de oorzaak van deze hoofdpijn mogelijk overmatig gebruik van hoofdpijnmedicatie is: ongemerkt treedt gewenning op; het niet innemen van het medicament leidt dan tot hoofdpijn en zo ontstaat een vicieuze cirkel.
- Ook bij kinderen kan overmatig of frequent gebruik van pijnmedicatie (op meer dan de helft van de dagen) leiden tot MOH.
- Leg uit dat het wegnemen van de oorzaak, door gedurende 2-3 maanden te stoppen met de aanvalsmedicatie, de beste optie is: het merendeel van de patiënten heeft na 3 maanden een reductie van meer dan 50% van het aantal hoofdpijndagen per maand bereikt.
- Waarschuw de patiënt dat de hoofdpijn aanvankelijk kan verergeren en dat werken of het ondernemen van dagelijkse activiteiten de eerste weken soms niet mogelijk is.
- Adviseer de patiënt om zijn omgeving (gezin, collega's, etcetera) van tevoren in te lichten over het stoppen van de medicatie.
- Leg uit dat de onderliggende episodische hoofdpijn, bijvoorbeeld migraine, opnieuw kan optreden tijdens en na de stopperiode.
- Na de stopperiode keert het oorspronkelijke hoofdpijnpatroon veelal terug en is aanvalsbehandeling opnieuw mogelijk, maar onder striktere voorwaarden dan voorheen (zie Behandeling).

Arbeidssituatie

Adviseer, als er (mogelijk) een relatie is met de arbeidssituatie, als er gevolgen zijn voor de inzetbaarheid in het werk of in geval van werkverzuim contact op te nemen met de bedrijfsarts, indien dat nog niet is gebeurd.

Behandeling

Acuut staken van analgetica en triptanen

- Adviseer om in 1 keer met alle hoofdpijnmedicatie te stoppen en deze niet te vervangen door andere middelen. Bespreek met de patiënt wat een geschikte datum is om de medicatie te stoppen.
- Houd voor triptanen een stopperiode van 2 maanden aan en voor analgetica 3 maanden. Deze periode is van belang omdat pas na die periode de overblijvende klachten beoordeeld kunnen worden en ingeschat kan worden of preventieve medicatie zinvol is.
- Bij het staken van triptanen treedt sneller verbetering (na 7-10 dagen) op dan bij het staken van analgetica (na 2-3 weken).
- Overweeg bij een eerder mislukte poging om de medicatie te staken verwijzing naar een in hoofdpijn gespecialiseerde neuroloog/hoofdpijncentrum voor poliklinische begeleiding (door bijvoorbeeld een hoofdpijnverpleegkundige).
- Overweeg verwijzing naar een in hoofdpijn gespecialiseerde neuroloog/hoofdpijncentrum voor poliklinische begeleiding indien de huisarts en/of patiënt inschat dat het staken van de medicatie moeizaam is, op basis van factoren als inzicht van de patiënt, mate waarin de patiënt in staat is problemen op te lossen (motivatie en coöperatie) en comorbiditeit.

Methodes ter ondersteuning

- Verwijs niet voor klinische opname als ondersteuning bij acuut staken van alle analgetica en/of triptanen bij (mogelijke) MOH.
- Schrijf geen prednison voor als ondersteuning bij acuut staken van alle analgetica en/of triptanen bij (mogelijke) MOH.
- Preventieve medicatie tijdens de stopperiode is niet zinvol: niet altijd is de primaire hoofdpijndiagnose bekend en na ontwenning is preventieve medicatie vaak niet nodig.

Begeleiding tijdens de stopperiode

- Begeleid de patiënt intensief gedurende deze periode. De onttrekking van medicatie kan een grote impact op het welbevinden en dagelijks functioneren hebben. Bepaal samen met de patiënt op welke manier u de patiënt kan begeleiden. Veelal volstaat (wekelijks) telefonisch contact. Bespreek de therapietrouw, eventuele toename van hoofdpijn, invloed op dagelijkse bezigheden en voorkomen van terugval.
- Er is vaak sprake van psychiatrische comorbiditeit, met name depressie of een angststoornis. Psychiatrische comorbiditeit is geassocieerd met een slechtere uitkomst van de behandeling; in dit geval is intensievere begeleiding (bijvoorbeeld door de POH-GGZ) en optimalisering van de behandeling van de comorbiditeit op zijn plaats.

Na de stopperiode

- Het percentage patiënten dat terugvalt is hoog: 17-43% na 1 jaar. Bij terugval gebeurt dat meestal in het eerste jaar.

- Frequente controles na de stopperiode zijn van belang om terugval te voorkomen en om het onderliggende type hoofdpijn te bepalen en deze adequaat te behandelen.
- Gebruik zo nodig het hoofdpijndagboek (versie diagnostiek) om het onderliggende type hoofdpijn te bepalen.
- Behandel zo nodig de onderliggende episodische hoofdpijn na de stopperiode:
    - Schrijf aanvalsmedicatie onder striktere voorwaarden voor, bijvoorbeeld door toepassing van de 2x2 regel bij migraine (maximaal 2 aanvallen per maand behandelen gedurende maximaal 2 dagen achtereen) of halvering van het maximaal aantal dagen per maand (paracetamol en NSAID's maximaal 8 dagen per maand, triptanen of combinaties van analgetica maximaal 5 dagen per maand).
    - Overweeg start van preventieve medicatie bij chronische spanningshoofdpijn of episodische migraine met een aanvalsfrequentie ≥ 2 per maand.

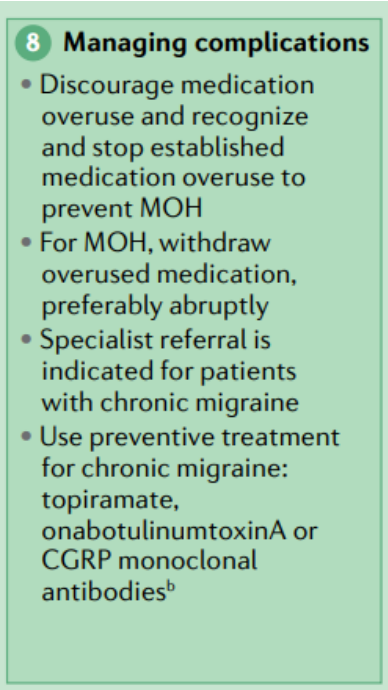
Controle

- Houd tijdens de stopperiode frequent contact met de patiënt, afhankelijk van diens klachten en wensen.
- Bied na het staken van de medicatie frequente controles aan om terugval te voorkomen.
- Bepaal vervolgens de frequentie van de controleafspraken aan de hand van de onderliggende hoofdpijn en de bijbehorende behandeling.

Consultatie en verwijzing

Overweeg consultatie van of verwijzing naar een neuroloog met expertise op het gebied van hoofdpijn bij onvermogen om, ondanks begeleiding, te stoppen met medicatie.

5.3.5 Eigenbrodt 2021



Medication overuse headache.
MOH is a chronic headache disorder characterized by headache on ≥15 days per month. It develops over a variable period of time in patients with a pre-existing headache disorder as a result of regular overuse of acute or symptomatic headache medication. Patients with migraine account for approximately two thirds of all cases of MOH, although this estimate is based on limited evidence and might be too low.
Withdrawal of the overused medication is the necessary and only remedy for MOH. Expert consensus is that abrupt withdrawal is preferable to slow withdrawal, except for opioids. This process can be managed in primary care unless addictive drugs, such as opioids, are involved. Patient education is a key component of the clinical management of MOH, as withdrawal is usually followed by worsening before recovery. Preventive therapy (pharmacological and/or non-pharmacological) appropriate to the antecedent headache can be started in parallel with acute medication withdrawal or upon re-emergence of the headache disorder, although this topic remains a subject of debate.

Recommendations.
• Educate patients with migraine about the risk of MOH with frequent overuse of acute medication.
• Manage established MOH by explanation and withdrawal of the overused medication; abrupt withdrawal is preferred, except for opioids.
• Recognize and, when possible, modify risk factors for the transformation of episodic migraine to chronic migraine.
• Refer patients with chronic migraine to specialist care.
• Once MOH is ruled out, initiate preventive medication therapy for chronic migraine; evidence-based treatment options are topiramate, onabotulinumtoxinA and CGRP monoclonal antibodies.

5.3.6 FR 2021

Acute migraine treatment

Rt4 - Explain that the use of acute treatments should be limited to a maximum of eight days per month, because overusing medication carries the risk of medication overuse headache. (Strength of the recommendation: strong)

Since some oral gepants are currently investigated in the prophylactic treatment of migraine, gepants could potentially be associated with a reduced risk of medication overuse headache as compared to the other acute migraine drugs, although currently available evidence is insufficient to support or refute this hypothesis.

Therapeutic doses of lasmiditan were associated with a significant increased risk of drug-liking effects as compared to placebo, suggesting there is a potential risk of lasmiditan misuse or abuse (level of evidence medium). Effects of lasmiditan in relation to medication overuse headache are unknown.

Rt8 - Avoid prescribing opiates to treat migraine due to the risks of misuse, abuse, and of medication overuse headache. (Strength of the recommendation: strong)

Pharmacological prophylaxis

Rt 24 - In patients with chronic migraine and medication overuse headache, prescribe a first-line prophylactic medication and advise an ambulatory withdrawal of the overused acute medication. (Strength of the recommendation: strong)

Rt27 - In case of insufficient efficacy and/or tolerability, choose one or several strategies to optimize the prophylaxis, and educate the patient (Strength of the recommendation: strong):
a. Check for compliance
b. Check for medication overuse, including analgesics for non-headache pain
c. In case of insufficient efficacy and good tolerability, increase daily doses to the maximal recommended dose with an acceptable tolerance
d. Switch to another prophylaxis

4.3. What is the evidence for prophylactic treatment of medication overuse headache?
There has been a long debate about the practical strategy in patients with chronic migraine with medication overuse headache (MOH). Some authors recommended a two months abrupt and complete withdrawal before considering the introduction of prophylaxis. Nevertheless, when patients with MOH are treated solely by withdrawal without any other preventive treatment, about one-third cannot tolerate or will not complete the process, one-third withdraws and improves, and one-third withdraws but does not improve. Furthermore, evidence shows that the frequency of headache is significantly reduced in patients with chronic migraine receiving prophylaxis with topiramate, onabotulinumtoxinA or CGRP-MABs, whether or not they overuse acute medication at inclusion (level of evidence high). Of note, patients overusing opioids were not included in GCRP-MABs trials. In MOH, recent evidence suggests that the best therapeutic strategy is withdrawal combined with preventive treatment from the start (level of evidence medium). Evidence also suggests that educating patients about the risks of migraine chronicization induced by medication overuse can improve global outcomes (level of evidence fair).

5.3.7 EUR 2022

In individuals with migraine and medication overuse, we suggest offering monoclonal antibodies targeting the CGRP pathway. (Expert consensus statements)

All the available RCTs on chronic migraine included individuals with migraine and medication overuse. In those studies, the efficacy of all four mAbs seemed to be independent of whether the patient had medication overuse.

There is also evidence from real-world studies suggesting that CGRP-mAbs are highly effective even in the absence of prior detoxification in individuals with medication overuse and that the response to CGRP-mAbs does not depend on detoxification.

5.4 Specific populations - Elderly

5.4.1.1 Summary

Summary

Guidelines do not provide recommendations regarding the pharmacological treatment of older patients with migraine. Eigenbrodt 2021 mentions for this age group the poor evidence base for all drugs and the increased risk of drug-specific adverse effects. Furtermore, they mention that clinicians are advised to regularly monitor blood pressure in older patients with migraine who use triptans, in addition to periodical assessment of cardiovascular risk factors.

5.4.1.2 SIGN 2022

No recommendations were provided.

5.4.1.3 NICE 2021

No recommendations were provided.

5.4.1.4 NHG 2021

No recommendations were provided.

5.4.1.5 Eigenbrodt 2021

Older people

- Secondary headache, comorbidities and adverse events are all more likely
- Poor evidence base for all drugs in this age group

Migraine often remits with older age whereas the incidence of many secondary headaches increases. Onset of apparent migraine after the age of 50 years should, therefore, arouse suspicion of an underlying cause. In individuals whose migraine persists from earlier life into later years, clinical management often remains unchanged in practice. Little formal evidence is available with respect to therapeutic approaches in older people with migraine.
Nonetheless, known and possible unknown comorbidities need to be considered, as well as harm that might be caused by drug-specific adverse effects, to which older people are generally more susceptible. For instance, use of triptans in older people is often advised against owing to the relatively high likelihood that these patients have cardiovascular disease and/or cardiovascular risk factors. However, no robust evidence supports an increased risk of cerebrovascular or cardiovascular events in older people owing to triptan use per se. Nonetheless, clinicians are advised to regularly monitor blood pressure in older patients with migraine who use triptans, in addition to periodical assessment of cardiovascular risk factors.

Recommendations.

In older people, consider the higher risks of secondary headache, comorbidities and adverse events with older age.

5.4.1.6 FR 2021

No recommendations were provided.

5.5 Specific populations – Migraine associated with menstruation

5.5.1 Acute pharmacological treatment

5.5.1.1 Summary

Summary

For the acute treatment of menstrual migraine, it is recommend to follow the recommendations for any migraine attack (NHG 2021, FR 2021).
SIGN 2022 recommends triptans for the treatment of acute migraine associated with menstruation. No other recommendations were provided for this population.
NHG 2021 has a preference for NSAID over triptans because NSAID are often also effective against menstrual problems like heavy menstrual bleeding. Furthermore, short-term use of NSAID are related to fewer adverse events compared to triptans.

5.5.1.2 SIGN 2022

Triptans are recommended for the treatment of patients with acute migraine associated with menstruation.

For patients with menstrually-related migraine (MRM), sumatriptan resulted in a therapeutic gain with 25% of patients pain free at two hours with 50 mg and 34% with 100 mg compared to placebo. Rizatriptan, frovatriptan and zolmitriptan were also reported to provide benefit for acute treatment of patients with MRM.

5.5.1.3 NICE 2021

Menstrual-related migraine

1.2.5 Suspect menstrual-related migraine in women and girls whose migraine occurs predominantly between 2 days before and 3 days after the start of menstruation in at least 2 out of 3 consecutive menstrual cycles. [2012]

1.2.6 Diagnose menstrual-related migraine using a headache diary (see recommendation 1.1.4) for at least 2 menstrual cycles. [2012]

The first step in management is to optimise the usual acute medications and avoid any known triggers.

5.5.1.4 NHG 2021

Aanvalsbehandeling

- De aanvalsbehandeling is hetzelfde als bij 'gewone' migraine (zie Migraine bij volwassenen), maar menstruele migraine lijkt moeilijker te behandelen.
- NSAID's zijn even effectief als triptanen en hebben vaak ook een gunstig effect op menstruatieklachten, zoals overmatig bloedverlies (zie NHG-Standaard Vaginaal bloedverlies). Daarnaast hebben ze bij kortdurend gebruik minder bijwerkingen dan triptanen. Ze hebben daarom de voorkeur boven triptanen.

5.5.1.5 Eigenbrodt 2021

Women with menstrual migraine.
Approximately 8% of women with migraine experience migraine attacks that are exclusively related to their menstruation, referred to as pure menstrual migraine. If optimized acute medication therapy does not suffice for these patients, initiation of perimenstrual preventive treatment should be considered. …

Recommendations.
In women with menstrual migraine, consider perimenstrual preventive therapy with a long-acting NSAID or triptan.

5.5.1.6 FR 2021

Table 8 – Recommendations for diagnosis and treatment of menstrual migraine.

Recommendations for diagnosis and treatment of menstrual migraine		Strength of the recommendation
Rw10	Diagnose menstrual migraine according to ICHD-3 criteria, with the use a prospective headache diary over three months	Strong
Rw11	Treat menstrual attacks following recommendations for any acute attack, i.e. with an NSAID and/or a triptan	Strong
Rw12	In women with bothersome menstrual migraine who are already under hormonal contraception, propose a continuous intake of the contraception or a shortened hormone-free interval	Strong
Rw13	Women with bothersome menstrual migraine, the treatment and especially hormonal interventions should be decided by the primary care physician and a gynecologist	Strong

5.2.2. What are the effective treatments for menstrual migraine?
Triptans, NSAIDs, paracetamol, and the combination of aspirin with caffeine are effective acute treatments for menstrual migraine (level of evidence high). Women with frequent migraine including menstrual attacks are eligible for standard prophylactic medications. …

5.5.2 Pharmacological prevention

5.5.2.1 Summary

Summary

For menstrual migraine, a distinction should be made between “menstrual-related” migraine and “pure menstrual migraine”. With pure menstrual migraine, attacks occur exclusively with menstruation. With menstrual-related migraine, attacks also occur at other times of the month. Both types of migraine are often more difficult to manage than other types of migraine.

Guidelines recommend to consider perimenstrual preventive treatment when optimized acute medication therapy does not suffice for patients with menstrual migraine. Triptans or NSAID are recommended on the days migraine is expected. This is often 2 days before until 3 days after menstruation in patients with predictable menstrual-related migraine.

SIGN 2022 states that frovatriptan (2.5 mg twice daily) should be considered and that zolmitriptan (2.5 mg three times daily) or naratriptan (2.5 mg twice daily) are alternatives for the treatment of perimenstrual migraine. Similarly, NICE 2021 states to consider frovatriptan (2.5 mg twice a day) or zolmitriptan (2.5 mg twice or three times a day) for the treatment of predictable menstrual-related migraine.

NHG 2021 recommends the use of NSAID (ibuprofen or naproxen) as first choice and triptans as second choice for the prophylactic treatment of pure menstrual migraine. For menstrual-related migraine, for which drugs are used for migraine at other times of the month, prophylactic use of NSAID or triptans can lead to medication-overuse headache, and are therefore not recommended for menstrual-related migraine.

Eigenbrodt 2021 recommends to consider a long-acting NSAID (for example, naproxen) or triptan (for example, frovatriptan or naratriptan).

FR 2021 does not recommend short-term perimenstrual prophylactic strategies with NSAID, triptans, and cutaneous estradiol. (strength of recommendation: strong against)

Multiple guidelines state that women with pure menstrual migraine without aura can benefit from continuous use (that is, without a break) of combined hormonal contraceptives (NHG 2021,

Eigenbrodt 2021, FR 2021) or from a shortened hormone-free interval (FR 2021). However, the patient should already be taken these contraceptives (NHG 2021, FR 2021) and have a regular menstrual cycle. Combined hormonal contraceptives are contraindicated in women with migraine with aura.

Progestin-only contraception as prophylactic treatment for menstrual migraine is not recommended (NHG 2021).

5.5.2.2 SIGN 2022

The drop in oestrogen just prior to menstruation is a known trigger for migraine and in women migraine is more frequent, more severe and harder to treat just before and during menstruation. In some women migraine only occurs (pure menstrual migraine) or predominantly occurs (menstrually-related migraine) from two days before the start of bleeding until three days after. In these women perimenstrual strategies may be used instead of, or in addition to, standard, continuous prophylaxis. The menstrual cycle has to be regular for treatment to be effective.

Triptans

Frovatriptan (2.5 mg twice daily) should be considered as a prophylactic treatment in women with perimenstrual migraine from two days before until three days after bleeding starts.

Zolmitriptan (2.5 mg three times daily) or naratriptan (2.5 mg twice daily) can be considered as alternatives to frovatriptan as prophylactic treatment in women with perimenstrual migraine from two days before until three days after bleeding starts.

Good-practice point. Women with menstrual-related migraine who are using triptans at other times of the month should be advised that additional perimenstrual prophylaxis increases the risk of developing medication overuse headache.

[Bib. group] The SIGN 2022 guideline also mentions prostaglandin inhibitors, NSAID, oestrogens, and hormonal prophylaxis. No recommendations were made due to very limited data.

5.5.2.3 NICE 2021

1.3.25 For women and girls with predictable menstrual-related migraine that does not respond adequately to standard acute treatment, consider treatment with frovatriptan (2.5 mg twice a day) or zolmitriptan (2.5 mg twice or three times a day) on the days migraine is expected. [2012]

In November 2015, this was an off-label use of frovatriptan and zolmitriptan. See NICE's information on prescribing medicines.

Quality of evidence
This recommendation is based on low quality evidence from two studies showing reduced acute medication use and increased responder rate with frovatriptan or zolmitriptan compared to placebo. Only one study reported responder rate. Additional evidence and advice was gained from an expert advisor to inform the recommendations.

Other considerations
Menstrual migraine and menstrual related migraine are treated with the same strategies. One of the important issues in deciding on treatment is frequency of migraine as infrequent migraine is best treated using acute treatments. Studies included in this review have shown a benefit with the use of triptans in doses of 2.5 mg with up to twice daily (with the highest dose of 2.5mg demonstrating better efficacy) dosing for long acting triptans (frovatriptan) and three times a day dosing for short acting triptans (zolmitriptan). The later trials have used longer acting triptans. This treatment is off licence and menstruation needs to be predictable to use this method. The GDG considered that peri menstrual prophylaxis is only required for a small number of people who have regular periods.
The co-opted expert considered that oestrogen supplementation e.g. using gels is rarely required even in specialist practice. Women who require contraception and can safely use combined hormonal contraceptives, can manipulate their cycles to reduce the number of periods they have e.g. by tricycling combined hormonal contraception or by reducing the hormone free interval.

5.5.2.4 NHG 2021

Preventieve behandeling

- De preventieve behandeling is bij menstruatiegerelateerde migraine gelijk aan de behandeling van ‘gewone’ migraine.
- Bij vrouwen met menstruele migraine kan gekozen worden voor kortdurende preventieve behandeling met NSAID’s (eerste keus) of triptanen (tweede keus) of het doorslikken van de combinatiepil (indien patiënte deze reeds slikt).

Kortdurende preventieve behandeling menstruele migraine
Overweeg kortdurende behandeling met een NSAID (ibuprofen of naproxen) of (bij contraindicaties of onvoldoende effect) een triptaan (off-label):

- Op grond van het bijwerkingenprofiel en het gunstige effect op menstruatiegerelateerde buikpijn en bloedverlies gaat de voorkeur uit naar NSAID’s boven triptanen.
- Geef deze medicatie op de dagen dat de migraine verwacht wordt (meestal dag 2 voor de menstruatie tot dag 3 van de menstruatie).
- Als er ook migraineaanvallen op andere momenten zijn (menstruatiegerelateerde migraine) waarvoor medicatie gebruikt wordt, kan preventief gebruik van NSAID’s en triptanen leiden tot MOH en wordt daarom bij menstruatiegerelateerde migraine niet aanbevolen.

Preventieve behandeling met de combinatiepil

- Overweeg alleen vrouwen die de combinatiepil al gebruiken en migraine zonder aura in de stopweek hebben, te adviseren de pil te gebruiken zonder stopweek (zie NHG-Standaard Anticonceptie).
- Schrijf de combinatiepil niet met dit doel voor aan vrouwen met migraine, vanwege het verhoogde risico op HVZ.

Preventieve behandeling met anticonceptiemethoden met alleen progestagenen

- We bevelen de pil met alleen progestagenen (of andere anticonceptiva met alleen progestagenen) niet aan als preventieve behandeling bij vrouwen met menstruele migraine of menstruatiegerelateerde migraine.
- De effectiviteit hiervan is te beperkt (pil met alleen progestagenen) of niet onderzocht (andere anticonceptiva met alleen progestagenen).

5.5.2.5 Eigenbrodt 2021

Women with menstrual migraine.
Approximately 8% of women with migraine experience migraine attacks that are exclusively related to their menstruation, referred to as pure menstrual migraine. If optimized acute medication therapy does not suffice for these patients, initiation of perimenstrual preventive treatment should be considered. This approach typically involves daily intake of a long-acting NSAID (for example, naproxen) or triptan (for example, frovatriptan or naratriptan) for 5 days, beginning 2 days before the expected first day of menstruation. Some women with pure menstrual migraine without aura benefit from continuous use (that is, without a break) of combined hormonal contraceptives. By contrast, combined hormonal contraceptives are contraindicated in women with migraine with aura regardless of any association with their menstrual cycle, owing to an associated increase in the risk of stroke.

Recommendations.
In women with menstrual migraine, consider perimenstrual preventive therapy with a long-acting NSAID or triptan.

5.5.2.6 FR 2021

Table 8 – Recommendations for diagnosis and treatment of menstrual migraine.

Recommendations for diagnosis and treatment of menstrual migraine		Strength of the recommendation
Rw10	Diagnose menstrual migraine according to ICHD-3 criteria, with the use a prospective headache diary over three months	Strong
Rw11	Treat menstrual attacks following recommendations for any acute attack, i.e. with an NSAID and/or a triptan	Strong
Rw12	In women with bothersome menstrual migraine who are already under hormonal contraception, propose a continuous intake of the contraception or a shortened hormone-free interval	Strong
Rw13	Women with bothersome menstrual migraine, the treatment and especially hormonal interventions should be decided by the primary care physician and a gynecologist	Strong

5.2.2. What are the effective treatments for menstrual migraine?

Triptans, NSAIDs, paracetamol, and the combination of aspirin with caffeine are effective acute treatments for menstrual migraine (level of evidence high). Women with frequent migraine including menstrual attacks are eligible for standard prophylactic medications. In women with a regular hormonal cycle, some studies have shown that menstrual attacks may be prevented by short-term perimenstrual (sequential) prophylaxis. Naproxen is effective (level of evi- dence fair) and its use may be relevant in case of associated dysmenorrhea. Three triptans were shown to be effective (frovatriptan and naratriptan 2.5 mg twice daily, zolmitriptan 2.5 mg three times daily) (level of evidence high), but they were used at high daily doses and this strategy should be balanced with the limit of eight monthly days of intake in order to prevent triptan overuse. Cutaneous estradiol (1.5 mg/day for 7 days) is effective (level of evidence fair), but its use may delay the attack some days later, following hormonal with- drawal (level of evidence fair). Overall, we do not recommend these short-term perimenstrual prophylactic strategies (strength of recommendation: strong against). In eligible women, hormonal contraception can be used with the purpose of preventing menstrual migraine, either with an extended-cycle regimen and a shortened hormone- free interval, or with a continuous regimen (level of evidence fair). In patients with migraine with aura, combined hormonal contraception (CHC) is contraindicated because of the increased risk of stroke, and progesterone-only contra-ceptives can be used (see below).

5.6 Specific populations – Pregnancy, contraception and menopause

5.6.1.1 Summary

Summary

Pregnancy: acute treatment

Guidelines recommend paracetamol as a first choice during any trimester of pregnancy due to its safety profile.

During pregnancy, NSAID are contraindicated in the 3th trimester (all guidelines). NHG 2021 states only to use NSAID incidentally at the lowest possible dose during the first 2 trimesters. According to Eigenbrodt 2021, NSAID can only be used in the 2^{e} trimester. For FR 2021 NSAID and aspirin (> 500 mg/day) are contraindicated after the 2^{e} trimester, and recommend to limit their use before the 2^{e} trimester. SIGN 2022 also states that aspirin, in doses for migraine, should not be used in the third trimester of pregnancy.

Triptans can be used after failure of paracetamol or NSAID. Triptans can be used in all trimesters of pregnancy.
Among the triptans, sumatriptan is the preferred choice (SIGN 2022, NHG 2021, FR 2021). NHG 2021 does not recommend other triptans besides sumatriptan. For FR 2021, rizatriptan or zolmitriptan can be used after failure of sumatriptan (after failure of paracetamol). Eigenbrodt

2021 states that triptans should be used only under the strict supervision of a specialist due to limited safety date.

For nausea associated with migraine during pregnancy, metoclopramide can be used (NHG 2021, Eigenbrodt 2021). Domperidone is advised against (NHG 2021).

FR 2021 also provide recommendations for women that desire pregnancy. Paracetamol is recommended for mild attacks and triptans for moderate to severe attacks. NSAID and aspirin (> 500 mg/day) are to be avoided because of the potential risk of early miscarriage.

Pregnancy: prevention

SIGN 2022 mentions that women with migraine without aura should aim to stop prophylactic treatments before pregnancy given that migraine without aura often improves during pregnancy. Furhtermore, the guideline mentions that no evidence was identified on which to base recommendations on preventative treatments for women during pregnancy.

NICE 2021 recommends to seek specialist advice if prophylactic treatment for migraine is needed.

NHG 2021 recommends to stop prophylactic treatment for migraine if there is a maternity whish. Refer to the neurologist in case of severe symptoms and/or insufficient effect of the acute treatment.

Eigenbrodt 2021 states that prophylactic treatment is best avoided during pregnancy. If indicated, best available data support propranolol or, if propranolol is contraindicated, amitriptyline. Both should be used under specialist supervision. Topiramate, candesartan and sodium valproate are contraindicated.

When pharmacological prophylaxis is necessary, FR 2021 recommends propranolol, metoprolol or amitriptyline during pregnancy. Valproic acid, topiramate, candesartan, lisinopril and all the ergots are contraindicated in pregnant women. In case of bothersome migraine during pregnancy, the patient should be managed both by a neurologist and a gyneacologist.

Because of the absence of data, CGRP monoclonal antibodies should not be used during pregnancy (SIGN 2022, FR 2021). A washout period of 6 months is advised before trying for a pregnancy (SIGN 2022). EUR 2022 suggests avoiding CGRP monoclonal antibodies in pregnant or nursing women.

<u>During lactation</u>

SIGN 2022 recommends to not use CGRP monoclonal antibodies during breast feeding due to limited data. Topiramate should not be used during breastfeeding as it can be present in breast milk.

NHG 2021 states that during lactation paracetamol, NSAID (ibuprofen preferred), domperidone and metoclopramide can be used safely. Domperidone is preferred to metoclopramide. Consider sumatriptan in case of insufficient effect of these drugs.
The guideline recommends to refer patients with severe symptoms during lactation to the neurologist.

Eigenbrodt 2021 recommends in breastfeeding women paracetamol as first choice (although ibuprofen and sumatriptan are also considered safe) for acute treatment. It is recommended to avoid preventive medication whenever possible. If preventive medication is required, propranolol is the recommended first choice as it has the best safety profile.

EUR 2022 suggests avoiding CGRP monoclonal antibodies in nursing women.

Summary

<u>Patients with aura: contraception</u>

Two guidelines (Eigenbrodt 2021, FR 2021) state that combined hormonal contraceptives for contraception are contraindicated due to an increased risk for stroke. Progestin-only contraception is possible (FR 2021). NICE 2021 recommends to not routinely offer them. NHG 2021 states that they are relatively contraindicated and in combination with smoking they are an absolute contraindication.

<u>Patients without aura: contraception</u>

FR 2021 provides recommendations.

Every hormonal contraception can be used in absence of any arterial risk factor. In the presence of ≥1 arterial risk factor, oral combined contraception is contraindicated; progestin-only contraception is possible. Arterial risk factors are: Age > 35; Smoking; familial history of stroke or myocardial infarction; Arterial hypertension; Dyslipidemia; Diabetes; Obesity.

For the continuous use of combined hormonal contraception to prevent menstrual migraine: see section “migraine associated with menstruation”.

Summary

Menopause

NHG 2021 does not recommend hormonal treatment for an increase in migraine attacks during menopause.

FR 2021 mentions that the impact of hormone replacement therapy on migraine course is debated. Hormonal replacement therapy is not contraindicated in migraine without other vascular risk factors.

5.6.2 SIGN 2022

Pregnancy

…An algorithm of a suggested treatment pathway can be found in Annex 3 (see section “acute pharmacological treatment”). The decision regarding which medication to try first is dependent on evidence of effectiveness, patient comorbidities, other risk factors, drug interactions and patient preference. It is important to ensure adequate contraception whilst on preventative therapies as some have risks of teratogenicity and others can potentially cause harm to unborn babies. Given that migraine without aura often improves during pregnancy women should aim to stop migraine prophylactic treatments before pregnancy. Migraine with aura often continues unchanged. Before commencing treatment, potential harmful effects of therapies need to be discussed with women who are, or may become, pregnant. No evidence was identified on which to base recommendations on preventative treatments for women during pregnancy.

The use of aspirin during pregnancy, especially of intermittent high doses, should be avoided. Aspirin is contraindicated during the third trimester of pregnancy.

Good-practice point. Aspirin, in doses for migraine, is not an analgesic of choice during pregnancy and should not be used in the third trimester of pregnancy.

In pregnancy, ibuprofen is the anti-inflammatory agent of first choice until gestational week 28. After 28 weeks of gestation, repeated use of ibuprofen should be avoided.

Paracetamol is commonly used in all trimesters of pregnancy although routine use should be avoided.
Good-practice point. Due to its safety profile, paracetamol is first choice for the short-term relief of mild to moderate headache during any trimester of pregnancy.

Sumatriptran is the preferred triptan based on efficacy, safety profile and cost. For patients with early vomiting, a nasal or subcutaneous triptan may be more effective. Nasal zolmitriptan 5 mg and sumatriptan 6 mg subcutaneous are effective (see Table 1, section 3.9). Where treatment with paracetamol (all trimesters) or ibuprofen (first and second trimester only) fail, the use of triptans, in particular sumatriptan, in all stages of pregnancy can be considered. None of the triptans are classed as non-teratogenic.

Sumatriptan can be considered for treatment of acute migraine in pregnant women in all stages of pregnancy. The risks associated with use should be discussed before commencing treatment.

There is limited evidence on the safety of use of CGRP monoclonal antibodies during pregnancy and breast feeding. Until further information is available CGRP monoclonal antibodies should not be used during pregnancy or breast feeding. A washout period of 6 months is advised before trying for a pregnancy.

Contraception

Migraine with aura increases the risk of stroke. Combined oral contraception (COC) also increases the risk of stroke. The prescribing of hormonal contraception for women with migraine should follow Faculty of Sexual and Reproductive Healthcare guidance.

Lactation

Topiramate … It should not be used by women who are breastfeeding as it can be present in breast milk.

5.6.3 NICE 2021

Pregnancy

1.3.26 Offer pregnant women paracetamol for the acute treatment of migraine. Consider the use of a triptan or an NSAID after discussing the woman's need for treatment and the risks associated with the use of each medication during pregnancy. [2012]

Trade off between clinical benefits and harms
The GDG noted that many people continue to suffer migraine during pregnancy as they avoid medication due to not being certain of the risks. It was agreed that the evidence reviewed did not indicate an increased risk of the use of triptans during pregnancy and therefore people should be made aware of this to avoid suffering unnecessarily. There is not conclusive evidence of safety, but the evidence is reassuring. High doses of aspirin recommended for migraine are considered

potentially harmful in pregnancy so should be avoided in pregnancy. The GDG agreed that possible risks NSAID during pregnancy are known and their use should be avoided during the third trimester.

Quality of evidence
The evidence reviewed was very low quality evidence. The use of NSAID was not reviewed as the GDG agreed this was already established.

Other considerations
The reviewed evidence was in people with mild to moderate migraine only. The relative contraindications depending on the stage of pregnancy should be considered when prescribing acute treatments. There is some evidence that migraine often resolves during pregnancy (in 70% of people) which may reduce the need for acute treatment in many people.

1.3.27 Seek specialist advice if prophylactic treatment for migraine is needed during pregnancy. [2012]

Trade off between clinical benefits and harms
The GDG agreed that some people may require prophylaxis during pregnancy, in the absence of evidence for safety of recommended prophylactic treatment during pregnancy, a specialist should be consulted.

Quality of evidence
This recommendation was based on GDG consensus.

Other considerations
The GDG considered that if prophylaxis was required, specialist advice should be obtained so that women could receive treatment during their pregnancy. This could be advice over the telephone, to avoid any delay in prescribing treatment that would be associated with referral.

<u>Contraception</u>
1.3.24 Do not routinely offer combined hormonal contraceptives for contraception to women and girls who have migraine with aura. [2012]

Trade off between clinical benefits and harms
There is an increased risk of ischaemic stroke in people with migraine with aura. This is multiplied in people using combined hormonal contraception.

Quality of evidence
This recommendation was based on the consensus opinion of the GDG. There was limited evidence from this review regarding the use of hormonal contraception in women with migraine. The population in one study 34 consisted of over 70% of people with migraine with aura which is a greater proportion of people with aura than in the migraine population. No economic evidence was found on this question.

Other considerations

The GDG used expert advice and informal consensus to inform the development of this recommendation. The GDG agreed that although the evidence available was of low quality, and the absolute numbers of people affected is low, the potentially devastating effect of a stroke in a young woman should be avoided if possible. Given that there are many other forms of contraception now available the GDG considered the use of combined hormonal contraception is not justified in this group. The combined oral contraceptive pill can used for other medical reasons, for example, to manage conditions such as polycystic ovarian syndrome. The balance of risks and benefits are likely to be different than for a woman using the combined hormonal contraception for contraception alone and this balance would need consideration between healthcare professional and patient. This recommendation is therefore specific to contraception. The current advice from the WHO in Medical Eligibility criteria forcontraceptive use recommends that oral contraceptive pill should not be used in women with aura at any age. The UK eligibility criteria for contraceptive (UKMEC) use recommends that the use of combined hormonal contraceptive methods represents an unacceptable risk for women with aura; and that if a person has not had any migraine with aura for more than 5 years the risk generally outweigh the benefits. The UK Faculty of Sexual and Reproductive Health (www.fsrh.org/) in recent guidance on use of combined hormonal contraception re-iterates the UKMEC advice that the use of combined hormonal contraception presents an unacceptable risk in women with migraine with aura. The GDG were aware that the recommendation could be viewed as potentially restrictive in that the ICHD criteria indicate that two attacks of migraine with aura are required for an ICHD diagnosis of migraine with aura disorder and this guideline is recommending a less strict definition for the generalist. The GDG considered that the wording of the recommendation allowed the healthcare professional to use clinical judgement or call on expert advice if needed.

5.6.4 NHG 2021

Aanvalsbehandeling tijdens de zwangerschap

- Paracetamol kan veilig worden gebruikt tijdens de zwangerschap.
- Adviseer NSAID's alleen voor incidenteel gebruik en in zo laag mogelijke dosering tijdens het eerste en tweede trimester van de zwangerschap. Adviseer geen NSAID's in het derde trimester van de zwangerschap.
- Overweeg bij onvoldoende effect incidenteel gebruik van sumatriptan oraal in een zo laag mogelijke dosering. Overige triptanen worden ontraden tijdens de zwangerschap.
- Metoclopramide kan veilig worden gebruikt. Domperidon wordt ontraden tijdens de zwangerschap.

Aanvalsbehandeling tijdens de borstvoedingsperiode

- Paracetamol, NSAID's (voorkeur ibuprofen), domperidon en metoclopramide kunnen veilig worden gebruikt. Domperidon heeft de voorkeur boven metoclopramide.
- Overweeg sumatriptan bij onvoldoende effect hiervan.

Preventieve medicatie bij zwangerschapswens, tijdens de zwangerschap en borstvoedingsperiode

Staak preventieve behandeling bij een zwangerschapswens. Tijdens de zwangerschap nemen de frequentie en ernst van migraine over het algemeen af. Verwijs naar de neuroloog bij ernstige klachten tijdens de zwangerschap en/of lactatie en onvoldoende effect van aanvalsbehandeling.

Anticonceptie
Migraine met aura is, in verband met het verhoogde risico op HVZ, een relatieve contra-indicatie voor combinatiepreparaten, zoals de combinatiepil. Bij vrouwen die roken is sprake van een absolute contra-indicatie.

Migraine zonder aura is geen contra-indicatie voor de combinatiepil. Het is echter onzeker of combinatiepreparaten het risico op HVZ bij vrouwen met migraine zonder aura verder verhogen. Adviseer daarom alle vrouwen met migraine om bij de wens tot anticonceptie een andere anticonceptiemethode te overwegen, zoals een koperspiraal of methoden met alleen progestageen. Zie de NHG-Standaard Anticonceptie.

Hormonale behandeling bij een toename van de aanvalsfrequentie tijdens de menopauze wordt niet aanbevolen.

[Bib. group] Zie ook sectie “specific populations – Migraine associated with menstruation” i.v.m. preventieve behandeling met de combinatiepil en met anticonceptiemethoden met alleen progestagenen.

5.6.5 Eigenbrodt 2021

Women with menstrual migraine.
…Some women with pure menstrual migraine without aura benefit from continuous use (that is, without a break) of combined hormonal contraceptives. By contrast, combined hormonal contraceptives are contraindicated in women with migraine with aura regardless of any association with their menstrual cycle, owing to an associated increase in the risk of stroke.

Pregnant and breastfeeding women.

Migraine often remits during pregnancy, but if treatment is continued, the potential for harm to the fetus demands special consideration. Despite relatively poor efficacy, paracetamol should be used as the first-line medication for acute treatment of migraine in pregnancy; NSAIDs can be used only during the second trimester. Triptans should be used only under the strict supervision of a specialist, as the safety data available are limited and originate from post-marketing surveillance; most data relate to the use of sumatriptan. For nausea associated with migraine in pregnancy, metoclopramide can be used.
Preventive migraine medications are best avoided during pregnancy owing to the potential for fetal harm. However, if preventive therapy is considered clinically indicated because of frequent and disabling migraine attacks, the best available safety data support the use of propranolol or, if propranolol is contraindicated, amitriptyline. Both should be used under specialist supervision to adequately monitor any potential fetal harm. Topiramate, candesartan and sodium valproate are contraindicated; sodium valproate is known to be teratogenic, so must not be used, and the use of topiramate and candesartan is associated with adverse effects on the fetus.

Migraine medication therapy in the post-partum period also requires caution because of potential risks to the infant. Paracetamol is the preferred acute medication, although ibuprofen and sumatriptan are also considered safe. If preventive medication is required, propranolol is the recommended first choice as it has the best safety profile. Pharmacological treatments for migraine during pregnancy and breastfeeding have been reviewed in more detail elsewhere.

Recommendations.
In pregnant or breastfeeding women, use paracetamol for acute treatment and avoid preventive medication whenever possible.

5.6.6 FR 2021

Pregnancy

Table 7 – Recommendations for management of migraine in women desiring pregnancy and during pregnancy.

Recommendations for management of migraine in women desiring pregnancy		Strength of recommendation
Rw1	Explain that migraine can be treated during pregnancy and in case of breastfeeding but self-medication should be formally avoided	Strong
Rw2	Explain that migraine usually improves during pregnancy, notably after the first trimester and in migraine without aura	Strong
Rw3	Explain that migraine does not modify the overall outcome of pregnancy, but is associated with an increased risk of gravid hypertension and preeclampsia	Strong
Rw4	For acute migraine treatment in women desiring pregnancy a. Prescribe paracetamol for mild attacks b. Prescribe triptans for moderate or severe attacks c. Avoid NSAIDs and aspirin (> 500 mg/day) because of the potential risk of early miscarriage	Strong
Rw5	For the prophylaxis of migraine in women desiring a pregnancy a. Stop current prophylactic medication whenever possible b. Contraindicate sodium valproate, topiramate, candesartan, lisinopril, and CGRP-MABs c. When prophylaxis is necessary, propose a non-pharmacological approach (lifestyle changes, exercise, neuromodulation, acupuncture) and/or prescribe amitriptyline, propranolol or metoprolol	Strong
Recommendations for management of migraine during pregnancy		**Strength of recommendation**
Rw6	Plan regular follow-up visits during pregnancy when remission of bothersome attacks was not achieved during the first trimester	Strong
Rw7	For acute treatment of migraine during pregnancy a. Prescribe paracetamol for mild attacks b. Prescribe a triptan for moderate or severe attacks, and after failure of paracetamol. Favor sumatriptan and use rizatriptan or zolmitriptan after failure of sumatriptan c. Contraindicate NSAIDs and aspirin (> 500 mg/day) after 24 weeks of pregnancy, and limit their use before 24 weeks	Strong
Rw8	Regarding migraine prophylaxis during pregnancy a. Encourage lifestyle changes and adapted exercise to each woman b. Propose neuromodulation and acupuncture to women asking for a non-pharmacological approach c. When pharmacological prophylaxis is necessary, prescribe propranolol, metoprolol or amitriptyline (propranolol and amitriptyline can be used during breastfeeding)	Strong
Rw9	In case of bothersome migraine during pregnancy, the patient should be managed both by a neurologist and a gynecologist	Strong

NSAIDs: nonsteroidal anti-inflammatory drugs; CGRP-MABs: calcitonin-gene-related peptide-receptor monoclonal antibodies.

5.1.2. Which medications can be used for acute migraine treatment during pregnancy?
Evidence shows that paracetamol (acetaminophen) and triptans have a good safety profile (level of evidence high). The French reference center for teratogenic agents (CRAT) recommends to favor sumatriptan after failure of paracetamol, and zolmitriptan or rizatriptan after failure of sumatriptan. NSAIDs are contraindicated after 24 weeks of pregnancy due to the risk of premature closure of the ductus arteriosus. NSAIDs exposure close to the conception may increase the risk of miscarriage

(level of evidence fair). Some studies suggested to avoid NSAIDs during the first trimester, but a recent large database study found that the risks of spontaneous abortion and major birth defects did not differ between women exposed and non-exposed to ibuprofen (level of evidence medium).

5.1.3. Which medications can be used for migraine prophylaxis during pregnancy?
Beta-blockers are not associated with an increased risk of malformations (level of evidence high). Amitriptyline may be used and studies suggesting an increased risk of fetal/child adverse events are scarce (level of evidence fair). The French CRAT states that published data about the use of amitriptyline during pregnancy are numerous and reassuring. Neonatal symptoms may rarely appear in the first days of life of newborns when the mother took high doses of amitriptyline until delivery. Symptoms are usually transient and mild (respiratory distress, hyperexcitability, tone disturbances, slowed transit, sedation). A neonatal withdrawal syndrome may also occur and seems to be favored by an abrupt cessation of amitriptyline before childbirth. According to the French CRAT, venlafaxine may be used during pregnancy in women with depression requiring a pharmacological treatment, and may thus be used in women with depression and associated migraine during pregnancy.

5.1.4. Which migraine medications are contraindicated during pregnancy?
Valproic acid is contraindicated because of a significant increased risk of severe fetal malformations as well as of cognitive deficits, mental retardation and autism in children exposed in utero. Topiramate is contraindicated in pregnant women and in those who wish to become pregnant because of an increased risk of severe malformations in fetuses exposed in utero. Candesartan and lisinopril are contraindicated because of fetal renal toxicity. All the ergots are contraindicated. Because of the absence of data, CGRP-MABs should not be used during pregnancy.

Contraception - menopause

Box 1. Management of migraine with aura
…
3. Prevention of stroke
Migraine with aura is associated with an increased risk of ischemic stroke. Educate the patients to prevent cardio-vascular outcomes by encouraging smoking cessation, prescribing progestin-only contraceptive or non-hormonal contraception (see chapter V), regularly assessing blood pressure, and promoting regular exercise.

Box 2. Type of contraception recommended according to the arterial risk factors and type of migraine.

First step: check for arterial risk factors before prescriptions of hormonal contraception

- Age > 35
- Smoking, familial history of stroke or myocardial infarction
- Arterial hypertension
- Dyslipidemia
- Diabetes
- Obesity

Second step: choose contraception according to the arterial risk factors and type of migraine

- Migraine without aura
  - Absence of any arterial risk factor: every hormonal contraception can be used
  - ≥ 1 risk factor: oral combined contraception is contraindicated; progestin-only contraception is possible

- Migraine with aura
  - Oral combined contraception is contraindicated; progestin-only contraception is possible

5.3.1. Does contraception aggravate migraine?

There is no data on the risk of migraine for non-oral contraception and for oral combined hormonal contraception (CHC) containing estradiol. No study is available about the impact of the levonorgestrel intrauterine device on migraine.

5.3.3. What is the impact of menopause and hormonal replacement therapy (HRT) on migraine?

While menopause, especially natural menopause, is frequently associated with an improvement of migraine, perimenopause is often associated with more frequent migraine attacks. The impact of hormone replacement therapy on migraine course is debated.

Table 9 – Recommendations for contraception and HRT prescription in women with migraine.			
Recommendations for contraception in women with migraine		Level of evidence	Strength of the recommendation
Rw14	Before prescribing any hormonal contraception, always screen for migraine, with and without aura, in addition to other arterial risk factors	High	Strong
Rw15	In women with migraine *without* aura a. CHC can be prescribed in the absence of any other arterial risk factor b. When any arterial risk factor is present, contraindicate CHC and propose progestin-only or non-hormonal contraception	High	Strong
Rw16	In women with migraine *with* aura, contraindicate CHC and propose progestin-only or non-hormonal contraception	High	Strong
Recommendations for HRT prescription in women with migraine		Level of evidence	Strength of the recommendation
Rw17	Before any HRT prescription, always screen for migraine with and without aura in addition to other arterial risk factors	High	Strong
Rw18	HRT is not contraindicated in migraine without other vascular risk factor	Medium	Strong
HRT: hormonal replacement therapy; CHC: combined hormonal contraception.			

5.6.7 EUR 2022

Expert consensus statement 7

We suggest avoiding monoclonal antibodies targeting the CGRP pathway in pregnant or nursing women. We suggest caution and decision on a case-by-case basis in the presence of vascular disease or risk factors and Raynaud phenomenon. We suggest caution in erenumab use in individuals with migraine and history of severe constipation. (Expert consensus statements)

Pregnant and nursing women were excluded from RCTs and there is no robust information on the risk for the fetus or the newborn driven by CGRP-mAbs.The limited real-life data available so far have not shown major concerns with the accidental and short-lived exposure to erenumab, galcanezumab, and fremanezumab in pregnancy and lactation. However, caution is needed because experimental data indicate that erenumab crosses the placenta. Concerns in the use of those drugs in women of childbearing potential are related also to the long (around 1 month) half-life of the CGRP-mAbs that implies that these drugs can only be considered as eliminated from the circulation 6 months after stopping.

5.7 Specific populations - Children

5.7.1 Acute pharmacological treatment

5.7.1.1 Summary

Summary

US_treatment 2019 is a guideline for migraine in both children and adolescents. The guideline recommends ibuprofen oral solution (10 mg/kg) as an initial treatment option for children and adolescents. For adolescents sumatriptan/naproxen oral tablet (10/60, 30/180, 85/500 mg), zolmitriptan nasal spray (5 mg), sumatriptan nasal spray (20 mg), rizatriptan oral disintegrating tablet (5 or 10 mg), or almotriptan oral tablet (6.25 or 12.5 mg) are recommended.
Switching between triptans to find most effective agent is recommended. Nonoral drugs are recommended when headaches peak in severity quickly, is accompanied by nausea or vomiting, or oral formulations fail to provide pain relief.
After failure of triptans in adolescents, ibuprofen or naproxen in addition to a triptan is recommended. Triptans are safe for adolescents during a typical aura, but triptans may be more effective if taken at the onset of a headache. Triptans are not recommended in patients with a history of ischemic vascular disease or accessory conduction pathway disorders.
Antiemetics are recommended for children and adolescents who experience prominent nausea or vomiting; nasal spray formulations of zolmitriptan and sumatriptan may be easier in these patients.

The recommendations from SIGN 2022 and NICE 2021 also apply to adolescents besides adults. NICE 2021 recommends to consider a nasal triptan in preference to an oral triptan for young people aged 12 to 17. Because of the association with Reye's syndrome, preparations containing aspirin should not be offered to under 16s.

NHG 2021 recommends paracetamol as a first step at the onset of migraine in children. After failure of paracetamol, ibuprofen is recommended as a second step. Other NSAID and aspirin are not recommended for children. Combinations of paracetamol with ibuprofen are not recommended.
After failure of paracetamol or ibuprofen, triptans are recommended as third step. For age <12 years, referral to a (pediatric) neurologist or pediatrician is recommended. For age ≥ 12 years, consider sumatriptan nasas spray or oral rizatriptan. Triptans are recommended at the onset of

migraine. They are not recommended at the start of aura or in the prodromal phase. In the absence of an effect, a second dose of a triptan is not useful. If there is a response, a second dose of sumatriptan is allowed after 2 hours. A second dose of rizatriptan is not useful.
For age <12 year or <35 kg, do not prescribe antiemetics such as metoclopramide, domperidone and ondansetron because of extrapyramidal side effects and the lack of evidence in migraine. For age ≥12 year or ≥35 kg, consider domperidone besides paracetamol or NSAID for severe nausea and/or vomiting. Prescribe domperidone as briefly as possible and in the lowest possible dosage.

Eigenbrodt 2021 states that in children and adolescents with migraine, bed rest alone might suffice. If not, ibuprofen at a dose appropriate for body weight is recommended for acute treatment. The guideline does not provide formal recommendations for triptans but mentions that benefit of triptans has not been demonstrated in children, probably due a high placebo response in clinical trials. Furthermore, they mention that for adolescents (12-17 years) some evidence indicates that nasal spray formulations of sumatriptan and zolmitriptan are the most effective Domperidone can be used for nausea in adolescents aged 12–17 years, although oral administration is unlikely to prevent vomiting.

5.7.1.2 US_treatment 2019

Treatments

The authors included RCTs on the acute pharmacologic treatment of migraine in children (individuals younger than 12 years) and adolescents (individuals aged 12–17 years).

Table 3 Confidence in evidence by drug and outcome

	Pain response at 30 minutes	Pain response at 1 hour	Pain response at 2 hours	Pain-free at 1 hour	Pain-free at 2 hours	Relief of nausea at 2 hours	Relief of vomiting at 2 hours	Relief of photophobia at 2 hours	Relief of phonophobia at 2 hours
Ibuprofen OS 7.5–10 mg/kg			Low		Moderate	Very low			
Acetaminophen OS 15 mg/kg			Low		Very low				
Sumatriptan OT 25 mg	Very low	Very low	Very low		Very low				
Sumatriptan OT 50 mg	Very low	Very low	Very low		Very low				
Sumatriptan NS 5 mg	Very low	Moderate: probably no more likely than placebo	Very low			Moderate: probably no more likely than placebo	Moderate: probably no more likely than placebo	Very low	Low
Sumatriptan NS 10 mg		Low	Very low			Very low	Low: possibly no more likely than placebo	Very low	Very low
Sumatriptan NS 20 mg	Low	Low	Low		Moderate	Moderate: probably no more likely than placebo	Moderate: probably no more likely than placebo	Very low	Low
Sumatriptan/ naproxen OT 10/ 60 mg					High	Very low		Moderate	Moderate
Sumatriptan/ naproxen OT 30/ 180 mg					High	Very low		Very low	Low
Sumatriptan/ naproxen OT 85/ 500 mg					High	Moderate: probably no more likely than placebo		Moderate	Moderate
Rizatriptan ODT 5 or 10 mg			Moderate: probably no more likely than placebo		Low	Very low	Low: possibly no more likely than placebo	Very low	Moderate: probably no more likely than placebo
Eletriptan OT 40 mg			Low: possibly no more likely than placebo		Very low	Low: possibly no more likely than placebo		Low: possibly no more likely than placebo	Low: possibly no more likely than placebo
Zolmitriptan NS		Low	Low	Moderate	High			Low	Very low
Almotriptan OT 6.25 mg			Low		Very low				
Almotriptan OT 12.5 mg			Low		Low: possibly no more likely than placebo				
Almotriptan OT 25 mg			Very low		Very low				

Abbreviations: NS = nasal spray; ODT = oral disintegrating tablet; OS = oral solution; OT = oral tablet.

Acute migraine treatment

Abbreviations: NS = nasal spray; ODT = oral disintegrating tablet; OS = oral solution; OT = oral tablet;

Statement 2a
Clinicians should counsel that acute migraine treatments are more likely to be effective when used earlier in the migraine attack, when pain is still mild. (Level B)

Statement 2b
Clinicians should prescribe ibuprofen OS (10 mg/kg) as an initial treatment option to reduce pain in children and adolescents with migraine. (Level B)

Statement 2c
For adolescents with migraine, clinicians should prescribe sumatriptan/naproxen OT (10/60, 30/180, 85/500 mg), zolmitriptan NS (5 mg), sumatriptan NS (20 mg), rizatriptan ODT (5 or 10 mg), or almotriptan OT (6.25 or 12.5 mg) to reduce headache pain. (Level B)

Recommendation 2 rationale
In adults, early treatment of migraine (within less than 1 hour of headache onset) improves pain-free rates. Improved efficacy with early treatment is likely to be seen in children and adolescents as well. Many children and adolescents use and benefit from nonprescription oral analgesics like acetaminophen, ibuprofen, and naproxen. Triptans are less commonly prescribed in children than in adults, and only almotriptan (for patients aged 12 years and older), rizatriptan (for patients aged 6–17 years), sumatriptan/naproxen (for patients aged 12 years and older), and zolmitriptan NS (for patients aged 12 years and older) are approved by the Food and Drug Administration (FDA) for use in children. Ergots and oral naproxen alone have not been studied in children.

Statement 3a
Clinicians should counsel patients and families that a series of medications may need to be used to find treatments that most benefit the patient. (Level B)

Statement 3b
Clinicians should instruct patients and families to use the medication that best treats the characteristics of each migraine to provide the best balance of efficacy, side effects, and patient preference. (Level B)

Statement 3c
Clinicians should offer an alternate triptan, if 1 triptan fails to provide pain relief, to find the most effective agent to reduce migraine symptoms. (Level B)

Statement 3d
Clinicians may prescribe a nonoral route when headache peaks in severity quickly, is accompanied by nausea or vomiting, or oral formulations fail to provide pain relief. (Level C)

Statement 3e
Clinicians should counsel patients and families that if their headache is successfully treated by their acute migraine medication but headache recurs within 24 hours of their initial treatment, taking a second dose of acute migraine medication can treat the recurrent headache. (Level B)

Recommendation 3 rationale

… Migraine features (severity, associated symptoms, disability, and most bothersome symptoms) differ among individuals and among different attacks in the same individual. Intranasal sumatriptan and zolmitriptan are absorbed more quickly than the oral form and have a faster onset of action. For migraines that rapidly peak in severity or are associated with nausea and vomiting, nonoral forms of treatment may be more effective. Thus, children with migraine may benefit from more than 1 acute treatment choice and different delivery routes, depending on their individual headache characteristics.

Statement 4

In adolescents whose migraine is incompletely responsive to a triptan, clinicians should offer ibuprofen or naproxen in addition to a triptan to improve migraine relief. (Level B)

Recommendation 4 rationale

Sumatriptan/naproxen OT (10/60, 30/180, and 85/500 mg) is more likely than placebo to result in headache pain-free status at 2 hours. Sumatriptan and naproxen have different pharmacokinetic profiles targeted to aid in migraine relief.

Given the distinct mechanisms of action among medications in the triptan class
and the nonsteroidal anti-inflammatory drug (NSAID) class, the addition of an NSAID to a triptan may improve rates of pain response and pain-free status.

<u>Treatment of associated symptoms</u>

Statement 5

For children and adolescents with migraine who experience prominent nausea or vomiting, clinicians should offer additional antiemetic treatments. (Level B)

Recommendation 5 rationale

In pediatric migraine trials, the treatment effects on migraine-associated symptoms were less pronounced than the treatment effects on pain. While photophobia and phonophobia were responsive to zolmitriptan NS and sumatriptan/naproxen, none of the treatments studied had demonstrated effectiveness against nausea or vomiting.

Antiemetics are available to treat nausea and vomiting related to other pediatric conditions (acute gastroenteritis, postoperative state, chemotherapy) and may be of benefit for migraine-associated nausea, although no clinical trials specifically evaluating antiemetics for pediatric migrain-associated nausea have been performed.

NS formulations of zolmitriptan and sumatriptan may be easier to administer in adolescents with migraine with prominent nausea or vomiting.

<u>Contraindications and precautions to triptan use</u>

Statement 7

Clinicians must not prescribe triptans to those with a history of ischemic vascular disease or accessory conduction pathway disorders to avoid the morbidity and mortality associated with aggravating these conditions. (Level A)

Recommendation 7 rationale
According to the FDA, triptans are contraindicated in patients with a history of cardiovascular disease, including stroke, TIA, myocardial infarction, severe peripheral vascular disease, ischemic bowel disease, and coronary vasospasm, including Prinzmetal angina. Triptans are also contraindicated in patients with cardiac accessory conduction pathway disorders, including Wolff-Parkinson-White syndrome. Although the 2004 American Headache Society consensus statement does not consider these as absolute contraindications, these contraindications are based on the known pharmacology of the triptans and triptan effects on vascular muscle. While these medical contraindications are less prevalent in the pediatric population, they are important to consider.

Statement 8a
Clinicians should counsel adolescent patients with migraine with aura that taking their triptan during a typical aura is safe, but that the triptan may be more effective if taken at the onset of head pain (Level B).

Statement 8b
Clinicians may consider referral of children and adolescents with hemiplegic migraine or migraine with brainstem aura who do not respond to other treatments to a headache specialist to find effective treatment (Level C).

Recommendation 8 rationale
In adults who have migraine with typical aura, there is evidence that it is safe to take triptans during the aura, although the triptan may be more effective if taken at the onset of pain. The use of triptans during the aura phase is of concern because of potential difficulties differentiating early stroke symptoms from migraine aura. While this is unlikely a problem in those with established migraine with visual aura, caution is warranted in those with more complex aura presentations. According to the FDA, triptans are contraindicated in those with a history of hemiplegic aura or migraine with brainstem aura. This contraindication was based on a view of migraine pathophysiology that is no longer considered current.

5.7.1.3 SIGN 2022

Studies of children with migraine were not included, however the recommendations could be considered for treating adolescents with migraine.

5.7.1.4 NICE 2021

The guideline is, besides adults, applicable for young people (12 years and older).

1.3.10 Offer combination therapy with an oral triptan and an NSAID, or an oral triptan and paracetamol, for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of adverse events. For young people aged 12 to 17 years consider a nasal triptan in preference to an oral triptan. [2012]

1.3.11 For people who prefer to take only one drug, consider monotherapy with an oral triptan, NSAID, aspirin (900 mg) or paracetamol for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of adverse events. [2012]

Because of the association with Reye's syndrome, preparations containing aspirin should not be offered to under 16s.

Quality of evidence
The direct evidence is of moderate to very low quality. Only one study of triptan use included people less than 18 years. Network meta-analysis of the evidence shows moderate efficacy for these treatments. All evidence is from oral administered drugs and is for the NSAIDs at 400mg minimum, aspirin at 900mg minimum and paracetamol at 1000mg.

Other considerations
The GDG agreed that there is evidence that compliance may be better with single administrations than dual administration of treatment. Patient preference and experience should inform the decision of which treatment to prescribe. The GDG considered the use of triptans for the 12-17 age groups and agreed that triptans were an appropriate option for younger people. Oral triptans are not licensed for use in people aged under 18 but sumatriptan is licensed to use as a nasal spray in the under 18 age group. GDG consensus opinion was that failure to respond to a particular triptan may not be indicative that another triptan will also not work, therefore it may be worth considering an alternative triptan if there's no response to the first one. Studies for aspirin were either 500mg or 1000mg, these were pooled for analysis. GDG consensus opinion was that the higher doses are more effective, therefore agreed to recommend 900mg.

5.7.1.5 NHG 2021

Migraine bij kinderen

Voorlichting
- Bij korte aanvallen volstaat uitleg aan de omgeving en het advies om het kind even met rust te laten.
- Voor de effectiviteit van andere niet-medicamenteuze behandelingen is weinig bewijs.
- Richt het beleid vooral op het leren omgaan met de pijnaanvallen:
    - Het is van belang dat de omgeving rekening houdt met het kind bij een migraineaanval.
    - Adviseer de ouders bij doorgaans kortdurende aanvallen de school te vragen of het kind bij een aanval even in een aparte kamer kan liggen zodat het na een korte aanval weer verder kan met de lessen.

Slaapritme
Een verstoord slaapritme kan leiden tot een migraineaanval; het is belangrijk dit slaapritme te herstellen. Zie NHG-Standaard Slaapproblemen en slaapmiddelen.

De medicamenteuze behandeling bestaat uit:

- aanvalsbehandeling met paracetamol, ibuprofen of triptanen
- preventieve behandeling (zelden)

Aanvalsbehandeling

- Bij weinig frequente migraineaanvallen volstaat meestal paracetamol; bij onvoldoende effect kan ibuprofen worden voorgeschreven.
- Adviseer de pijnmedicatie in te nemen bij de start van de hoofdpijn, voordat de aanval op zijn maximum is; dan is er meer kans op bekorting van de aanval.
- Wijs op de noodzaak van een voldoende hoge dosering, afhankelijk van lichaamsgewicht (zie tabel 19 en NHG-Standaard Pijn).
- Geef bij frequente migraine in combinatie met spanningshoofdpijn alleen pijnmedicatie voor de migraine en niet voor de spanningshoofdpijn, om MOH te voorkomen.
- Verwijs bij onvoldoende effect van paracetamol of ibuprofen bij kinderen < 12 jaar naar een (kinder)neuroloog of kinderarts voor diagnostiek en het eventueel instellen op triptanen.
- Overweeg bij onvoldoende effect van paracetamol of ibuprofen bij kinderen ≥ 12 jaar sumatriptan neusspray of rizatriptan oraal (offlabel) indien de diagnose migraine voldoende duidelijk is.

Medicamenteus stappenplan aanvalsbehandeling

Stap 1 Paracetamol

- Adviseer paracetamol in adequate dosering en adviseer de paracetamol in te nemen bij het begin van de hoofdpijn.
- Waarschuw de patiënt (of de ouders) dat gebruik van paracetamol ≥ 15 dagen per maand (ongeacht de dosering) MOH kan veroorzaken.

Stap 2 Ibuprofen

- Adviseer bij onvoldoende effect van paracetamol ibuprofen in te nemen.
- Schrijf geen acetylsalicylzuur of andere NSAID's voor aan kinderen (zie NHG-Standaard Pijn).
- Combineer paracetamol niet met ibuprofen.
- Waarschuw de patiënt (of de ouders) dat gebruik van ibuprofen (≥ 15 dagen per maand) MOH kan veroorzaken.

Stap 3 Triptanen

- Leeftijd < 12 jaar: verwijs bij onvoldoende effect van paracetamol of ibuprofen naar een (kinder)neuroloog of kinderarts voor diagnostiek en het eventueel instellen op triptanen.
- Leeftijd ≥ 12 jaar: overweeg sumatriptan neusspray of rizatriptan oraal (offlabel) indien de diagnose migraine voldoende duidelijk is.
    - Adviseer het triptaan te gebruiken bij het begin van de hoofdpijn (en de patiënt de hoofdpijn herkent als migraine). Het is niet zinvol om een triptaan in te nemen bij het begin van een eventueel aura of in de prodromale fase.

- Indien het triptaan geen effect heeft, is het niet zinvol om een tweede dosis in te nemen. Indien er wel respons is, mag de dosis sumatriptan worden herhaald na minimaal 2 uur na laatste toediening. Dit is niet zinvol bij rizatriptan.
- Sumatriptan neusspray kan een bittere smaak in de mond geven. Dit is te voorkomen door het hoofd licht voorover te houden bij het sprayen en de neus niet op te trekken na het sprayen.

Anti-emetica

- Leeftijd < 12 jaar of < 35 kg: schrijf geen anti-emetica, zoals metoclopramide, domperidon en ondansetron, voor vanwege de extrapiramidale bijwerkingen die met name op jonge leeftijd voorkomen. Daarnaast is er gebrek aan bewijs voor effectiviteit bij migraine.
- Leeftijd ≥ 12 jaar en ≥ 35 kg: overweeg bij migraine met hevige misselijkheid en/of braken domperidon voor te schrijven naast paracetamol of NSAID. Schrijf domperidon zo kort mogelijk en in een zo laag mogelijke dosering voor.

Tabel 19. Overzicht geneesmiddelen aanvalsbehandeling migraine bij kinderen

Middel	Startdosering	Maximale dosering per 24 uur bij incidenteel gebruik	Contra-indicaties	Bijwerkingen
Paracetamol	Zie NHG-Standaard Pijn			
Ibuprofen	Zie NHG-Standaard Pijn			
Triptanen				
Sumatriptan neusspray	≥ 12 jaar, gewicht < 40 kg: 10 mg	20 mg	Zie tabel 17	• epistaxis, bittere smaak, beïnvloeding van de smaak (neusspray) • misselijkheid • braken • moeheid • sufheid/slaperigheid • duizeligheid • coronaire vaatspasmen, drukkend gevoel op de borst • tintelingen, paraesthesieën en warmte-sensaties
	≥ 12 jaar, gewicht ≥ 40 kg: 20 mg	40 mg		
Rizatriptan (smelt)tablet (offlabel)	≥ 12 jaar, gewicht < 40 kg: 5 mg	5 mg		
	≥ 12 jaar, gewicht ≥ 40 kg: 10 mg	10 mg		
Anti-emetica				
Domperidon Tablet (offlabel)	≥ 12 jaar gewicht ≥ 35 kg: 10 mg	30 mg	• verlengde QT-tijd • hartritmestoornissen • leverfunctie-stoornissen • bekende elektrolyt-stoornissen (hyperkaliëmie, hypomagnesiëmie)	• droge mond • hartritmestoornissen (zelden) • extrapiramidale verschijnselen (soms)

5.7.1.6 Eigenbrodt 2021

Children and adolescents.
Migraine is common among children and its prevalence increases in adolescence. As in adults, diagnosis is primarily based on the medical history, although the criteria are slightly different — the duration of migraine attacks can be 2 to 72 h. The clinical features of migraine in children and adolescents also differ somewhat from those in adults — the attacks are often shorter, the headache is more often bilateral and less often pulsating, and gastrointestinal disturbances are commonly prominent. Descriptions of these features might be more reliably provided by parents than children, and parents will also provide a better account of lifestyle factors that might need to be addressed. In children and young adolescents, clinical management usually requires active help from family members and teachers, so education of both is necessary. Bed-rest alone might suffice in children with attacks that have a short duration. When needed, ibuprofen is recommended as first-line medication, at a dose appropriate for body weight. Domperidone can be used for nausea in adolescents aged 12–17 years, although oral administration is unlikely to prevent vomiting. The evidence base for medication therapy in children and adolescents is confounded by a high placebo response in clinical trials. As a consequence, the apparent therapeutic gain is low, and this effect probably explains why a benefit of triptans has not been demonstrated in children. For adolescents aged 12–17 years, multiple NSAIDs and triptans have been approved for acute treatment of migraine, and some evidence indicates that nasal spray formulations of sumatriptan and zolmitriptan are the most effective. If acute medication provides insufficient pain relief, referral to specialist care is indicated. In practice, propranolol, amitriptyline and topiramate are used for preventive treatment, although their effectiveness in children and adolescents has not been proven in clinical trials.

Recommendations.
In children and adolescents with migraine, bed rest alone might suffice; if not, use ibuprofen for acute treatment and propranolol, amitriptyline or topiramate for prevention.

5.7.1.7 FR 2021

No recommendations were provided.

5.7.2 Pharmacological prevention

5.7.2.1 Summary

Summary

Besides adults, the recommendations from SIGN 2022 and NICE 2021 also apply to adolescents.

The guidelines emphasize the lack of evidence for preventive treatment in children and the need to refer to specialist care.

US_prevention_2019 recommends to discuss the high placebo response in clinical trials and that the majority of preventive drugs were not superior to placebo in children and adolescents. Acknowledging the limitations of currently available evidence, shared decision making is required for short-term treatment trials (minimum 2 months) with preventive drugs. It is recommended to discuss the evidence for amitriptyline combined with cognitive behavioural therapy, topiramate, and propranolol for migraine prevention in this population. This includes the potential side effects of amitriptyline such as risk of suicide and the side effects of topiramate and propranolol in children and adolescents.
US_prevention_2019 also provides recommendations regarding counselling for patients of child bearing potential. It is recommended to consider the teratogenic effect of topiramate and valproate and to counsel the patients who are offered these drugs about potential effects on fetal-childhood development. Counsel these patients about the potential of decreased efficacy of oral combined hormonal contraceptives in combination with topiramate, particularly at doses over 200 mg daily. When topiramate or valproate are prescribed, discuss optimal contraception methods with their health care provider during treatment. Daily folic acid supplementation to patients of childbearing potential who take topiramate or valproate is recommended.

NHG 2021 states that efficacy of preventive treatment in children is uncertain and that propranolol, candesartan and flunarizine are used in the secondary care. Consider referral for preventive treatment to a specialist in case of high frequency of attacks (≥2 per month), prolonged attacks, ineffective acute treatment, or frequent school absence.

Eigenbrodt 2021 recommends referral to specialist care if acute medication provides insufficient pain relief. They state that propranolol, amitriptyline and topiramate are used in practice for preventive treatment.

5.7.2.2 US_prevention 2019

Table 1.—Outcomes and Confidence in Evidence

Outcome	High confidence (more likely than placebo)	Moderate confidence (probably more likely than placebo)	Low confidence (possibly more likely than placebo)	Moderate confidence (probably no more likely than placebo)	Low confidence (possibly no more likely than placebo)	Very low confidence (insufficient evidence)
Decreased frequency of migraine or headache days	amitriptyline (1 mg/kg/d) combined with CBT	topiramate (100 mg/d or 2–3 mg/kg/d)				DVPX ER (250 mg/d, 500 mg/d, or 1,000 mg/d) amitriptyline (1 mg/kg/d) flunarizine (5 mg/d) nimodipine (10–20 mg, three times a day) onabotulinumtoxinA (74 U IM or 155 U IM)
Decreased headache severity		cinnarizine (1.5 mg/kg/d if <30 kg or 50 mg/d if >30 kg) cinnarizine (1.5 mg/kg/d if <30 kg or 50 mg/d if >30 kg)				
At least a 50% reduction in headache frequency	amitriptyline (1 mg/kg/d) combined with CBT		propranolol (20–40 mg, three times a day) cinnarizine (1.5 mg/kg/d if <30 kg or 50 mg/d if >30 kg)			topiramate (100 mg/day or 2–3 mg/kg/d) DVPX ER (250 mg/d, 500 mg/d, or 1,000 mg/d) amitriptyline (1 mg/kg/d) onabotulinumtoxinA (74 U IM or 155 U IM)
Decreased migraine-related disability		amitriptyline (1mg/kg/d) combined with CBT			topiramate (100 mg/day or 2–3 mg/kg/d)	amitriptyline (1 mg/kg/d)

Abbreviations: CBT=cognitive behavioral therapy, DVPX ER=extended-release divalproex sodium, IM=intramuscularly.

Starting preventive treatment

Statement 3a

Clinicians should inform patients and caregivers that in clinical trials of preventive treatments for pediatric migraine many children and adolescents who received placebo improved and the majority of preventive medications were not superior to placebo. (Level B)

Statement 3b

Acknowledging the limitations of currently available evidence, clinicians should engage in shared decision making regarding the use of short-term treatment trials (a minimum of 2 months) for those who could benefit from preventive treatment. (Level B)

Statement 3c

Clinicians should discuss the evidence for amitriptyline combined with CBT for migraine prevention, inform them of the potential side effects of amitriptyline including risk of suicide, and work with families to identify providers who can offer this type of treatment. (Level B)

Statement 3d

Clinicians should discuss the evidence for topiramate for migraine prevention in children and adolescents and its side effects in this population. (Level B)

Statement 3e

Clinicians should discuss the evidence for propranolol for migraine prevention and its side effects in children and adolescents. (Level B)

Recommendation 3 rationale

The majority of randomized controlled trials that studied the efficacy of preventive medications for pediatric migraine fail to demonstrate superiority to placebo. Pediatric migraine trial results

demonstrated a high response to placebo, with 30% to 61% of children who received placebo having had a 50% or greater reduction in headache frequency. Children and adolescents with migraine receiving topiramate are probably more likely than those receiving placebo to have a decrease in headache days and migraine attacks; however, there is insufficient evidence to determine whether children with migraine who are receiving topiramate are more or less likely than those receiving placebo to have at least a 50% reduction in migraine frequency or headache days, and this is also the case for reduction in migraine-related disability. Children who receive propranolol are possibly more likely than those who receive placebo to have more than a 50% reduction in headache frequency. Patients receiving amitriptyline combined with CBT as compared with those treated with amitriptyline who receive headache education are more likely to experience a decreased headache frequency and have more than a 50% reduction in headache frequency and are probably more likely to have decreased migraine-associated disability. There is insufficient evidence to judge the independent effectiveness of amitriptyline on migraine prevention in children and adolescents. A Food and Drug Administration (FDA) black box warning regarding risk of suicidal thoughts and behavior with amitriptyline use especially in children, adolescents, and young adults is in effect at the time of this guideline. It is possible that CBT alone is effective in migraine prevention, and individual barriers to access may exist. There is insufficient evidence to evaluate the effects of flunarizine, nimodipine, valproate, and onabotulinumtoxinA for use in migraine prevention in children and adolescents. Although there is evidence that cinnarizine is probably more effective than placebo for migraine prevention, this medication is not available in the United States or Canada.

Counseling for patients of child bearing potential

Statement 4a
Clinicians must consider the teratogenic effect of topiramate and valproate in their choice of migraine prevention therapy recommendations to patients of childbearing potential. (Level A)

Statement 4b
Clinicians who offer topiramate or valproate for migraine prevention to patients of childbearing potential must counsel these patients about potential effects on fetal-childhood development. (Level A)

Statement 4c
Clinicians who prescribe topiramate for migraine prevention to patients of childbearing potential must counsel these patients about the potential of this medication to decrease the efficacy of oral combined hormonal contraceptives, particularly at doses over 200 mg daily. (Level A)

Statement 4d
Clinicians who prescribe topiramate or valproate for migraine prevention to patients of childbearing potential should counsel patients to discuss optimal contraception methods with their health care provider during treatment. (Level B)

Statement 4e
Clinicians must recommend daily folic acid supplementation to patients of childbearing potential who take topiramate or valproate. (Level A)

Recommendation 4 rationale

Balancing benefit and risk is important when deciding among available medical treatments. Topiramate and valproate have well-demonstrated teratogenic effects, especially when used in polytherapy. Valproate use during pregnancy is also associated with developmental disorders in offspring. An FDA black box warning regarding fetal risk from valproate use exists as of the time of this guideline. Topiramate at a daily dose of 200 mg or less does not interact with oral combined hormonal contraceptives; however, at higher doses it can have drug interactions that decrease their effectiveness. The risk of major congenital malformation in offspring of women with epilepsy taking anticonvulsants is possibly decreased by folic acid supplementation.

5.7.2.3 SIGN 2022

Studies of children with migraine were not included, however the recommendations could be considered for treating adolescents with migraine.

5.7.2.4 NICE 2021

The guideline is, besides adults, applicable for young people (12 years and older).

5.7.2.5 NHG 2021

Preventieve behandeling

- Het effect van preventieve behandeling van migraine bij kinderen is onzeker. In de tweede lijn worden propranolol, candesartan en flunarizine toegepast.
- Overweeg verwijzing voor preventieve behandeling naar een (kinder)neuroloog of kinderarts met expertise op het gebied van hoofdpijn bij kinderen in geval van:
    - hoge aanvalsfrequentie (≥ 2 per maand)
    - langdurige aanvallen
    - ineffectieve aanvalsbehandeling
    - veel (school)verzuim

5.7.2.6 Eigenbrodt 2021

… (see section “Acute pharmcological treatment”)
If acute medication provides insufficient pain relief, referral to specialist care is indicated. In practice, propranolol, amitriptyline and topiramate are used for preventive treatment, although their effectiveness in children and adolescents has not been proven in clinical trials.

Recommendations.
In children and adolescents with migraine, bed rest alone might suffice; if not, use ibuprofen for acute treatment and propranolol, amitriptyline or topiramate for prevention.

5.7.2.7 FR 2021

No recommendations were provided.

5.8 Follow-up of treatment

5.8.1 Adults

5.8.1.1 Summary

Summary

SIGN 2022 provides a checklist for provision of information to patients. They discuss items to consider when consulting the GP at the initial consultation, at first follow-up after 2-8 weeks, at a follow-up review after 6-8 weeks and further follow-ups.

For medication-overuse headache: see section “medication-overuse headache”.

Eigenbrodt 2021 states that primary care should be responsible for the long-term management of patients with migraine, maintaining stability and reacting to change. Referral from specialist back to primary care should be timely and accompanied by a comprehensive treatment plan. The patient can be referred back to primary care once sustained efficacy with preventive therapy for up to 6 months is obtained with no substantial treatment-related adverse effects.

<u>Acute pharmacological treatment</u>
Some found information in the recommendations regarding the timing of treatment are the following.
SIGN 2022 states that acute treatment is given once, with the option of repeating after two hours (with the same or different treatment) if there is an inadequate response.
NHG 2021 recommends, if necessary, repeating ibuprofen for persistent or recurrent pain after 6 hours and naproxen after 12 hours. If a triptan is effective but the headache returns, another tablet can be administered after two hours or opt for a combination therapy. Consider combination therapy (triptan + NSAID) as initial treatment in patients in who a triptan initially was effective but the migraine returned within 24 hours.
Eigenbrodt 2021 states that upon relapse (return of symptoms within 48 h) after apparently successful treatment with triptans, patients can repeat their triptan treatment or combine the triptan with simultaneous intake of fast-acting formulations of naproxen sodium, ibuprofen lysine or diclofenac potassium.
FR 2021 recommends NSAID for a mild headache and the addition of a triptan is recommended in case of insufficient response after one hour. For moderate or severe headache a triptan is

recommended and the addition of a NSAID is recommended in case of insufficient response after one hour.

Guidelines recommend to evaluate the effectiveness of acute treatment after 2-3 attacks. When treatment is considered effective, NHG 2021 recommends to check once a year.

Eigenbrodt 2021 and FR 2021 recommend The Migraine Treatment Questionnaire (mTOQ) at each visit to assess acute treatment. Eigenbrodt 2021 also recommends the eight-item HURT questionnaire (Headache Under-Response to Treatment) to assess the effectiveness of an intervention. This tool also generates suggestions for changes to improve effectiveness. Other guidelines recommend the use of headache diaries but do not specify which tools.

FR 2021 provides recommendations regarding the diagnosis of resistance to NSAID or triptans. Resistance to NSAID is diagnosed only after complete inefficacy of at least two NSAID, used with adequate dose and route, each tested on at least three distinct attacks. The same recommendation applies for triptans. Other guidelines recommend to switch between NSAID or between triptans, but do not set a limit on how many times you can switch before diagnosis of resistance. Eigenbrodt 2021 points out that a conclusion that treatment has failed should be made with caution and must always be preceded by a thorough review of the underlying reasons. In some cases, apparent failures might be remediable.

<u>Pharmacological prevention</u>

SIGN 2022 mentions that prophylactic treatment should be used for at least three months at the maximum tolerated dose before deciding if it is effective or not. In many patients prophylactic medication can be successfully phased out again and the need for ongoing prophylaxis should be considered after six to 12 months.

NHG 2021 recommends to follow-up preventive treatment after 2 weeks. Check for side effects and assess blood pressure en heart rate when using candesartan or a beta blockers. Furthermore, determine eGFR 2 weeks after candesartan was started.
For all prophylactic treatments, the guideline recommends to evaluate efficacy after at least 3 months of use.
The authors recommend to taper beta blockers, candesartan or amitriptyline at maximum dose after 3 months in case of insufficient efficacy (see section “pharmacological prevention”). In case

of insufficient efficacy, taper beta blockers or candesartan in 14 days (one week half dose, then one week quarter dose). In case of good efficacy, taper beta blockers or candesartan in 14 days (one week half dose, then one week quarter dose) on a trial basis after 6-12 months. In case of insufficient efficacy, taper amitriptyline after 3 months in 2-4 weeks (halve the dose each 1-2 weeks). In case of good efficacy after 6-12 months, taper amitriptyline on a trial basis in 2-4 weeks weeks (halve the dose each 1-2 weeks).
The frequency of follow-up is determined based on effectiveness, the need for dose increases and adverse events. In case of good efficacy, continue treatment for 6 to 12 months. After this, taper treatment on a trial basis and restart treatment if symptoms increase. Check once a year, in case of continuous treatment.

Eigenbrodt 2021 recommends to evaluate treatment responses shortly after initiation (after 2–3 months) or a change of treatment and regularly thereafter (every 6–12 months).
Eigenbrodt 2021 states that if a therapeutic dose of an oral preventive medication is ineffective after 2–3 months, an alternative should be tried. For CGRP monoclonal antibodies, efficacy should be assessed only after 3–6 months. For onabotulinumtoxinA, efficacy should be assessed after 6–9 months.
The guidelines states that for most preventive medications, clinical experience suggests that pausing can be considered when treatment has been successful for 6–12 months. The purpose of pausing is to ascertain whether preventive treatment can be stopped, which minimizes the risk of unnecessary drug exposure and allows some patients to manage their migraine with acute medications only. A useful measure to quantify the degree of preventive treatment success is to calculate the percentage reduction in monthly migraine days or monthly headache days of moderate-to-severe intensity. However, a pragmatic approach is needed and clinicians should decide to pause preventive therapy on a case-by-case basis.

FR 2021 recommends to evaluate efficacy of preventive treatment during the third month of treatment (weeks 8–12), except for onabotulinumtoxinA whose efficacy should be evaluated after six months. The guideline recommends the systematic use of HIT-6 and HAD scales at each visit.
The guideline provides recommendations regarding switching prophylaxis in episodic and chronic migraine and regarding prophylaxis of resistant or refractory migraine (see section “pharmacological prevention”).

If patients respond well to prophylactic treatment, the guidelines recommend to evaluate the need or to taper prophylactic treatment after 6-12 months.

For CGRP monoclonal antibodies, EUR 2022 suggests to evaluate efficacy after a minimum of 3 consecutive months treatment. The guideline suggests to consider a pause in the treatment with CGRP monoclonal antibodies after 12-18 months of continuous treatment and to restart treatment if migraine worsens.

Setting of care or the role of other healthcare professionals

SIGN 2022 recommends to consider referral to neurology/headache clinic if three or more preventive therapies have failed.

NHG 2021 recommends referral to a neurologist with expertise in headache if preventive treatment is not sufficiently effective.
The guideline mentions that CGRP monoclonal antibodies are possible treatment options in secondary care.
For chronic migraine, NHG 2021 recommends to follow the prophylactic treatment as recommended for episodic migraine after excluding medication-overuse headache or after persistent symptoms despite the discontinuation of all analgesics and triptans. The authors state to start treatment yourself (optionally in consultation with the neurologist) or refer to the neurologist with expertise in headache.

Regarding primary care and referral between specialist care and primary care, see statements above from Eigenbrodt 2021.

Medication-overuse headache
NICE 2021 recommends to not routinely offer inpatient withdrawal for medication overuse headache. Specialist referral and/or inpatient withdrawal of overused medication is to be considered for people who are using strong opioids, or have relevant comorbidities, or in whom previous repeated attempts at withdrawal of overused medication have been unsuccessful.

NHG 2021 recommends to consider referral to a neurologist specialized in headache/headache center for outpatient counselling after a previously unsuccessful attempt to discontinue medication or if the GP and/or patient assesses that discontinuation of the medication is difficult, based on factors such as patient insight, extent of patient's ability to solve problems (motivation and cooperation) and comorbidity.

Eigenbrordt 2021 prefers the abrupt withdrawal of overused medication (not opioids). This can be managed in primary care unless addictive drugs (e.g. opioids) are involved.
Patients with chronic migraine are recommended to be referred to specialist care.

FR 2021 recommends for chronic migraine with medication overuse headache, first-line prophylactic medication and advises the ambulatory withdrawal of the overused acute medication.

Mentrual migraine

FR 2021 recommends that treatment and especially hormonal interventions should be decided by the primary care physician and a gynecologist for women with bothersome mentrual migraine.

Pregnancy

SIGN 2022 recommends in their recommendations for sodium valproate to seek further advice on migraine prophylaxis for women who are pregnant or who are planning a pregnancy.

NICE 2021 recommends to seek specialist advice if prophylactic treatment for migraine is needed.

NHG 2021 recommends to refer to the neurologist in case of severe symptoms during pregnancy and/or lactation and insufficient effect of acute treatment.

Eigenbrodt 2021 states that triptans should be used only under the strict supervision of a specialist due to limited safety date.
Eigenbrodt 2021 states that prophylactic treatment is best avoided during pregnancy. If indicated, best available data support propranolol or, if propranolol is contraindicated, amitriptyline. Both should be used under specialist supervision.

FR 2021 recommends that patients should be managed both by a neurologist and a gynecologist in case of bothersome migraine during pregnancy.

5.8.1.2 SIGN 2022

Overusing acute medication can limit the effectiveness of preventative medication and medication overuse should also be assessed and addressed. Prophylactic treatment should be used for at least three months at the maximum tolerated dose before deciding if it is effective or not. In many patients prophylactic medication can be successfully phased out again and the need for ongoing prophylaxis should be considered after six to 12 months.

Acute treatment should be taken as early as possible in the headache phase with the aim of aborting an attack. It is given once, with the option of repeating after two hours (with the same or different treatment) if there is an inadequate response.

Patients have a variable response to individual triptans and it is worth sequencing through different triptans to find the most effective one. Acute treatment will not always work for every migraine. Patients should be offered appropriate rescue medication for this situation, for example subcutaneous sumatriptan may be appropriate in some patients who don't respond to oral or nasal triptan.

[Bib. group]. In their treatment algorithm (see "section acute pharmacological treatment"), the authors mention:

- Referral to neurology/headache clinic Consider referral if three or more therapies have failed. Treatment options include flunarazine, botulinum toxin A, or CGRP monoclonal antibodies.
- If the patient responds well to prophylactic treatment a trial of gradual drug withdrawal should be considered after six months to one year.

CHECKLIST FOR PROVISION OF INFORMATION TO PATIENTS
This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

Initial consultation with GP	• Exclude a serious cause for headache by appropriate history and examination. • If time allows: o Make a diagnosis if possible (remember the majority of patients with disabling headache will have migraine). o Consider if the headache/migraine is episodic (<15 days a month) or chronic (>15 days a month). o If a migraine diagnosis has been made, consider providing appropriate information leaflets or web addresses on migraine and its treatment, potential side effects and medication overuse headache (see section 7.1). o Ask the patient to complete a migraine diary. The diary may include: o all headaches and their severity o medication taken o menstruation o normal activities missed. Possible additional information: o food and drink o sleep times o exercise o stressful days o complementary therapies used. Ask what medication and what doses the patient has tried so far. Consider acute and/or prophylactic treatment where appropriate. If appropriate, give the patient an explanation that they have a primary headache called migraine.
First follow up with GP (after 2–8 weeks)	• Consolidate the first consultation which may involve repeating some of the initial consultation. • Find out what medication and what doses the patient has tried so far. • Consider the possibility of medication overuse and discuss the withdrawal of drugs where necessary. • Consider the impact the headaches have on the patient's work, education, family and social life. • Consider acute and/or prophylactic treatment where appropriate. • Give clear advice on timing of acute treatment. • Check that the patient has been given appropriate information leaflets or web addresses on migraine. • Look at any migraine diary they have completed and, if appropriate, ask them to continue it until the next review with any changes, if needed.

Follow-up review with GP (after 6–8 weeks)	• Review the migraine diary for frequency and severity of headaches, medication and triggers for migraine. • Discuss lifestyle improvements. • If appropriate discuss the impact headaches have on education, job, family, social life and holidays. • If appropriate discuss other factors, such as pre- and postpregnancy planning. • Review current medication and any changes needed. • Tell the patient that other treatments are available should they be needed but several drugs may need to be tried to find the best medication and other health problems need to be taken into account.
Further follow up reviews with GP	• As above. • Review of current medication should include dose, side effects and headache recurrence if it occurs after initial acute treatment. • Consider whether referral to a hospital specialist is required, eg because of treatment failure or uncertain diagnosis.

5.8.1.3 NICE 2021

1.3.22 Review the need for continuing migraine prophylaxis 6 months after the start of prophylactic treatment. [2012]

Trade off between clinical benefits and harms
The aim of prophylaxis is to reduce the frequency and severity of migraine. Continuing to take treatment when it is no longer required puts the patient at risk of side effects and drug interactions.

Quality of evidence
All evidence reviewed was for 3-6 months treatment. This recommendation was based on GDG consensus opinion.

Other considerations
The GDG experience is that people are able to stop prophylaxis after 6 months of treatment and have continued benefit from the prophylactic treatment. They considered that all people on prophylactic treatment should have their need to continue treatment reviewed at 6 months.

All headache disorders
1.3.1 Consider using a headache diary:

- **to record the frequency, duration and severity of headaches**
- **to monitor the effectiveness of headache interventions**
- **as a basis for discussion with the person about their headache disorder and its impact. [2012]**

Trade off between clinical benefits and harms
Some people may consider the diaries burdensome to complete and therefore there may be some issues with compliance. This should be considered when deciding if a diary is an appropriate tool to use.

Quality of evidence
The evidence was of low quality, based on questionnaires and surveys reported in three studies. The limitations of the studies included poor reporting of the methods and analysis. Two of the studies were conducted in tertiary care settings with one including people from a clinical trial and hence, were indirect to the target population in the clinical question.

Other considerations
The GDG used the evidence and their experience when considering the use of diaries. The GDG agreed that the importance of communication and understanding the impact of headache should not be undervalued and diaries played an important role in acknowledging this. Diaries can help in the legitimisation of headache. Equality issues should be considered when developing and using headache diaries including; reading/writing skills, language and cultural differences.

1.3.3 Do not refer people diagnosed with tension-type headache, migraine, cluster headache or medication overuse headache for neuroimaging solely for reassurance. [2012]

5.8.1.4 NHG 2021

See also sections “acute pharmacological treatment” and “pharmacological prevention”.

Preventieve behandeling
…

- Voor alle middelen geldt (zie tabel 18):
    - Start met een lage dosering en bouw stapsgewijs op bij onvoldoende effect.
    - Bouw de medicatie langzaam op om bijwerkingen te voorkomen. Op geleide van effectiviteit en bijwerkingen kan de dosering eventueel sneller opgebouwd worden.
    - Tijdens een preventieve behandeling mag, indien nodig, aanvalsmedicatie gebruikt worden.
    - Evalueer het effect na minimaal 3 maanden gebruik:
        - Ga, als de klachten onvoldoende onder controle zijn, de therapietrouw na en kies eventueel voor een ander middel.
        - Zet de behandeling bij een goed effect voort gedurende 6 tot 12 maanden. Bouw daarna de medicatie op proef af. Indien de klachten weer toenemen kan de behandeling weer gestart worden.
- Verwijs bij onvoldoende effectiviteit naar de neuroloog met expertise op het gebied van hoofdpijn; behandelopties in de tweede lijn zijn onder andere valproïnezuur en topiramaat.

<u>1) Adults</u>

Controle

Aanvalsbehandeling

- Controleer het effect van de aanvalsbehandeling na 2-3 aanvallen:
    - ga na op welk moment van de migraine en in welke dosering het medicament werd ingenomen.
    - ga na of het gewenste effect optrad (na hoeveel tijd was de pijn weg, wanneer kon de patiënt weer functioneren, kwam de hoofdpijn weer terug?).
    - ga na of er bijwerkingen waren.
    - gebruik desgewenst het hoofdpijndagboek (versie behandeling).
- Als de aanvalsbehandeling het gewenste effect had, spreek dan met de patiënt af wanneer het nodig is de behandeling opnieuw te evalueren en vraag de patiënt naar zijn wensen.
- Evalueer met de patiënt het klachtenpatroon en het medicatiegebruik bij toename van hoofdpijnklachten en/of aanvalsfrequentie of bij verandering van de migrainekarakteristieken.
- Wees bij het verstrekken van herhalingsrecepten voor triptanen en analgetica alert op het risico op MOH.
- Controleer, wanneer het gewenste effect is bereikt, eenmaal per jaar.
- Bespreek vanaf de leeftijd van 40 jaar nogmaals het verhoogde risico op HVZ en overweeg een cardiovasculair risicoprofiel op te stellen (vooral bij vrouwen met migraine met aura of patiënten met andere risicofactoren voor HVZ).
- Herhaal de schatting van het risico op HVZ, bijvoorbeeld elke 5 jaar (of vaker indien het geschatte risico dicht bij een behandelgrens ligt, zie NHG-Standaard Cardiovasculair risicomanagement).

Preventieve behandeling

- Controleer na 2 weken. Let hierbij op eventuele bijwerkingen en meet de bloeddruk en hartfrequentie bij gebruik van candesartan of een bètablokker. Bepaal de eGFR na 2 weken gebruik van candesartan.
- Bepaal de frequentie van verdere controles aan de hand van effectiviteit, noodzaak tot ophogen van de dosis en het optreden van bijwerkingen.
- Zet de behandeling bij een goed effect gedurende 6 tot 12 maanden voort. Bouw daarna de medicatie op proef af. Indien de klachten weer toenemen kan de behandeling weer gestart worden.
- Controleer bij voortgezet gebruik eenmaal per jaar.

Consultatie en verwijzing

- Consulteer of verwijs naar een neuroloog voor verdere diagnostiek bij:
    - twijfel aan de diagnose
    - plotselinge verandering van de migrainekenmerken
    - plotselinge duidelijke toename van de aanvalsfrequentie
- Consulteer of verwijs naar een neuroloog met expertise op het gebied van hoofdpijn bij:
    - falen van alle in deze standaard genoemde aanvalsbehandelingen
    - onvoldoende effect van preventieve behandeling van episodische en chronische migraine
- Verwijs naar of overleg met de bedrijfsarts bij werkgerelateerde klachten, (dreigend) ziekteverzuim of als het behandelbeleid gevolgen heeft voor de inzetbaarheid in het werk

2) Migraine associated with menstruation

See adults

3) Children

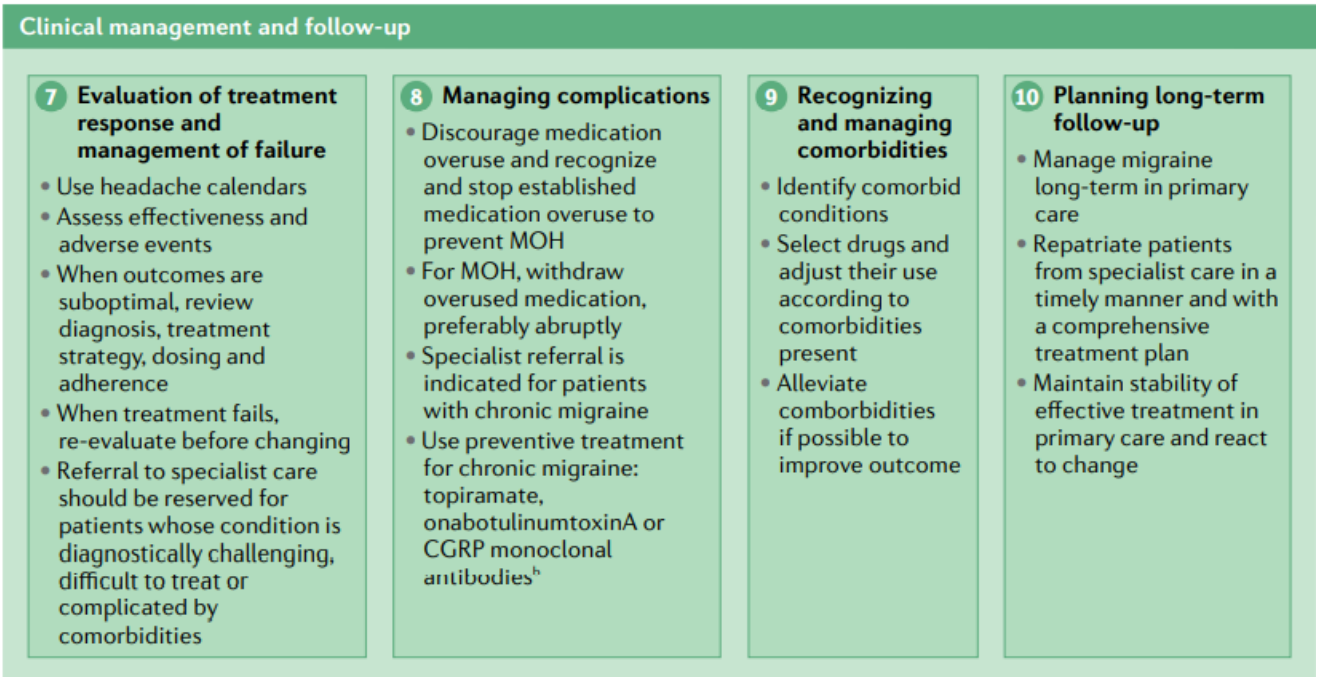
See section “Children”.

4) Medication-overuse headache

See section “Medication-overuse headache”

5.8.1.5 Eigenbrodt 2021

See also sections “acute pharmacological treatment” and “pharmacological prevention”.



Step 7: Follow-up, treatment response and failure
Active follow-up is the only appropriate means of determining outcome and provides the opportunity to review both diagnosis and treatment strategies. The response to treatment should be evaluated within 2–3 months after initiation or a change in treatment, and regularly thereafter, though not necessarily at short intervals (for example, 6–12 months). Evaluation of treatment responses should include a review of effectiveness, adverse events and adherence. Key outcome measures for effectiveness are attack frequency, attack severity and migraine-related disability. Attack frequency is usually measured in headache or migraine days per month. Severity is usually expressed as pain intensity rather than functional consequence, which should be separately assessed. Headache calendars are extremely useful for capturing these measures and require little

time commitment if completed only on symptomatic days. In addition, headache calendars are valuable for monitoring acute medication use. At follow-up assessments, the self-administered Migraine Treatment Optimization Questionnaire (mTOQ-4) can be used to evaluate the effectiveness of acute medications, whereas the self-completed eight-item HURT questionnaire (Headache Under-Response to Treatment) can be used to assess the effectiveness of an intervention and generates suggestions for changes to improve effectiveness (Box 3).

Box 3 | **Tools for evaluation of treatment response**

HURT questionnaire

The Headache Under-Response to Treatment (HURT) questionnaire is an eight-item, self-administered questionnaire developed specifically to guide follow-up in primary care[103]. The questionnaire assesses treatment outcome in several domains, and responses are coupled to suggested changes in management. It has been validated for clinical use in English and Arabic[133,134] and is available online in 12 languages (see Related links for where to access the HURT questionnaire).

mTOQ-4

The Migraine Treatment Optimization Questionnaire (mTOQ-4) is a self-administered questionnaire that can be used to assess acute treatment, including treatment efficacy[102]. This questionnaire has been validated for use in primary care and used in several studies to assess treatment outcomes[102,118,135].

When treatment fails.

A conclusion that treatment has failed should be made with caution and must always be preceded by a thorough review of the underlying reasons. In some cases, apparent failures might be remediable, such as when failure is due to poor adherence or suboptimal dosing. Whereas some patients benefit from higher doses, others might benefit from lower doses that have fewer adverse effects and therefore improve adherence. Alternatives when first-line medications fail are outlined above (see Step 4 and Step 5). If all treatments fail, the diagnosis should be questioned and specialist referral is indicated.

When specialist referral is needed.

Approximately 90% of people who seek professional care for migraine should be treated in primary care. Referral to specialist care should be reserved for the minority of patients whose condition is diagnostically challenging, difficult to treat or complicated by comorbidities. Specialist care provides access to greater expertise maintained by experience and to multidisciplinary care. However, specialist capacity is limited and the cost is much higher.

Recommendations.

- **Evaluate treatment responses shortly after initiation (after 2–3 months) or a change of treatment and regularly thereafter (every 6–12 months).**
- **Evaluate the effectiveness of treatment by assessing attack frequency, attack severity and migraine-related disability.**
- **When outcomes are suboptimal, review the diagnosis, treatment strategy, dosing and adherence.**
- **If all treatment fails, question the diagnosis and consider specialist referral.**

Step 8: Managing complications

Medication overuse headache.
See section “Medication-overuse headache”.

Transformation to chronic migraine.
Some estimates suggest that up to 3% of patients with episodic migraine experience transformation to chronic migraine each year. The reliability of such estimates is uncertain because chronic migraine is often conflated with MOH, but transformation to chronic migraine does occur. Recognized risk factors include female sex, a high headache frequency, inadequate treatment, overuse of acute medications and a range of comorbidities, including depression, anxiety and obesity. Recognition of these risk factors is part of good clinical management, as their modification can prevent transformation. Once chronic migraine has developed, its management is challenging and referral to specialist care is usually necessary. If MOH, which frequently causes symptoms that suggest chronic migraine, can be ruled out, then a preventive treatment should be established. Individuals with chronic migraine should also be educated on the modifiable risk factors for chronic migraine so that they can make lifestyle changes that might help.
Preventive medications for which evidence supports effectiveness in chronic migraine include topiramate, onabotulinumtoxinA and CGRP monoclonal antibodies. Topiramate is the drug of first choice owing to its much lower cost. Regulatory restrictions generally limit the use of onabotulinumtoxinA and CGRP antibodies to patients in whom two or three other preventive medications have failed, despite the fact that topiramate is the only other treatment with evidence supporting its use. Three CGRP antibodies (erenumab, fremanezumab and galcanezumab) have been proven to be beneficial for patients in whom at least two other preventive medications have failed. As in episodic migraine, the choice of preventive medication and their order of use depends on local practice guidelines, availability, cost and reimbursement policies. No robust data from random controlled trials support the use of beta blockers, candesartan or amitriptyline for the preventive treatment of chronic migraine, although they are commonly used in clinical practice.

Recommendations.
• Educate patients with migraine about the risk of MOH with frequent overuse of acute medication.
• Manage established MOH by explanation and withdrawal of the overused medication; abrupt withdrawal is preferred, except for opioids.
• Recognize and, when possible, modify risk factors for the transformation of episodic migraine to chronic migraine.
• Refer patients with chronic migraine to specialist care.
• Once MOH is ruled out, initiate preventive medication therapy for chronic migraine; evidence-based treatment options are topiramate, onabotulinumtoxinA and CGRP monoclonal antibodies.

Step 9: Recognizing and managing comorbidities
Migraine is associated with anxiety, depression, sleep disturbances and chronic pain conditions (for example, neck and lower back pain). These associations are more pronounced in people with chronic migraine than in those with episodic migraine. Obesity is also an important risk factor for transformation from episodic migraine to chronic migraine and should be accounted for in the

clinical evaluation. Furthermore, migraine with aura has been associated with cardiovascular events in women.
Recognition of comorbid conditions in migraine is important because they can influence drug choice. For example, topiramate is the preferred treatment for patients with obesity owing to its association with weight loss. For patients with depression or sleep disturbances, amitriptyline is most likely to be of benefit. Recognition of comorbidities is also important because their alleviation can improve treatment outcomes for migraine, and vice versa.

Recommendations.
• Ensure that comorbidities are identified in patients with migraine, as they can affect treatment choice and outcomes.
• Adjust treatments accordingly and consider possible interactions between drug-related adverse effects and the patient's comorbidity profile.

Step 10: Long-term follow-up
Long-term management of migraine should be the responsibility of primary care. Referral from specialist care back to primary care should be timely, coordinated with the general practitioner and accompanied by a comprehensive treatment plan that includes recommendations for re-evaluation and steps to be taken for each of the likely outcomes. In general, timely return to primary care can be made once the patient experiences sustained efficacy with preventive therapy for up to 6 months with no substantial treatment-related adverse effects.
In primary care, the main goal of follow-up is to maintain stability of adequate outcomes, whether achieved in primary or specialist care, and to react appropriately to any change that might call for review. Neither purpose requires regular routine contact, which should, therefore, be avoided unless necessary in the context of repeat prescriptions. Instead, primary care physicians should emphasize patient education and self-efficacy with respect to judging when a return visit is necessary.

Recommendations.
• Primary care should be responsible for the long-term management of patients with migraine, maintaining stability and reacting to change.
• Referral from specialist back to primary care should be timely and accompanied by a comprehensive treatment plan.
• The patient can be referred back to primary care once sustained efficacy with preventive therapy for up to 6 months is obtained with no substantial treatment-related adverse effects.

5.8.1.6 FR 2021

[Bib. group]. See the recommendation tables in section "acute pharmacological treatment" and section "pharmacological prevention".

5.8.1.7 EUR 2022

Expert consensus statement 3

In individuals with episodic or chronic migraine who start a new treatment with one monoclonal antibody targeting the CGRP pathway we suggest evaluating efficacy after a minimum of 3 consecutive months on treatment. (Expert consensus statements)

We recognize that some individuals with migraine may take more time to achieve a relevant benefit. In selected cases decision on treatment maintenance can be readdressed after an additional period of 3 months.

Expert consensus statement 4
In individuals with episodic or chronic migraine we suggest considering a pause in the treatment with monoclonal antibodies targeting the CGRP pathway after 12-18 months of continuous treatment. If deemed necessary, treatment should be continued as long as needed. In individuals with migraine who pause treatment, we suggest restarting the treatment if migraine worsens after treatment withdrawal. (Expert consensus statements)

Monthly or quarterly administration of CGRP mAbs is more accepted by individuals with migraine than the daily oral regimen. Moreover, the excellent tolerability profile makes the CGRP-mAbs more suitable for prolonged treatments. So far, there are no studies which provide a clear guidance on the optimal duration of migraine preventive treatments. It is highly probable that a broadly generalizable approach does not exist and that also treatment duration needs to be adapted on a case-by-case strategy or considering homogeneous groups of individuals with migraine.

5.8.2 Children

5.8.2.1 Summary

Summary

US_treatment 2019 and US_prevention 2021 provide multiple recommendations regarding how to counsel children, adolescents and their families. For example regarding migraine-healthy habits, including lifestyle modification, identification/disproof/resolution of migraine triggers/aggravating factors, and avoidance of medication overuse.

US_prevention 2021 recommends to periodically monitor medication effectiveness and adverse events when prescribing migraine preventive treatments and to counsel patient and families about risks and benefits of stopping preventive medication once good migraine control is established. There is little information about when preventive treatment should be stopped, and the risk of relapse after discontinuation varies.

NHG 2021 provides recommendations for the follow-up of acute treatment of children which are in general similar for adults. For example, the evaluation of the effectiveness of acute treatment after 2-3 attacks.
However there are some differences. After failure of paracetamol or ibuprofen, triptans are recommended as third step for acute treatment. But for age <12 years, referral to a (pediatric) neurologist or pediatrician is recommended. (see section “specific population-children”).
The authors recommend to consult or refer to a (pediatric) neurologist or pediatrician, with expertise in headache in children, in case of: doubt about the diagnosis, insufficient effect of acute treatment, the initiation of preventive treatment.
The authors recommend for children to consider relaxation therapy or referral to a child psychologist if many symptoms remain despite education and drug treatment and analysis by the neurologist or pediatrician.

Setting of care or the role of other healthcare professionals

See NHG 2021 guideline in the paragraph above.

NHG 2021 states that efficacy of preventive treatment is uncertain and that propranolol, candesartan and flunarizine are used in secondary care. Consider referral for preventive treatment to a specialist in case of high frequency of attacks (≥2 per month), prolonged attacks, ineffective acute treatment, or frequent school absence.

Eigenbrodt 2021 recommends referral to specialist care if acute medication provides insufficient pain relief.

5.8.2.2 US_treatment 2019

Counseling

Statement 6a
Clinicians should counsel children and adolescents with migraine and their families about migraine-healthy habits, including lifestyle modification, identification/disproof/resolution of migraine triggers/aggravating factors, and avoidance of medication overuse (Level B).

Statement 6b

Clinicians should make collaborative agreements with children and adolescents with migraine and their families on treatment goals that are individualized to the patient (Level B).

Statement 6c

Clinicians may counsel children and adolescents with migraine and their families to maintain a headache diary to monitor their response to treatments (Level C).

Statement 6d

Clinicians should counsel patients and families to use no more than 14 days of ibuprofen or acetaminophen per month, no more than 9 days of triptans per month, and no more than 9 days per month of any combination of triptans, analgesics, or opioids for more than 3 months to avoid medication overuse headache (Level B). (There is no evidence to support the use of opioids in children with migraine. Opioids are included in this statement to be consistent with the International Classification of Headache Disorders regarding medication overuse.)

Recommendation 6 rationale

Patient education can improve patient safety and adherence to interventions. It is important to learn about the behavioral aspects of self-care that might improve migraine, including healthy habits with lifestyle modification, potential migraine triggers/aggravating factors, and the risk of overusing medication. Maintaining a headache diary is helpful to track response to any new therapy. Patients and families will benefit from understanding the limitations of current available treatments. Overuse of medication to treat acute attacks has been associated with medication overuse headache in adults but has not been well-studied in children. Methods to prevent medication overuse headache are included in adult treatment plans.

About triptans

Clinicians should counsel adolescent patients with migraine with aura that taking their triptan during a typical aura is safe, but that the triptan may be more effective if taken at the onset of head pain. (Level B)

Clinicians may consider referral of children and adolescents with hemiplegic migraine or migraine with brainstem aura who do not respond to other treatments to a headache specialist to find effective treatment. (Level C)

The use of triptans during the aura phase is of concern because of potential difficulties differentiating early stroke symptoms from migraine aura. While this is unlikely a problem in those with established migraine with visual aura, caution is warranted in those with more complex aura presentations. According to the FDA, triptans are contraindicated in those with a history of hemiplegic aura or migraine with brainstem aura. This contraindication was based on a view of migraine pathophysiology that is no longer considered current.

5.8.2.3 US_prevention 2019

Counseling and education for children and adolescents with migraine and their families

Statement 1a

Clinicians should discuss the potential role of preventive treatments in children and adolescents with frequent headache or migraine-related disability or both. (Level B)

Statement 1b

Clinicians should discuss the potential role of preventive treatments in children and adolescents with medication overuse. (Level B)

Recommendation 1 rationale

Individuals with a family history of migraine are at higher risk of developing migraine, and female sex is a risk factor of migraine that persists into adulthood. Disease prevention is the cornerstone of medical care. Migraine has multiple behavioral factors that influence headache frequency. Recurrent headache in adolescents is associated with being overweight, caffeine and alcohol use, lack of physical activity, poor sleep habits and tobacco exposure. Depression is associated with higher headache disability in adolescents. Weight loss can contribute to headache reduction in children who are overweight. Identification and avoidance of factors that contribute to headache risk can reduce migraine frequency.

Statement 2a

Clinicians should discuss the potential role of preventive treatments in children and adolescents with frequent headache or migraine-related disability or both (Level B).

Statement 2b

Clinicians should discuss the potential role of preventive treatments in children and adolescents with medication overuse (Level B).

Recommendation 2 rationale

In adults with migraine, headache on more than 6 days in a month is a risk factor for progression to chronic migraine, with medication overuse contributing to this progression. Taking triptans, ergotamines, opioids, and combination analgesics on more than 9 days in a month or taking over-the-counter simple analgesics on more than 14 days in a month can lead to medication overuse headache (There is no evidence to support the use of opioids in children with migraine. Opioids are included in this rationale to be consistent with the International Classification of Headache Disorders regarding medication overuse). It has been suggested that clinicians consider preventive treatments in these populations. Although there are no data on this topic in pediatric populations, it is hypothesized that similar relationships between frequent headache, medication overuse, and progression to chronic migraine may occur in children. In clinical trials of pediatric migraine prevention, inclusion criteria for headache frequency were variable and included a minimum of 4 headache days per month with no maximum and 3 to 4 migraine attacks per month for at least 3 months. In teenagers with migraine, those with a PedMIDAS score over 30, indicating a moderate to severe migraine related disability, had a higher risk of mood and anxiety disorders and increased severity and frequency of headache.

<u>Monitoring and stopping medication</u>

Statement 5a

Clinicians must periodically monitor medication effectiveness and adverse events when prescribing migraine preventive treatments (Level A).

Statement 5b
Clinicians should counsel patient and families about risks and benefits of stopping preventive medication once good migraine control is established (Level B).

Recommendation 5 rationale
Migraine is a chronic disorder with spontaneous remissions and relapses. Clinical trials follow patients for limited periods of time. Patients and families often inquire about the duration of treatment. There is little information about when preventive treatment should be stopped, and the risk of relapse after discontinuation varies.

Mental illness in children and adolescents with migraine

Statement 6a
Children and adolescents with migraine should be screened for mood and anxiety disorders because of the increased risk of headache persistence. (Level B)

Statement 6b
In children and adolescents with migraine who have comorbid mood and anxiety disorders, clinicians should discuss management options for these disorders. (Level B)

Recommendation 6 rationale
…This review found high-quality evidence suggesting that children with negative emotional states, manifesting through anxiety, depression, or mental distress, are not at greater risk of developing recurrent headache; however, it found moderate-quality evidence that suggested the presence of comorbid negative emotional states in children with headache is associated with an increased risk of headache persistence in those who already experience recurrent headaches.

5.8.2.4 NGH 2021

See also sections “acute pharmacological treatment” and “pharmacological prevention”.

Migraine bij kinderen

Voorlichting
- Bij korte aanvallen volstaat uitleg aan de omgeving en het advies om het kind even met rust te laten.
- Voor de effectiviteit van andere niet-medicamenteuze behandelingen is weinig bewijs.
- Richt het beleid vooral op het leren omgaan met de pijnaanvallen:
    - Het is van belang dat de omgeving rekening houdt met het kind bij een migraineaanval.
    - Adviseer de ouders bij doorgaans kortdurende aanvallen de school te vragen of het kind bij een aanval even in een aparte kamer kan liggen zodat het na een korte aanval weer verder kan met de lessen.

Slaapritme
Een verstoord slaapritme kan leiden tot een migraineaanval; het is belangrijk dit slaapritme te herstellen. Zie NHG-Standaard Slaapproblemen en slaapmiddelen.

[Bib. group]. For non-pharmacological treatment: see section “non-pharmacological treatment”.

Controle

- Controleer het effect van de aanvalsbehandeling na 2-3 aanvallen:
    - Ga na op welk moment van de migraine en in welke dosering het medicament werd ingenomen.
    - Ga na of het gewenste effect optrad (na hoeveel tijd was de pijn weg, wanneer kon de patiënt weer functioneren, kwam de hoofdpijn weer terug?).
    - Ga na of er bijwerkingen waren.
    - Gebruik desgewenst het hoofdpijndagboek (versie behandeling).
    - Ga bij onvoldoende effect van de behandeling over naar de volgende stap.
- Als de aanvalsbehandeling het gewenste effect had, spreek dan met de patiënt en diens ouders af wanneer het nodig is de behandeling opnieuw te evalueren en vraag de patiënt naar zijn wensen.
- Evalueer het klachtenpatroon en het medicatiegebruik bij toename van hoofdpijnklachten en/of aanvalsfrequentie of bij verandering van de migrainekarakteristieken.
- Controleer, wanneer het gewenste effect is bereikt, eenmaal per jaar.
- Wees bij het verstrekken van herhalingsrecepten voor triptanen en analgetica alert op het risico op MOH.

Consultatie en verwijzing

- Consulteer of verwijs naar een (kinder)neuroloog of kinderarts, met expertise op het gebied van hoofdpijn bij kinderen, bij:
    - twijfel aan de diagnose
    - onvoldoende effect van aanvalsbehandeling van migraine
    - instellen op preventieve behandeling van migraine
- Overweeg verwijzing naar een psychosomatisch fysiotherapeut of psycholoog bij migraine waarbij er ondanks voorlichting, medicamenteuze behandeling en analyse door de (kinder)neuroloog of kinderarts veel klachten blijven.

5.8.2.5 Eigenbrodt 2021

See section “Specific population-children”

5.9 Non-pharmacological treatment

5.9.1 Summary

Summary

There are differences between the guidelines regarding recommendations for acupuncture, exercise, and dietary supplements. For neuromodulation devices: see section “devices for migraine therapy”.

Regarding acupuncture, NICE 2021 recommends to consider a course of up to 10 sessions of acupuncture over 5 to 8 weeks if both topiramate and propranolol are unsuitable or ineffective. Furthermore they recommend to advise people that riboflavin (400 mg once a day) may be effective in reducing migraine frequency and intensity for some people.
They state that there was not enough evidence to form a recommendation for or against the use of manual therapies, psychological therapies, or exercise for the prophylactic treatment of migraine.

NHG 2021 does not recommend acupuncture as a preventive treatment for migraine.
For children with migraine, they recommend to consider relaxation therapy or referral to a child psychologist if many symptoms remain despite education and drug treatment and analysis by the neurologist or paediatrician.

Eigenbrodt 2021 recommends to consider neuromodulatory devices, biobehavioural therapy and acupuncture as adjuncts to acute and preventive medication or as stand-alone preventive treatment when medication is contraindicated. They also mention that contrary to popular belief, little to no evidence exists for physical therapy, spinal manipulation and dietary approaches. They make no recommendations about other therapeutic options, such as melatonin, magnesium and riboflavin, as limited evidence for their efficacy is available and their use in clinical practice is limited.

FR-non-med_2021 recommends weekly aerobic exercise as an alternative or a supplement to pharmacological prophylaxis. They mention that up to now evidence remains too scarce to make any recommendations for yoga.

They recommend to propose co-enzyme Q10, high-dose riboflavin or melatonin in patients with episodic migraine asking for a prophylactic treatment with limited side-effects. Plants for migraine prophylaxis are not recommended because feverfew has no demonstrated efficacy and butterbur has a heterogeneous composition carrying a risk of hepatotoxicity. They mention that specific diets (gluten-free, lactose free…) should not be recommended as data are too scarce.
In patients with episodic migraine asking for non-pharmacological treatments or achieving insufficient efficacy with pharmacological treatments, propose acupuncture as an alternative or a supplement to pharmacological prophylaxis.
In patients with episodic or chronic migraine with significant stress, anxiety, or migraine-induced disability, propose behavioral therapies (relaxation, biofeedback and cognitive behavioral therapies) or mindfulness-based stress reduction as add-on therapy to pharmacological treatments.

5.9.2 SIGN 2022

[Bib. group]. No formal recommendations were provided. However, in their treatment algorithm (see "section acute pharmacological treatment") they mention:

For patients with migraine, maintaining a regular routine is important, including the following:
- Encourage regular meals, adequate hydration with water, sleep and exercise
- Avoid specific triggers if known
- Consider activities that encourage relaxation such as mindfulness, yoga or meditation.

5.9.3 NICE 2021

Acupuncture

1.3.20 If both topiramate and propranolol are unsuitable or ineffective, consider a course of up to 10 sessions of acupuncture over 5 to 8 weeks according to the person's preference, comorbidities and risk of adverse events. [2012, amended 2015]

Dietary supplements

1.3.23 Advise people with migraine that riboflavin (400 mg once a day) may be effective in reducing migraine frequency and intensity for some people. [2012]

In November 2015, this was an off-label use of riboflavin, but this is available as a food supplement.

[Bib. group]. For more details about quality of evidence and other considerations: see section “acute pharmacological treatment”.

Manual therapies

Although there is some preliminary evidence to suggest that seeing a practitioner who utilises manual therapies may be of benefit, the GDG decided there was not enough evidence to make a recommendation for or against the use of manual therapies for the prophylactic treatment of tension type headache or migraine.

Psychological therapies

The GDG agreed not to make a recommendation on the use of psychological therapies for the prophylactic treatment of primary headaches as there was not enough evidence to form a recommendation for or against its use.

Exercise

The GDG decided that there was not enough evidence to form a recommendation for or against the use of exercise for migraine.

Quality of evidence

There was low quality evidence from one small trial (n=72) comparing yoga and self-care, and one small trial (n=61) comparing exercise and topiramate. In the yoga trial, the population was very specific and therefore the results are not directly applicable to the general migraine population in the UK. Both studies reported some evidence that exercise may be beneficial compared to usual care or relaxation or equally effective to topiramate. However this was from open label studies with low or very low quality evidence. The effect of exercise programmes on the management of primary headaches other than migraine was not assessed.

Other considerations

The GDG agreed that there was not enough evidence to form a recommendation for or against aerobic exercise or yoga for the prophylactic treatment of migraine. The available data for yoga was specific to a particular approach, the full details of which were not available. The programme was quite intensive, 5 days a week for one hour a day, in a very specific population, likely to be highly motivated (20-25 years old females who were paid to take part). The GDG agreed that this was not necessarily directly applicable to the UK health care system and would be difficult to replicate.

Education and self management

Self management and education programmes are used for a wide range of chronic disorders. Self management programmes combine elements of psychological treatments such as cognitive behavioural therapy, mind-body therapies such as relaxation along with exercise and activity. Such programmes are widely available through initiatives such as the expert patient programme. These are usually lay-led group activities lasting for a period of weeks. In the context of headache management these might also include educational components addressing drug and other specific treatments for headaches. People living with chronic headache might also join generic pain self management courses. The shared experience of others within the group may also support any therapeutic effect. Stand-alone educational programmes for headaches would aim to impart

knowledge around headache management using a variety of media. The GDG were interested in the evidence for both of these management strategies in primary headache.

The GDG decided that there was not enough evidence to form a recommendation for or against the use of education and self management programmes.

5.9.4 NHG 2021

Migraine bij Volwassenen

Acupunctuur

Acupunctuur wordt als preventieve behandeling bij migraine niet aanbevolen.

> Waarom deze aanbeveling?
> Acupunctuur lijkt beperkt effectief ten opzichte van gebruikelijke zorg; dit effect lijkt grotendeels op een placebo-effect te berusten, gezien het contrast met de vergelijking met sham acupunctuur. Daarnaast is het werkingsmechanisme van acupunctuur bij migraine niet bekend en is er een kans op (over het algemeen) geringe bijwerkingen. Daarom is de werkgroep van mening dat acupunctuur niet actief moet worden aanbevolen aan patiënten met episodische migraine.
> Indien patiënten graag acupunctuur willen proberen, bijvoorbeeld bij eerdere goede ervaringen, zijn er geen zwaarwegende argumenten om deze behandeling te ontraden.

Migraine bij kinderen

Psychosomatische oefentherapie

Overweeg ontspanningstherapie indien er ondanks voorlichting en medicamenteuze behandeling en analyse door de neuroloog of kinderarts veel klachten blijven.

Gedragspsychologische interventies

Overweeg verwijzing naar een kinderpsycholoog indien er ondanks voorlichting en medicamenteuze behandeling en analyse door de neuroloog of kinderarts veel klachten blijven.

Zie voor details Niet-medicamenteuze behandeling bij kinderen met spanningshoofdpijn.

5.9.5 Eigenbrodt 2021

Non-pharmacological therapies.

A range of non-pharmacological preventive therapies can be used either as adjuncts to acute and preventive medications or instead of them if medication use is contraindicated. Some evidence supports the use of non-invasive neuromodulatory devices, biobehavioural therapy and acupuncture, although a study of acupuncture indicated that it is not superior to sham acupuncture. Contrary to popular belief, little to no evidence exists for physical therapy, spinal manipulation and dietary approaches. We make no recommendations about other therapeutic options, such as melatonin, magnesium and riboflavin, as limited evidence for their efficacy is available and their use in clinical practice is limited.

Recommendations.
Consider neuromodulatory devices, biobehavioural therapy and acupuncture as adjuncts to acute and preventive medication or as stand-alone preventive treatment when medication is contraindicated.

5.9.6 FR_non-med_2021

Recommendations for non-pharmacological treatment of migraine.

	For non-pharmacological treatment of migraine, our recommendations are	Strength of recommendation
Rnpt1	Encourage any patient with migraine to practice weekly aerobic exercise as an alternative or a supplement to pharmacological prophylaxis	Strong
Rnpt2	In patients with episodic migraine asking for a prophylactic treatment with limited side-effects, propose co-enzyme Q10, high-dose riboflavin or melatonin	Moderate
Rnpt3	Do not prescribe plants for the prophylaxis of migraine because feverfew has no demonstrated efficacy and butterbur has a heterogeneous composition carrying a risk of hepatotoxicity	Strong
Rnpt4	In patients with episodic migraine asking for non-pharmacological treatments or achieving insufficient efficacy with pharmacological treatments, propose neuromodulation therapies, favoring remote electrical neuromodulation for the acute migraine treatment and supra-orbital transcutaneous electrical nerve stimulation for migraine prevention	Strong
Rnpt5	In patients with episodic migraine asking for non-pharmacological treatments or achieving insufficient efficacy with pharmacological treatments, propose acupuncture as an alternative or a supplement to pharmacological prophylaxis	Strong
Rnpt6	In patients with episodic or chronic migraine with significant stress, anxiety, or migraine-induced disability, propose behavioral therapies (relaxation, biofeedback and cognitive behavioral therapies) or mindfulness-based stress reduction as add-on therapy to pharmacological treatments	Strong
Rnpt7	Do not recommend PFO closure for migraine prophylaxis	Strong

<u>Acupuncture</u>
Acupuncture can be effective over sham in the short-term **prophylaxis of episodic migraine** (level of evidence medium), and has similar efficacy and fewer side effects than many of the standard pharmaceutical agents.
Long-term studies of acupuncture in episodic migraine, and studies in chronic migraine are lacking.

<u>Dietary supplements and diet</u>
Studies show that co-enzyme Q10 supplementation (mostly 300 mg/day) (level of evidence fair), high-dose riboflavin (vitamin B2, 400 mg/day) (level of evidence fair), oral magnesium (600 mg/day) (level of evidence fair), and oral melatonin (mostly immediate-release 3 mg) (level of evidence fair) may be of potential benefit for **migraine prophylaxis**.
Some data suggest that feverfew may have a small positive effect on migraine prophylaxis, but other studies are negative (level of evidence for efficacy unknown). Studies show that butterbur is effective in the prophylaxis of migraine (level of evidence moderate) but preparations are heterogeneous with a risk of hepatotoxicity in those containing pyrrolizidine alkaloids.

Specific diets (gluten-free, lactose free…) should not be recommended as data are too scarce to make any recommendation for a specific diet for migraineurs. Further studies are needed to confirm the encouraging results of ketogenic diets in overweight migraine patients.

Physical exercise

Recent systematic reviews and meta-analyses provide moderate-quality evidence that aerobic exercise therapy can decrease the number of migraine days in patients with migraine (level of evidence medium). Although the type of physical activities varied according to the studies, multi-weekly aerobic exercise (endurance) has a clear benefit. Exercise therapy can be efficient when used as the sole preventative option and might also potentiate pharmacological prophylaxis. The benefit of yoga for migraine prevention remains uncertain: a recent meta-analysis including six low-quality randomized-controlled trials (RCT) in migraine and tension-type headache patients revealed a global benefit but which related to tension-type headache. However, a more recent,notincluded, large RCT showed a benefit of yoga as add-on therapy for migraine prevention, with positive outcomes on headache days, disability and quality of life. Up to now, evidence remains too scarce to make any recommendation for this activity.

Behavioural interventions and mindfulness therapy

Because of their safety and acceptability, behavioural therapies and mindfulness-based stress reduction should be considered in patients with episodic or chronic migraine with significant stress, anxiety or migraine induced-disability, as add-on therapy to pharmacological treatments (level of evidence fair).

Behavioural therapies include relaxation, biofeedback and cognitive behavioral therapy. Depending on endpoints, inclusion criteria and analyses, divergent results have been reported in meta-analyses. A meta-analysis concluded that most of the 21 studies conducted up to 2018 to assess the efficacy of behavioral or cognitive-behavioral therapies such as coping strategies, biofeedback, relaxation, and eye movement sensitization for migraine prophylaxis are of very low quality. This Cochrane meta-analysis concluded that there is an absence of high-quality evidence to determine whether psychological interventions are effective for migraine prophylaxis in adults and that it remains uncertain whether there is any difference between psychological therapies and controls on the reduction of migraine days. Another meta-analysis, including all types of headache disorders, concluded that psychological treatments were promising to reduce headache frequency even though the diversity of treatment modalities and the heterogeneity of protocols limited interpretation of data. A previous review focused on cognitive behavioral therapy acknowledged the methodology inadequacy but suggested a potential benefit. Behavioral therapy can be used as add-on to classical pharmacological treatment. Wide heterogeneity also exists regarding mindfulness-based stress reduction benefit for migraine prophylaxis. Likewise, meta-analyses showed conflicting results, but a more recent narrative review, and two new large randomized studies suggest that mindfulness-based stress reduction may have beneficial effects, not always on headache days but on disability and quality of life. Because of their safety and acceptability, behavioral therapies and mindfulness-based stress reduction should be considered in patients with episodic or chronic migraine with significant stress, anxiety or migraine induced-disability, as add-on therapy to pharmacological treatments (level of evidence fair). The evidence regarding the efficacy of hypnosis is too scarce to make any recommendation.

Patent foramen ovale closure

Patent foramen ovale (PFO) is more frequent in migraineurs than in non-migraineurs but randomized controlled trials on PFO closure in migraine failed to demonstrate a significant benefit of PFO closure on the primary endpoints. To date, screening for a PFO and PFO closure is not recommended for migraine prophylaxis (level of evidence strong).

Surgical nerve decompression

Data supporting surgical nerve decompression are very scarce and mostly based on retrospective and unblinded studies. Up to now, we do not recommend such procedures.

5.10 Devices for migraine therapy

5.10.1 Summary

Summary

SIGN 2022 points out that few trials have been conducted on the efficacy and safety of devices for migraine therapy. No recommendations were provided. They describe some of the few available data for vagus nerve stimulation and transcranial magnetic stimulation. No randomized trials were found for transcutaneous supraorbital nerve stimulation

Eigenbrodt 2021 recommends to consider neuromodulatory devices as adjuncts to acute and preventive medication or as stand-alone preventive treatment when medication is contraindicated. They state that some evidence supports the use of non-invasive neuromodulatory devices. No further details were provided.

FR_non-med_2021 recommends to propose neuromodulation therapies in patients with episodic migraine asking for non-pharmacological treatments or achieving insufficient efficacy with pharmacological treatments. They favore remote electrical neuromodulation for the acute migraine treatment and supra-orbital transcutaneous electrical nerve stimulation for migraine prevention.

5.10.2 SIGN 2022

Devices may offer an alternative, or an addition, to pharmacological therapies, but few trials have been conducted on their efficacy and safety. A small number of trials are ongoing.

Vagus nerve stimulation

One small RCT on the safety and tolerability of non-invasive vagus nerve stimulation (VNS) for the **prevention of migraine** reported no safety issues and tolerability was comparable to sham treatment. The study was not sufficiently powered to determine efficacy. No further RCTs were identified.

Transcutaneous supraorbital nerve stimulation

No RCTs were identified on the use of transcutaneous supraorbital nerve stimulation (TSNS) for patients with either **acute or chronic migraine**.

Transcranial magnetic stimulation

Only one RCT was identified in the use of transcranial magnetic stimulation (TMS) for the **acute treatment** of patients with migraine. Following treatment for one migraine, 39% of patients had a pain-free response at two hours compared to 22% of patients given sham treatment. There was a therapeutic gain of 17%.

Two small RCTs reported conflicting results on the efficacy of TMS for **migraine prevention**. One trial reported benefit at one month, while another showed the sham treatment was superior after eight weeks. Further, larger trials are required.

5.10.3 NICE 2021

No recommendations were provided.

5.10.4 NHG 2021

No recommendations were provided.

5.10.5 Eigenbrodt 2021

Consider neuromodulatory devices, biobehavioural therapy and acupuncture as adjuncts to acute and preventive medication or as stand-alone preventive treatment when medication is contraindicated.

Some evidence supports the use of non-invasive neuromodulatory devices, biobehavioural therapy and acupuncture, although a study of acupuncture indicated that it is not superior to sham acupuncture. Contrary to popular belief, little to no evidence exists for physical therapy, spinal manipulation and dietary approaches.

5.10.6 FR_non-med_2021

Neuromodulation devices with proven efficacy and available in France.

Stimulation method Device™ (FDA cleared, CE marked)	Level of evidence for efficacy	Strength of recommendation by the French Headache Society	Availability	Practical use
Remote electrical neuromodulation (REN) (Yes)	Medium in acute migraine treatment	Moderate in acute treatment	Available online but not yet in France, price to be determined	Self-administered by the patients on his forearm for migraine attack treatment for 30–45 min, controlled by smartphone app
Single pulse transcranial magnetic stimulation (Yes)	Fair in acute aura treatment	Moderate in acute aura treatment	Available online but not in France, no data on a French availability or price	Self-administered by the patients for migraine with aura attack treatment: single-pulse on the occiput, repeated once 30 sec later, to be performed as soon as possible after the aura starts
Supra-orbital transcutaneous electrical nerve stimulation (TENS) (Yes)	Fair in acute migraine treatment Medium in migraine prevention	Weak in acute treatment Moderate in migraine prevention	Available online, for devices with acute and prophylactic settings	Self-administered by the patients on his forehead, 20 min every day for preventive treatment, punctual use for 60 min for migraine attack treatment
High frequency repetitive TMS on the primary motor cortex (Yes)	Fair in migraine prevention	Weak in migraine prevention	Classical rTMS device in the neurologist's office	Up to 3 sessions/week performed by a neurologist on the primary motor cortex for up to 4 consecutive weeks. ≥ 600 pulses per session, 10 Hz, 70 to 80% of the resting motor threshold. Further studies are needed to specify conditions and settings, especially to define sessions' rate for long-term use This technique should be restricted to tertiary centers until further studies are available (expert opinion)

TMS: transcranial magnetic stimulation.

Rnpt4

In patients with episodic migraine asking for non-pharmacological treatments or achieving insufficient efficacy with pharmacological treatments, propose neuromodulation therapies, favoring remote electrical neuromodulation for the acute migraine treatment and supra-orbital transcutaneous electrical nerve stimulation for migraine prevention (Strength of recommendation: strong)

What neuromodulation therapies are effective in migraine?

Neuromodulation therapies were evaluated in a 2020 systematic review and meta-analysis (Table 1). For the acute treatment of migraine, the number of well-conducted studies is limited. Conditioned pain modulation by non-painful remote electrical neuromodulation (REN) is effective (level of evidence medium). This neuromodulation technique relates on the principle that pain inhibits pain. Single pulse transcranial magnetic stimulation (TMS), with a portable self-administered device, is effective for migraine with aura (level of evidence fair). One openlabel study suggested that it might be of interest even in migraine without aura. Supra-orbital transcutaneous electrical nerve stimulation (TENS) is possibly effective (level of evidence fair). Non-invasive vagus nerve stimulation (VNS) is ineffective (level of evidence fair for inefficacy). Concerning migraine prevention, everyday self-administered supra-orbital TENS is effective (level of evidence medium). Data concerning occipital TENS are inconclusive. High frequency repetitive TMS on the primary motor cortex (M1) is effective (level of evidence fair). Percutaneous electrical nerve stimulation (PENS) or electroacupuncture is possibly effective (level of evidence fair). Data concerning transcranial direct current stimulation (tDCS) are heterogeneous and inconclusive overall. Self-administered noninvasive

percutaneous VNS is ineffective (medium level of evidence for inefficacy). Invasive occipital nerve stimulation is probably effective for chronic migraine prevention (level of evidence medium), but no implantable device is currently FDA approved or CE marked in this indication.

6 Treatment of acute migraine attacks in adults: summary and conclusions from the literature review

6.1 Paracetamol

6.1.1 Paracetamol vs placebo

Paracetamol vs placebo for the acute treatment of migraine in adults			
Bibliography: SR VanderPluym 2021(1) Including Lipton 2000(14), Prior 2010(15)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2h	729 (2 studies)	Paracetamol: 57/366 Placebo: 30/363 **RR (95% CI): 1.89 (1.24 to 2.86)** **SS in favour of paracetamol** I^2= 0%	⨁⨁⨁⊖ **MODERATE** Study quality: -1; moderate risk randomization in one study Consistency: ok Directness: ok Imprecision: ok
Pain free at 24h	729 (2 studies)	Paracetamol: 124/366 Placebo: 69/363 **RR (95% CI): 1.78 (1.38 to 2.30)** **SS in favour of paracetamol** I^2=0.00%	⨁⨁⨁⊖ **MODERATE** Study quality: -1; moderate risk randomization in one study Consistency: ok Directness: ok Imprecision: ok
Pain relief at 2h (Improvement of pain from moderate to severe at baseline to mild or none or pain scale improved at least 50% from baseline at defined assessment time)	729 (2 studies)	Paracetamol: 177/366 Placebo: 109/363 **RR (95% CI): 1.61 (1.33 to 1.95)** **SS in favour of paracetamol** I^2=0.00%	⨁⨁⨁⊖ **MODERATE** Study quality: -1; moderate risk randomization in one study Consistency: ok Directness: ok Imprecision: ok
Pain relief at 24h (Improvement of pain from moderate to severe at baseline to mild or none or pain scale improved at least 50% from	729 (2 studies)	Paracetamol: 196/366 Placebo: 114/363 **RR (95% CI): 1.71 (1.43 to 2.04)**	⨁⨁⨁⊖ **MODERATE** Study quality: -1; moderate risk randomization in one study Consistency: ok Directness: ok Imprecision: ok

baseline at defined assessment time)		**SS in favour of paracetamol** I^2=0.00%	
Restored function at 2h (No restriction to perform work or usual activities)	729 (2 studies)	Paracetamol: 76/366 Placebo: 42/363 **RR: 1.8; 95% CI: 1.27 to 2.54** **SS in favour of paracetamol**	⨁⨁⨁⨀ **MODERATE** Study quality: -1; moderate risk randomization in one study Consistency: nd Directness: ok Imprecision: ok
Restored function at 24h (No restriction to perform work or usual activities)	729 (2 studies)	Paracetamol: 155/366 Placebo: 88/363 **RR: 1.75; 95% CI: 1.41 to 2.17** **SS in favour of paracetamol**	⨁⨁⨁⨀ **MODERATE** Study quality: -1; moderate risk randomization in one study Consistency: nd Directness: ok Imprecision: ok
Pain scale at 2h	729 (2 studies)	**SMD (95% CI): 0.39 (0.25 to 0.54)** **SS in favour of paracetamol**	⨁⨁⨁⨀ **MODERATE** Study quality: -1; moderate risk randomization in one study Consistency: nd Directness: ok Imprecision: ok
Pain scale at 24h	351 (1 study)	**SMD (95% CI): 0.31 (0.10 to 0.52)** **SS in favour of paracetamol**	⨁⨁⨀⨀ **LOW** Study quality: -2; single study with moderate risk of bias for randomization Consistency: na Directness: ok Imprecision: ok
Function scale at 2h	378 (1 study)	**SMD (95% CI): 0.38 (0.18 to 0.59)** **SS in favour of paracetamol**	⨁⨁⨁⨀ **MODERATE** Study quality: -1 single study Consistency: na Directness: ok Imprecision: ok
Serious adverse events	194 (2 studies)	RR: 0.99; 95% CI 0.06 to 15.86 NS I^2= 0%	⨁⨀⨀⨀ **VERY LOW** Study quality: -2; moderate risk randomization in one study; risk of missing data for serious adverse events Consistency: ok Directness: ok Imprecision: -1
Total adverse events	729 (2 studies)	RR: 0.82; 95% CI: 0.64 to 1.06; NS I^2=0.00%	⨁⨁⨁⨀ **MODERATE** Study quality: -1; moderate risk randomization in one study Consistency: ok Directness: ok Imprecision: ok

Table 5

This systematic review by VanderPluym 2021 searched for RCTs comparing abortive pharmacologic or noninvasive nonpharmacologic therapy with placebo, usual care, another pharmacologic therapy,

noninvasive nonpharmacologic therapy, wait list, no treatment, or attention control in adults with migraine.

Two RCTs comparing paracetamol to placebo and meeting our inclusion criteria were found. Paracetamol 1000 mg was compared to placebo.

There are some methodological problems that limit our confidence in the estimate of the results: one RCT had a moderate risk of bias pertaining to randomization.

In **adults with migraine**, **paracetamol** resulted in **more pain freedom at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **paracetamol** resulted in **more pain freedom at 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **paracetamol** resulted in **more pain relief at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **paracetamol** resulted in **more pain relief at 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **paracetamol** resulted in **more restored function at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **paracetamol** resulted in **more restored function at 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **paracetamol** resulted in **more improved pain scale at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **paracetamol** resulted in **more improved pain scale at 24h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **paracetamol** resulted in **more improved function scale at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between paracetamol and placebo for **serious adverse events** in **adults with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between paracetamol and placebo for **total adverse events** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

6.2 Acetylsalicylic acid

6.2.1 Acetylsalicylic acid vs placebo

ASA vs placebo for the acute treatment of migraine attack of moderate to severe baseline pain intensity in adults			
Bibliography: SR Kirthi 2013(16) Including Boureau 1994(17), Diener 2004a(18), Diener 2004b(19), Lange 2000(20), Lipton 2005(21), MacGregor 2002(22)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2h	2027 (6 studies)	Acetylsalicylic acid: 240/1008 (24%) Placebo: 117/1019 (11%) **RR (95% CI): 2.1 (1.7 to 2.6)** NNT (95% CI): 8.1 (6.4 to 11) **SS in favour of acetylsalicylic acid** I^2:0.0%	⨁⨁⨁⊖ **MODERATE** Study quality: -1; unclear allocation concealment in all studies, unclear randomization in 4 studies, unclear blinding in one study Consistency: ok Directness: ok Imprecision: ok
Pain relief at 1h (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	1288 (4 studies)	Acetylsalicylic acid: 236/641 (37%) Placebo: 99/647 (15%) **RR (95% CI): 2.4 (2.0 to 3.0)** NNT (95% CI): 4.7 (3.8 to 5.9)	⨁⨁⨁⊖ **MODERATE** Study quality: -1; unclear allocation concealment, unclear randomization in 2 studies Consistency: ok Directness: ok Imprecision: ok

		SS in favour of acetylsalicylic acid I^2:28%	
Pain relief at 2h (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	2027 (6 studies)	Acetylsalicylic acid: 525/1008 (52%) Placebo: 23/1019 (32%) **RR (95% CI): 1.6 (1.5 to 1.8)** NNT (95% CI): 4.9 (4.1 to 6.2) **SS in favour of acetylsalicylic acid** I^2:0.0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment, unclear randomization in 4 studies, unclear blinding in one study Consistency: ok Directness: ok Imprecision: ok
Pain relief over 24h (Headache relief at 2 hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication)	1142 (3 studies)	Acetylsalicylic acid: 223/568 (39%) Placebo: 138/574 (24%) **RR (95% CI): 1.6 (1.4 to 2.0)** NNT (95% CI): 6.6 (4.9 to 10 **SS in favour of acetylsalicylic acid** I^2:0.0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment, unclear randomization in 1 study Consistency: ok Directness: ok Imprecision: ok
Relief of nausea at 2h	878 (4 studies)	Acetylsalicylic acid: 56% Placebo: 44% **RR (95% CI): 1.3 (1.1 to 1.4)** NNT (95% CI): 9.0 (5.6 to 22) **SS in favour of acetylsalicylic acid** I^2:84%	⊕⊕⊖⊖ **LOW** Study quality: -1; unclear allocation concealment, unclear randomization in 3 studies, unclear blinding in one study Consistency: -1 Directness: ok Imprecision: ok
Relief of vomiting at 2h	139 (3 studies)	Acetylsalicylic acid: 73% Placebo: 66% RR (95% CI): 1.1 (0.94 to 1.3) NS I^2:35%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment, unclear randomization in 2 studies, unclear blinding in one study Consistency: ok Directness: ok Imprecision: ok
Relief of photophobia at 2h	1235 (5 studies)	Acetylsalicylic acid: 47% Placebo: 33% **RR (95% CI): 1.4 (1.2 to 1.6)** NNT (95% CI): 7.7 (5.4 to 13)	⊕⊕⊖⊖ **LOW** Study quality: -1; unclear allocation concealment, unclear randomization in 3 studies, unclear blinding in one study Consistency: -1 Directness: ok Imprecision: ok

		SS in favour of acetylsalicylic acid I^2:68%	
Relief of phonophobia at 2h	1217 (5 studies)	Acetylsalicylic acid: 49% Placebo: 34% **RR (95% CI): 1.4 (1.3 to 1.7)** NNT (95% CI): 6.6 (4.9 to 10) **SS in favour of acetylsalicylic acid** I^2:52%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment, unclear randomization in 3 studies, unclear blinding in one study Consistency: ok Directness: ok Imprecision: ok
Improvement of functional disability	73 (1 study)	Acetylsalicylic acid: 22/53 Placebo: (3/61) **RR (95% CI): 1.4 (1.3 to 1.7)** NNT (95% CI): 6.6 (4.9 to 10) **SS in favour of acetylsalicylic acid**	⊕⊕⊖⊖ **LOW** Study quality: -2 single study with unclear allocation concealment and randomization Consistency: ok Directness: ok Imprecision: ok
Use of rescue medication	1881 (5 studies)	Acetylsalicylic acid: 44% Placebo: 63% **RR (95% CI): 0.67 (0.61 to 0.73)** NNT to prevent (95% CI): 4.8 (3.9 to 6.0) **SS in favour of acetylsalicylic acid** I^2:0.0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment, unclear randomization in 3 studies, unclear blinding in one study Consistency: ok Directness: ok Imprecision: ok
Adverse events over 24h	1892 (5 studies)	Acetylsalicylic acid: 12% Placebo: 9% RR (95% CI): 1.3 (1.00 to 1.7) NS I^2:4.0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment, unclear randomization in 3 studies, unclear blinding in one study Consistency: ok Directness: ok Imprecision: ok

Table 6

This systematic review by Kirthi 2010 searched for all double blind RCTs comparing aspirin to placebo or an active control to treat an acute migraine episode in adults.

Six RCTs comparing acetylsalicylic acid to placebo, and meeting our inclusion criteria, were found.

Studies using a single dose of aspirin in established pain of at least moderate intensity were analyzed separately from studies in which medication was taken before pain was well established or in which a second dose of medication was permitted.

All treatments were administered orally, and when the headache was of moderate or severe intensity, except in one study, where up to 15% of participants had “slight” headache at baseline. Acetylsalicylic acid doses of 900 mg and 1000 mg were considered sufficiently similar to combine for analysis. Different formulations were used: oral tablet, mouth dispersible or effervescent formulations.

There are some methodological problems that limit our confidence in the estimate of the results: all the included RCTs had an unclear risk of bias pertaining to allocation concealment, 4 RCTs had an unclear risk of bias pertaining to randomization, and one RCT had an unclear risk of bias pertaining to blinding.

In **adults with migraine attack of moderate to severe baseline pain intensity**, **ASA** resulted in **more pain freedom at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine attack of moderate to severe baseline pain intensity**, **ASA** resulted in **more pain relief at 1h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine attack of moderate to severe baseline pain intensity**, **ASA** resulted in **more pain relief at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine attack of moderate to severe baseline pain intensity**, **ASA** resulted in **more pain relief over 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine attack of moderate to severe baseline pain intensity**, **ASA** resulted in **more relief of nausea** at 2h compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between ASA and placebo for **relief of vomiting** at 2h in **adults with migraine attack of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine attack of moderate to severe baseline pain intensity**, **ASA** resulted in **more relief of photophobia at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine attack of moderate to severe baseline pain intensity**, **ASA** resulted in **more relief of phonophobia at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine attack of moderate to severe baseline pain intensity**, **ASA** resulted in **more improvement of functional disability** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine attack of moderate to severe baseline pain intensity**, **ASA** resulted in **less use of rescue medication** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between ASA and placebo for **adverse events over 24h** in **adults with migraine attack of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

6.2.2 Acetylsalicylic acid vs ibuprofen

ASA vs ibuprofen for the acute treatment of migraine attack of moderate to severe baseline pain intensity in adults			
Bibliography: SR Kirthi 2013(16) Including Diener 2004b(19)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2h	212 (1 study)	Acetylsalicylic acid: 60/221 Ibuprofen: 70/211 **Insufficient data for analysis**	***Insufficient data***
Pain relief at 1h (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	212 (1 study)	Acetylsalicylic acid: 76/221 Ibuprofen: 65/211 **Insufficient data for analysis**	***Insufficient data***
Pain relief at 2h (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	212 (1 study)	Acetylsalicylic acid: 116/221 Ibuprofen: 127/211 **Insufficient data for analysis**	***Insufficient data***

Use of rescue medication	212 (1 study)	Acetylsalicylic acid: 99/221 Ibuprofen: 87/211 **Insufficient data for analysis**	***Insufficient data***
Adverse events	212 (1 study)	Acetylsalicylic acid: 36/221 Ibuprofen: 26/211 **Insufficient data for analysis**	***Insufficient data***

Table 7

This systematic review by Kirthi 2010 searched for all double blind RCTs comparing aspirin to placebo or an active control to treat an acute migraine episode in adults.

One RCT comparing acetylsalicylic acid to ibuprofen, and meeting our inclusion criteria, was found.

Studies using a single dose of aspirin in established pain of at least moderate intensity were analysed separately from studies in which medication was taken before pain was well established or in which a second dose of medication was permitted.
All treatments were administered when the headache was of moderate or severe intensity.
In the study ASA 1000mg was compared to ibuprofen 400 mg.

Authors calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants. As only one study was found in SR for the comparison acetylsalicylic acid to ibuprofen, no data analysis was performed.

We have **insufficient data** to compare ASA versus ibuprofen.

6.2.3 Acetylsalicylic acid vs sumatriptan

ASA vs sumatriptan for the acute treatment of migraine attack of moderate to severe baseline pain intensity in adults			
Bibliography: SR Kirthi 2013(16) Including Diener 2004a(18), Diener 2004b(19)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2h	726 (2 studies)	Acetylsalicylic acid: 97/367 (26%) Sumatriptan: 116/359 (32%) RR (95% CI): 0.82 (0.65 to 1.03) NS I^2:48%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in all studies Consistency: ok Directness: ok Imprecision: ok
Pain relief at 1h (Pain reduced from moderate or severe to none or mild	726 (2 studies)	Acetylsalicylic acid: 138/367 (38%) Sumatriptan: 85/359 (24%) **RR (95% CI): 1.6 (1.3 to 2.0)**	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in all studies Consistency: ok

without the use of rescue medication)		NNT (95% CI) 7.2 (4.9 to 14) **SS in favour of acetylsalicylic acid** I^2:16%	Directness: ok Imprecision: ok
Pain relief at 2h (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	726 (2 studies)	Acetylsalicylic acid: 188/367 (51%) Sumatriptan: 191/359 (53%) RR (95% CI): 0.96 (0.84 to 1.1) NS I^2:0.0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in all studies Consistency: ok Directness: ok Imprecision: ok
Relief of photophobia at 2h	575 (2 studies)	Acetylsalicylic acid: 60% Sumatriptan 66% RR (95% CI): 0.91 (0.80 to 1.03) NS I^2:0.0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in all studies Consistency: ok Directness: ok Imprecision: ok
Relief of phonophobia at 2h	540 (2 studies)	Acetylsalicylic acid: 63% Sumatriptan 65% RR (95% CI): 0.98 (0.86 to 1.1) NS I^2:0.0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in all studies Consistency: ok Directness: ok Imprecision: ok
Use of rescue medication	726 (2 studies)	Acetylsalicylic acid: 44% Sumatriptan: 40% RR (95% CI): 1.1 (0.92 to 1.3) NS I^2:0.0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in all studies Consistency: ok Directness: ok Imprecision: ok
Adverse events over 24h	730 (2 studies)	Acetylsalicylic acid: 55/369 (15%) Sumatriptan: 64/361 (18%) RR (95% CI): 0.85 (0.61 to 1.2) NS I^2:0.0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in all studies Consistency: ok Directness: ok Imprecision: ok

Table 8

This systematic review by Kirthi 2010 searched for all double blind RCTs comparing aspirin to placebo or an active control to treat an acute migraine episode in adults.

Two RCTs comparing acetylsalicylic acid to sumatriptan, and meeting our inclusion criteria, were found.

Studies using a single dose of aspirin in established pain of at least moderate intensity were analysed separately from studies in which medication was taken before pain was well established or in which a second dose of medication was permitted.
All treatments were administered when the headache was of moderate or severe intensity.
Acetylsalicylic acid doses of 900 mg and 1000 mg were considered sufficiently similar to combine for analysis. Different formulations were used: oral tablet, mouth dispersible or effervescent formulations and compared to sumatriptan 50 mg.

There are some methodological problems that limit our confidence in the estimate of the results: both included RCTs had an unclear risk of bias pertaining to allocation concealment.

There was **no difference** between ASA and sumatriptan for **pain freedom at 2h** in **adults with migraine attack of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine attack of moderate to severe baseline pain intensity**, **ASA** resulted in **more pain relief at 1h** compared to sumatriptan.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between ASA and sumatriptan for **pain relief at 2h** in **adults with migraine attack of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between ASA and sumatriptan for **relief of photophobia** at 2h in **adults with migraine attack of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between ASA and sumatriptan for **relief of phonophobia** at 2h in **adults with migraine attack of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between ASA and sumatriptan for **the use of rescue medication** in **adults with migraine attack of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between ASA and sumatriptan for **adverse events over 24h** in **adults with migraine attack of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

6.3 NSAID

6.3.1 Diclofenac vs placebo

Diclofenac vs placebo for the acute treatment of migraine attack of moderate to severe baseline pain intensity in adults			
Bibliography: Derry 2013(23) Including DKSMSG 1999(24), Diener 2006(25), Lipton 2010(26), Vecsei 2007(27)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2h (Number of attacks reduced to less than 20 mm on a 100 mm VAS)	1477 (2 studies)	Diclofenac: 195/873 (22%) Placebo: 67/604 (11%) **RR (95% CI): 2.0 (1.6 to 2.6)** NNT (95% CI): 8.9 (6.7 to 13) **SS in favour of diclofenac** I^2: 40%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in 1 RCT and randomization in 1 RCT, unclear blinding and incomplete data in 1 RCT Consistency: ok Directness: ok Imprecision: ok
Pain relief at 2h (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	1477 (2 studies)	Diclofenac : 482/873 (55%) Placebo: 236/604 (39%) **RR (95% CI): 1.5 (1.3 to 1.7)** NNT (95% CI): 6.2 (4.7 to 9.1) **SS in favour of diclofenac** I^2: 0.0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in 1 RCT and randomization in 1 RCT, unclear blinding and incomplete data in 1 RCT Consistency: ok Directness: ok Imprecision: ok
Sustained pain free over 24h (headache relief at 2 hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication)	1578 (2 studies)	Diclofenac : 175/932 (19%) Placebo: 53/646 (8.2%) **RR (95% CI): 2.3 (1.7 to 3.0)** NNT (95% CI): 9.5 (7.2 to 14) **SS in favour of diclofenac** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in 1 RCT and randomization in 2 RCTs Consistency: ok Directness: ok Imprecision: ok

Improvement of functional disability	873 (2 studies)	Diclofenac : 143/431 Placebo: 62/442 **RR (95% CI): 2.36 (1.8 to 3.08)** NNT (95% CI): 5.2 (4.1 to 7.3) **SS in favour of diclofenac** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment and randomization in 2 RCTs Consistency: ok Directness: ok Imprecision: ok
Adverse events	1578 (3 studies)	Diclofenac : 109/596 (18%) Placebo: 78/479 (16%) RR (95% CI): 1.1 (0.86 to 1.5) NS I^2: 20%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in 2 RCTs and randomization in 3 RCTs Consistency: ok Directness: ok Imprecision: ok

Table 9

This systematic review by Derry 2013 searched for double-blind RCTs that compared diclofenac to placebo or an active control for the acute treatment of a migraine headache episode in adults.

4 RCTs that compared diclofenac to placebo were found.
Authors analysed studies using a single dose of diclofenac in established pain of at least moderate intensity **separately** from studies in which medication was taken before pain became well established, or in which a second dose of medication was permitted. In one study participants were instructed to wait until pain intensity was moderate or severe before taking study medication, and in two other, the vast majority (90%) had at least moderate pain at baseline, so this subset was analysed together.
In one RCT the majority of participants took a second dose. Authors did not combine the different dosing regimens for analysis. We are not reporting this study because this constitutes a different dosage regiment which does not meet our inclusion criteria.

Results presented in the MA report results for diclofenac potassium 50 mg. There were insufficient data for analysis of the 100 mg dose compared with placebo.

There are some methodological problems that limit our confidence in the estimate of the results: three of the RCTs had an unclear risk of bias pertaining randomization and allocation concealment. One RCT had an unclear risk of bias pertaining to blinding and incomplete outcome data.

In **adults with migraine of moderate to severe baseline pain intensity**, **diclofenac** resulted in **more pain freedom at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **diclofenac** resulted in **more pain relief at 2h** compared to placebo.

GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **diclofenac** resulted in **more sustained pain freedom over 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **diclofenac** resulted in **more improvement of functional disability** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between diclofenac and placebo for **adverse events** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

6.3.2 Ibuprofen vs placebo

Ibuprofen 200 mg vs placebo for the acute treatment of migraine of moderate to severe baseline pain intensity in adults			
Bibliography: SR Rabbie 2013(28) Including Codispoti 2001(29), Kellstein 2001(30)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2h	777 (2 studies)	Ibuprofen: 84/414 (20%) Placebo: 36/363 (10%) **RR (95% CI): 2.0 (1.4 to 2.8)** **NNT (95% CI): 9.7 (6.5 to 18)** **SS in favour of ibuprofen** **I^2: 0%**	⨁⨁⨁⊖ **MODERATE** Study quality: -1; one RCT with unclear allocation concealment and randomization Consistency: ok Directness: ok Imprecision: ok
Pain relief at 2h (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	777 (2 studies)	Ibuprofen: 217/414 (52%) Placebo: 133/363 (37%) **RR (95% CI): 1.4 (1.2 to 1.6)** **NNT (95% CI): 6.3 (4.4 to 11)** **SS in favour of ibuprofen** **I^2: 0%**	⨁⨁⨁⊖ **MODERATE** Study quality: -1; one RCT with unclear allocation concealment and randomization Consistency: ok Directness: ok Imprecision: ok

Pain relief at 1h (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	777 (2 studies)	Ibuprofen: 141/414 (34%) Placebo: 83/363 (23%) **RR (95% CI): 1.5 (1.2 to 1.8)** **NNT (95% CI): 8.9 (5.7 to 20)** **SS in favour of ibuprofen** **I^2: 0%**	⊕⊕⊕⊖ **MODERATE** Study quality: -1; one RCT with unclear allocation concealment and randomization Consistency: ok Directness: ok Imprecision: ok
Sustained pain relief over 24h (headache relief at 2 hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication)	340 (1 study)	Ibuprofen: 54% Placebo: 35% **No analysis provided**	Insufficient data
Relief of nausea at 2h	429 (2 studies)	Ibuprofen: 115/234 Placebo: 70/195 **RR (95% CI): 1.33 (1.06 to 1.67)** **SS in favour of ibuprofen** **I^2: 0%**	⊕⊕⊕⊖ **MODERATE** Study quality: -1; one RCT with unclear allocation concealment and randomization Consistency: ok Directness: ok Imprecision: ok
Relief of photophobia at 2h	751 (2 studies)	Ibuprofen: 102/401 Placebo: 62/350 **RR (95% CI): 1.4 (1.05 to 1.85)** **SS in favour of ibuprofen** **I^2: 0%**	⊕⊕⊕⊖ **MODERATE** Study quality: -1; one RCT with unclear allocation concealment and randomization Consistency: ok Directness: ok Imprecision: ok
Relief of phonophobia at 2h	724 (2 studies)	Ibuprofen: 113/386 Placebo: 68/338 **RR (95% CI): 1.4 (1.08 to 1.82)** **SS in favour of ibuprofen** **I^2: 0%**	⊕⊕⊕⊖ **MODERATE** Study quality: -1; one RCT with unclear allocation concealment and randomization Consistency: ok Directness: ok Imprecision: ok
Improvement of functional disability	757 (2 studies)	Ibuprofen: 187/406 Placebo: 104/351 **RR (95% CI): 1.4 (1.18 to 1.66)**	⊕⊕⊕⊖ **MODERATE** Study quality: -1; one RCT with unclear allocation concealment and randomization Consistency: ok Directness: ok

		SS in favour of ibuprofen **I^2: 0%**	Imprecision: ok
Use of rescue medication	777 (2 studies)	Ibuprofen: 112/414 Placebo: 1147/363 **RR (95% CI): 0.7 (0.58,0.86)** **SS in favour of ibuprofen** **I^2: 55%**	⊕⊕⊕⊖ **MODERATE** Study quality: -1; one RCT with unclear allocation concealment and randomization Consistency: ok Directness: ok Imprecision: ok
Adverse events over 24h	780 (2 studies)	Ibuprofen: 90/416 (22%) Placebo: 101/364 (28%) RR (95% CI): 0.85 (0.67 to 1.1) NS I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; one RCT with unclear allocation concealment and randomization Consistency: ok Directness: ok Imprecision: ok

Table 10

Ibuprofen 400 mg vs placebo for the acute treatment of migraine of moderate to severe baseline pain intensity in adults			
Bibliography: SR Rabbie 2013(28) Including Codispoti 2001(29), Diener 2004(31), Goldstein 2006(32), Misra 2004(33), Misra 2007(34), Saper 2006(35), Kellstein 2001(30), Sandrini 1998(36)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2h	2575 (6 studies)	Ibuprofen: 401/1553 (26%) Placebo: 128/1042 (12%) **RR (95% CI): 1.9 (1.6 to 2.3)** **NNT (95% CI): 7.2 (5.9 to 9.2)** **SS in favour of ibuprofen** I^2: 81%	⊕⊕⊖⊖ **LOW** Study quality: -1; unclear allocation concealment in 4 RCTs; unclear randomization in 2 RCTs, unclear blinding in 1 RCT, unclear risk of incomplete outcome data in 1 RCT Consistency:- 1 Directness: ok Imprecision: ok
Pain relief at 2h (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	1815 (7 studies)	Ibuprofen: 528/931 (57%) Placebo: 224/884 (25%) **RR (95% CI): 2.2 (1.9 to 2.5)** **NNT (95% CI): 3.2 (2.8 to 3.7)** **SS in favour of ibuprofen** I^2: 90%	⊕⊕⊖⊖ **LOW** Study quality: -1; unclear allocation concealment in 3 RCTs; unclear randomization in 1 RCT, unclear blinding in 1 RCT, unclear risk of incomplete outcome data in 1 RCT Consistency: -1 Directness: ok Imprecision: ok

Pain relief at 1h (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	1269 (4 studies)	Ibuprofen: 226/655 (35%) Placebo: 108/614 (18%) **RR (95% CI): 1.9 (1.5 to 2.3)** **NNT (95% CI): 5.9 (4.6 to 8.2)** **SS in favour of ibuprofen** I^2: 77%	⊕⊕⊖⊖ **LOW** Study quality: -1; unclear allocation concealment in 2 RCTs, unclear randomization in 1 RCT Consistency: -1 Directness: ok Imprecision: ok
Sustained pain free over 24h (headache relief at 2 hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication)	376 (1 study)	Ibuprofen: 18% Placebo: 3% No analysis provided	Insufficient data
Sustained pain relief over 24h (headache relief at 2 hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication)	879 (4 studies)	Ibuprofen: 208/467 (45%) Placebo: 80/412 (19%) **RR (95% CI): 2.2 (1.8 to 2.7)** **NNT (95% CI): 4.0 (3.2 to 5.2)** **SS in favour of ibuprofen** I^2: 75%	⊕⊕⊖⊖ **LOW** Study quality: -1; unclear allocation concealment in 2 RCTs unclear randomization in 1 RCT, unclear blinding in 1 RCT, unclear risk of incomplete outcome data in 1 RCT Consistency: -1 Directness: ok Imprecision: ok
Relief of nausea at 2h	336 (3 studies)	Ibuprofen: 170/328 Placebo: 102/306 **RR (95% CI): 1.54 (1.27 to 1.86)** **SS in favour of ibuprofen** I^2: 30%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in and randomization in 1 RCT, unclear risk of incomplete outcome data in 1 RCT Consistency: ok Directness: ok Imprecision: ok
Relief of vomiting at 2h	93 (2 studies)	Ibuprofen: 40/44 Placebo: 30/49 **RR (95% CI): 1.53 (1.21 to 1.92)** **SS in favour of ibuprofen** I^2: 86%	⊕⊕⊖⊖ **LOW** Study quality: -1 unclear risk of incomplete outcome data in 1 RCT Consistency: -1 Directness: ok Imprecision: ok
Relief of photophobia at 2h	1328 (4 studies)	Ibuprofen: 260/689 Placebo: 159/639 **RR (95% CI): 1.51 (1.29 to 1.77)**	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in 2 RCTs, unclear randomization in 1 RCT, unclear risk of incomplete outcome data in 1 RCT

		SS in favour of ibuprofen I^2: 43%	Consistency: ok Directness: ok Imprecision: ok
Relief of phonophobia at 2h	1261 (4 studies)	Ibuprofen: 274/652 Placebo: 159/609 **RR (95% CI): 1.63 (1.39 to 1.90)** **SS in favour of ibuprofen** I^2: 21%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in 2 RCTs, unclear randomization in 1 RCT, unclear risk of incomplete outcome data in 1 RCT Consistency: ok Directness: ok Imprecision: ok
Improvement of functional disability	114 (3 studies)	Ibuprofen: 245/583 Placebo: 129/531 **RR (95% CI): 1.61 (1.38 to 1.89)** **SS in favour of ibuprofen** I^2: 78%	⊕⊕⊖⊖ **LOW** Study quality: -1; unclear allocation concealment in and randomization in 1 RCT, unclear risk of incomplete outcome data in 1 RCT Consistency: -1 Directness: ok Imprecision: ok
Use of rescue medication	1815 (7 studies)	Ibuprofen: 353/931 Placebo: 516/884 **RR (95% CI): 0.67 (0.61 to 0.74)** **SS in favour of ibuprofen** I^2: 66%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in 3 RCTs; unclear randomization in 1 RCT, unclear blinding in 1 RCT, unclear risk of incomplete outcome data in 1 RCT Consistency: ok Directness: ok Imprecision: ok
Adverse events over 24h	1767 (7 studies)	Ibuprofen: 231/1557 (15%) Placebo: 206/1079 (19%) RR (95% CI): 0.97 (0.82 to 1.2) NS I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in 4 RCTs; unclear randomization in 2 RCTs, unclear blinding in 1 RCT, unclear risk of incomplete outcome data in 1 RCT Consistency: ok Directness: ok Imprecision: ok

Table 11

Ibuprofen 600 mg vs placebo for the acute treatment of migraine of moderate to severe baseline pain intensity in adults			
Bibliography: SR Rabbie 2013(28) Including Kellstein 2001(30)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2h	340 (1 study)	Ibuprofen: 58/198 Placebo: 19/142	⊕⊕⊖⊖ **LOW**

		RR (95% CI): 2.19 (1.37 to 3.51) **SS in favour of ibuprofen**	Study quality: -2; single study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: ok
Pain relief at 2h (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	340 (1 study)	Ibuprofen: 142/198 Placebo: 71/142 **RR (95% CI): 1.43 (1.19 to 1.73)** **SS in favour of ibuprofen**	⊕⊕⊖⊖ **LOW** Study quality: -2; single study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: ok

Table 12

This systematic review by Rabbie 2013 searched for all double-blind RCTs that compared ibuprofen to placebo or active control for the acute treatment of a migraine headache in adults.

9 RCTs that compared ibuprofen to placebo were found. Rabbie 2013 pooled the results for ibuprofen 200 mg (2 studies), ibuprofen 400 mg (8 studies) and ibuprofen 600 mg (1 study) separately.
Authors analysed studies using a single dose of ibuprofen in established pain of at least moderate intensity **separately** from studies in which medication was taken before pain was well established or in which a second dose of medication was permitted. All studies treated an attack with a single dose of study medication when pain was of at least moderate severity.
One study providing data for all the dosages used an oral liquigel formulation (solubilised ibuprofen potassium), and study providing data for the 400 mg dosage used oral ibuprofen arginine. Other studies used standard oral tablet.

There are some methodological problems that limit our confidence in the estimate of the results: Two of the studies did not meet our inclusion criteria for sample size; of the remaining studies 4 had an unclear risk of bias pertaining to allocation concealment, two had an unclear risk of bias pertaining to randomization, one RCT had an unclear risk of bias pertaining to blinding and one to incomplete outcome data. The heterogeneity was high for some of the outcomes.

Ibuprofen 200 mg

In **adults with migraine of moderate to severe baseline pain intensity**, **ibuprofen 200 mg** resulted in **more pain freedom at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **ibuprofen 200 mg** resulted in **more pain relief at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **ibuprofen 200 mg** resulted in **more pain relief at 1h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

We have **insufficient data** to compare **sustained pain relief over 24h** in ibuprofen 200 mg versus placebo.

In **adults with migraine of moderate to severe baseline pain intensity**, **ibuprofen 200 mg** resulted in **more relief of nausea at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **ibuprofen 200 mg** resulted in **more relief of photophobia at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **ibuprofen 200 mg** resulted in **more relief of phonophobia at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **ibuprofen 200 mg** resulted in **more improvement of functional disability** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **ibuprofen 200 mg** resulted in **less use of rescue medication** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between ibuprofen 200 mg and placebo for **adverse events over 24h** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

Ibuprofen 400 mg

In **adults with migraine of moderate to severe baseline pain intensity**, **ibuprofen 400 mg** resulted in **more pain freedom at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine of moderate to severe baseline pain intensity**, **ibuprofen 400 mg** resulted in **more pain relief at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine of moderate to severe baseline pain intensity**, **ibuprofen 400 mg** resulted in **more pain relief at 1h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

We have **insufficient data** to compare **sustained pain freedom over 24h** in ibuprofen 400 mg versus placebo.

In **adults with migraine of moderate to severe baseline pain intensity**, **ibuprofen 400 mg** resulted in **more sustained pain relief over 24h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine of moderate to severe baseline pain intensity**, **ibuprofen 400 mg** resulted in **more relief of nausea at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **ibuprofen 400 mg** resulted in **more relief of vomiting at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine of moderate to severe baseline pain intensity**, **ibuprofen 400 mg** resulted in **more relief of photophobia at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **ibuprofen 400 mg** resulted in **more relief of phonophobia at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **ibuprofen 400 mg** resulted in **more improvement of functional disability** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine of moderate to severe baseline pain intensity**, **ibuprofen 400 mg** resulted in **less use of rescue medication** compared to placebo.

GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between ibuprofen 400 mg and placebo for **adverse events over 24h** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

Ibuprofen 600 mg

In **adults with migraine of moderate to severe baseline pain intensity**, **ibuprofen 600 mg** resulted in **more pain freedom at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine of moderate to severe baseline pain intensity**, **ibuprofen 600 mg** resulted in **more pain relief at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

6.3.3 Naproxen vs placebo

Naproxen vs placebo for the acute treatment of migraine attacks of moderate to severe baseline pain intensity in adults			
Bibliography: Law 2013(37) Including Brandes 2007 (study 1 and 2)(38), Smith 2005(39), Wentz 2008(40)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2 h	2149 (4 studies)	Naproxen: 17% (183/1064) Placebo: 8.5% (92/1085) **RR (95% CI): 2.0 (1.6 to 2.6)** NNT (95%CI): 11 (8.7 to 17) **SS in favour of naproxen** I^2: 59%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment and randomization in 3 RCTs, unclear blinding in 2 RCTs Consistency: ok Directness: ok Imprecision: ok
Pain relief at 2 h (Headache relief was defined as a decrease from an initial moderate or severe	2149 (4 studies)	Naproxen: 45% (482/1064) Placebo: 29% (311/1085) **RR (95% CI): 1.6 (1.4 to 1.8)** NNT (95%CI): 6 (4.8 to 7.9)	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment and randomization in 3 RCTs, unclear blinding in 2 RCTs Consistency: ok Directness: ok

headache to mild or none.)		**SS in favour of naproxen** I^2: 0%	Imprecision: ok
Sustained pain-free over 24h (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	2149 (4 studies)	Naproxen: 12% (129/1064) Placebo: 6.7% (73/1085) **RR (95% CI): 1.8 (1.4 to 2.4)** NNT (95%CI): 19 (13 to 34) **SS in favour of naproxen** I^2: 62%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment and randomization in 3 RCTs, unclear blinding in 2 RCTs Consistency: ok Directness: ok Imprecision: ok
Sustained pain relief over 24 h (PO) (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.)	2149 (4 studies)	Naproxen: 30% (315/1064) Placebo: 18% (190/1085) **RR (95% CI): 1.7 (1.5 to 2.0)** NNT (95%CI): 8.3 (6.4 to 12) **SS in favour of naproxen** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment and randomization in 3 RCTs, unclear blinding in 2 RCTs Consistency: ok Directness: ok Imprecision: ok
Relief of nausea at 2h	782 (3 studies)	Naproxen: 156/398 Placebo: 88/384 **RR (95% CI): 1.73 (1.38 to 2.16)** **SS in favour of naproxen** I^2: 70%	⊕⊕⊖⊖ **LOW** Study quality: -1; unclear allocation concealment and randomization in 2 RCTs, unclear blinding in 2 RCTs Consistency: -1 Directness: ok Imprecision: ok
Relief of photophobia at 2h	1342 (3 studies)	Naproxen: 215/666 Placebo: 126/676 **RR (95% CI): 1.73 (1.43 to 2.10)** **SS in favour of naproxen** I^2: 0	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment and randomization in 2 RCTs, unclear blinding in 2 RCTs Consistency: ok Directness: ok Imprecision: ok
Relief of phonophobia at 2h	1313 (3 studies)	Naproxen: 221/637 Placebo: 140/676 **RR (95% CI): 1.68 (1.40 to 2.01)** **SS in favour of naproxen** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment and randomization in 2 RCTs, unclear blinding in 2 RCTs Consistency: ok Directness: ok Imprecision: ok
Relief of functional disability at 2h	1346 (3 studies)	Naproxen: 131/667 Placebo: 62/679	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment and

		RR (95% CI): 2.14 (1.62 to 2.84) **SS in favour of naproxen** I^2: 0%	randomization in 2 RCTs, unclear blinding in 2 RCTs Consistency: ok Directness: ok Imprecision: ok
Adverse events	2174 (4 studies)	Naproxen: 15% (165/1078) Placebo: 12% (128/1096) **RR (95% CI): 1.3 (1.1 to 1.6)** NNH (95%CI): 28 (15 to 132) **SS in favour of placebo (more adverse events with naproxen)** I^2: 48%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment and randomization in 3 RCTs, unclear blinding in 2 RCTs Consistency: ok Directness: ok Imprecision: ok
Use of rescue medication	2149 (4 studies)	Naproxen: 440/1064 Placebo: 630/1085 **RR (95% CI): 0.71 (0.65 to 0.78)** **SS in favour of naproxen (less rescue medication with naproxen)** I^2: 48%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment and randomization in 3 RCTs, unclear blinding in 2 RCTs Consistency: ok Directness: ok Imprecision: ok

Table 13

This systematic review by Law 2013 searched for all double-blind RCTs that compared naproxen to placebo or an active control to treat an acute episode of migraine in adults.

4 RCTs were found that compared naproxen to placebo.

Authors analysed studies using a single dose of naproxen in established pain of at least moderate intensity separately from studies in which medication was taken before pain was well established or in which a second dose of medication was permitted.
In all studies, medication was to be taken when the pain intensity was at least moderate.
For analysis of the placebo-controlled studies, authors chose to combine results from the three using naproxen 500 mg with the one using naproxen 825 mg.

There are some methodological problems that limit our confidence in the estimate of the results: 3 RCTs had unclear randomization and allocation concealment; 2 RCTs had unclear blinding.

In **adults with migraine attacks of moderate to severe baseline pain intensity**, **naproxen** resulted in **more pain freedom at 2h** compared to placebo.
GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine attacks of moderate to severe baseline pain intensity**, **naproxen** resulted in **more pain relief at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine attacks of moderate to severe baseline pain intensity**, **naproxen** resulted in **more sustained pain freedom over 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine attacks of moderate to severe baseline pain intensity**, **naproxen** resulted in **more sustained pain relief over 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine attacks of moderate to severe baseline pain intensity**, **naproxen** resulted in **more relief of nausea at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine attacks of moderate to severe baseline pain intensity**, **naproxen** resulted in **more relief of photophobia at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine attacks of moderate to severe baseline pain intensity**, **naproxen** resulted in **more relief of phonophobia at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine attacks of moderate to severe baseline pain intensity**, **naproxen** resulted in **more relief of functional disability at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine attacks of moderate to severe baseline pain intensity**, **naproxen** resulted in **more adverse events** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine attacks of moderate to severe baseline pain intensity**, **naproxen** resulted in **less use of rescue medication** compared to placebo.
GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

6.3.4 Diclofenac vs sumatriptan

Diclofenac vs sumatriptan for the acute treatment of migraine in adults			
Bibliography: SR Xu 2016(41) Including DKSMSG 1999(24)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 1 h	115 (1 study)	OR (95% CI): 1.19 (0.54 to 2.63) NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-2; single small study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision:-1
Absence of nausea at 2 h	115 (1 study)	OR (95% CI): 1.25 (0.87 to 1.81) NS	⨁⨁⊖⊖ **LOW** Study quality: -2; single small study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: ok
Migraine recurrence	115 (1 study)	OR (95% CI): 0.88 (0.54 to 1.43) NS	⨁⨁⊖⊖ **LOW** Study quality: -2; single small study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: ok
Adverse events	115 (1 study)	**OR (95% CI): 0.43 (0.26 to 0.71)** **SS in favour of diclofenac (fewer AE with diclofenac)**	⨁⨁⊖⊖ **LOW** Study quality: -2; single small study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: ok

Table 14

In this NMA, authors performed a systematic review for double-blind RCTs that compared NSAIDs and triptans. They initially carried out a conventional pair-wise meta-analysis which directly compares each pair of treatments then the NMA was performed for each endpoint. In this document we have only reported data from direct comparisons.

One RCT was found that compared diclofenac to sumatriptan.
Medication was taken at the first sign of a migraine attack.

There are some methodological problems that limit our confidence in the estimate of the results: this is a single small study with unclear risk of bias pertaining to randomization and allocation concealment. The attrition rate was high: 20%, 12% for reasons other than lack of qualifying headache.

There was **no difference** between diclofenac and sumatriptan for **pain freedom at 1h** in **adults with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between diclofenac and sumatriptan for **absence of nausea at 2h** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between diclofenac and sumatriptan for **migraine recurrence** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **diclofenac** resulted in **fewer adverse events** compared to sumatriptan.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low

6.3.5 Ibuprofen vs rizatriptan

Ibuprofen vs rizatriptan for the acute treatment of migraine in adults			
Bibliography: SR Xu 2016(41) Including Misra 2007(34)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2 h	155 (1 study)	OR (95% CI): 0.86 (0.40 to 1.85) NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-2; single small study with unclear allocation concealment and blinding Consistency: na Directness: -1, study included patients as young as 16 y Imprecision: ok
Pain relief at 2h	155 (1 study)	OR (95% CI): 0.72 (0.39 to 1.35) NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-2; single small study with unclear allocation concealment and blinding Consistency: na

			Directness: -1, study included patients as young as 16 y Imprecision: ok
Use of rescue medication	(155 (1 study)	OR (95% CI): 1.75 (0.82, 3.74) NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-2; single small study with unclear allocation concealment and blinding Consistency: na Directness: ok Imprecision: -1
Adverse events	155 (1 study)	OR (95% CI): 0.91 (0.33, 2.53) NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-2; single small study with unclear allocation concealment and blinding Consistency: na Directness: ok Imprecision: -1

Table 15

In this NMA, authors performed a systematic review for double-blind RCTs that compared NSAIDs and triptans. They initially carried out a conventional pair-wise meta-analysis which directly compares each pair of treatments then the NMA was performed for each endpoint. In this document we have only reported data from direct comparisons.

One RCT was found that compared ibuprofen to rizatriptan. Ibuprofen 400 mg was compared to rizatriptan 10 mg.

Medication was to be taken when the pain intensity was at least moderate.

There are some methodological problems that limit our confidence in the estimate of the results: this is a single small study with unclear risk of bias pertaining to allocation concealment and blinding. This study *described itself as double-blind, but used treatments that were potentially distinguishable if directly compared. It treated two or more attacks with single doses of the same study medication. It is not clear how the data for multiple attacks were combined in these studies. Level of evidence was also downgraded for directness as this study enrolled patients from 16 years.*

There was **no difference** between ibuprofen and rizatriptan for **pain freedom at 2h** in **adults with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between ibuprofen and rizatriptan for **pain relief at 2h** in **adults with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between ibuprofen and rizatriptan for **use of rescue medication** in **adults with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between ibuprofen and rizatriptan for **adverse events** in **adults with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

6.3.6 Ibuprofen vs sumatriptan

Ibuprofen vs sumatriptan for the acute treatment of migraine in adults			
Bibliography: SR Xu 2016(41) Including Diener 2004(31)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 1 h	312 (1 study)	OR (95% CI): 1.87 (0.90 to 3.89) NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1; single study with unclear allocation concealment Consistency: na Directness: ok Imprecision: ok
Pain relief at 1 h	312 (1 study)	OR (95% CI): 1.30 (0.87 to 1.96) NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1; single study with unclear allocation concealment Consistency: na Directness: ok Imprecision: ok
Pain free at 2h	312 (1 study)	OR (95% CI): 0.90 (0.62 to 1.30) NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1; single study with unclear allocation concealment Consistency: na Directness: ok Imprecision: ok
Pain relief at 2h	312 (1 study)	OR (95% CI): 1.09 (0.80 to 1.49) NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1; single study with unclear allocation concealment Consistency: na Directness: ok Imprecision: ok
Use of rescue medication	312 (1 study)	OR (95% CI): 1.01 (0.71 to 1.43) NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1; single study with unclear allocation concealment Consistency: na Directness: ok Imprecision: ok
Migraine recurrence	312 (1 study)	OR (95% CI): 0.84 (0.53 to 1.32) NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1; single study with unclear allocation concealment Consistency: na Directness: ok

			Imprecision: ok
Adverse events	312 (1 study)	OR (95% CI): 1.07 (0.07 to 17.2) NS	⨁⨁⨀⨀ **LOW** Study quality: -1; single study with unclear allocation concealment Consistency: na Directness: ok Imprecision: -1

Table 16

In this NMA, authors performed a systematic review for double-blind RCTs that compared NSAIDs and triptans. They initially carried out a conventional pair-wise meta-analysis which directly compares each pair of treatments then the NMA was performed for each endpoint. In this document we have only reported data from direct comparisons.

One RCT was found that compared ibuprofen to sumatriptan.

Medication was to be taken when the pain intensity was at least moderate. Ibuprofen 400 mg was compared to sumatriptan 50 mg.

There are some methodological problems that limit our confidence in the estimate of the results: this is a single study with unclear risk of bias pertaining to allocation concealment.

There was **no difference** between ibuprofen and sumatriptan for **pain freedom at 1h** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between ibuprofen and sumatriptan for **pain relief at 1h** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between ibuprofen and sumatriptan for **pain freedom at 2h** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between ibuprofen and sumatriptan for **pain relief at 2h** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between ibuprofen and sumatriptan for **use of rescue medication** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between ibuprofen and sumatriptan for **migraine recurrence** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between ibuprofen and sumatriptan for **adverse events** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

6.3.7 Naproxen vs sumatriptan

Naproxen vs sumatriptan for the acute treatment of migraine of moderate to severe baseline pain intensity in adults			
Bibliography: Law 2013(37) Including Smith 2005(39)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2 h	474 (1 study)	Naproxen: 45/248 (18%) Sumatriptan: 45/226 (20%) NS	⨁⨁⨀⨀ **LOW** Study quality: -2; single study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: na
Pain relief at 2 h (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	474 (1 study)	Naproxen: 114/248 (46%) Sumatriptan: 111/226 (49%) NS	⨁⨁⨀⨀ **LOW** Study quality: -2; single study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: na
Sustained pain-free over 24h (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	474 (1 study)	Naproxen: 30/248 (12%) Sumatriptan: 25/226 (11%) NS	⨁⨁⨀⨀ **LOW** Study quality: -2; single study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: na
Sustained pain relief over 24 h (Headache relief at two hours, sustained for 24 hours, with no	474 (1 study)	Naproxen: 62/248 (25%) Sumatriptan: 66/226 (29%) NS	⨁⨁⨀⨀ **LOW** Study quality: -2; single study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: na

use of rescue medication or a second dose of study medication.)			
Use of rescue medication	474 (1 study)	Naproxen: 129/248 Sumatriptan: 115/226 NS	⨁⨁⊖⊖ **LOW** Study quality: -2; single study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: na
Adverse events within 24 h	474 (1 study)	Naproxen: 43/250 (17%) Sumatriptan: 55/229 (24%) NS	⨁⨁⊖⊖ **LOW** Study quality: -2; single study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: na

Table 17

This systematic review by Law 2013 searched for all double-blind RCTs that compared naproxen to placebo or an active control to treat an acute episode of migraine in adults.

1 RCT was found that compared naproxen to sumatriptan. Naproxen 500 mg was compared to sumatriptan 50 mg.

Authors analysed studies using a single dose of naproxen in established pain of at least moderate intensity separately from studies in which medication was taken before pain was well established or in which a second dose of medication was permitted.
Medication was to be taken when the pain intensity was at least moderate.

There are some methodological problems that limit our confidence in the estimate of the results: this was a single study with an unclear risk of bias pertaining to randomization and allocation concealment.

There was **no difference** between naproxen and sumatriptan for **pain freedom at 2h** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between naproxen and sumatriptan for **pain relief at 2h** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between naproxen and sumatriptan for **sustained pain freedom over 24h** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between naproxen and sumatriptan for **sustained pain relief over 24h** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between naproxen and sumatriptan for **use of rescue medication** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between naproxen and sumatriptan for **adverse events within 24h** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

6.3.8 Naproxen vs naratriptan

A systematic review by Law 2013(37) searched for all double-blind RCTs that compared naproxen to placebo or an active control to treat an acute episode of migraine in adults.

2 RCTs were found that compared naproxen to naratriptan, but they did not meet our inclusion criteria (they did not report any of our prespecified outcomes, and only reported combined data for all attacks over 12 weeks (not useful data))

6.4 Associations with caffeine

6.4.1 Paracetamol + ASA + caffeine vs placebo

APC vs placebo for the treatment of a migraine attack in adults			
Bibliography: Diener 2022(42) Including Lipton 1998 (study 1, 2 and 3)(43), Goldstein 2005(44), Diener 2005(45), Goldstein 2006(46), Novartis 2012(47)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2 h (Pain reduced from "severe" or "moderate" to "no pain" pain reduced by 90% from baseline)	2934 (6 studies)	APC: 567/1879 ; median:19.6% (95% CI: 12.9 to 29.9) Placebo: 141/1055 ; median: 9%	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: -1 Directness: ok Imprecision: ok

		RR: 2.2 (95% CI: 1.5 to 3.1) NNT: 9.4 (95% CI 4.8–25.6) **SS in favour of APC** I^2: 82%	
Headache relief at 2 h (Pain reduced from "severe" or "moderate" to "mild" or "no pain", or pain reduced by 50% from baseline)	1771 (5 studies)	APC: 679/1025 ; median: 54.3% (95% CI: 48.7 to 60.2) Placebo: 265/746 ; median: 31.2% **RR: 1.7 (95% CI: 1.6 to 1.9)** NNT: 4.3 (95% CI: 3.4 to 5.7) **SS in favour of APC** I^2: 0%	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Pain free at 1 h (Pain reduced from "severe" or "moderate" to "no pain" pain reduced by 90% from baseline)	2565 (5 studies)	APC: 159/1631 ; median: 7.4% (95% CI: 5.1 to 10.6) Placebo: 36/934 ; median : 4.1% **RR: 1.80 (95% CI: 1.25 to 2.58)** **SS in favour of APC** I^2: 0%	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Headache relief at 1 h (Pain reduced from "severe" or "moderate" to "mild" or "no pain", or pain reduced by 50% from baseline)	1771 (5 studies)	APC: 420/1025 ; median: 36.3 (95 % CI: 30.6to 43.1) Placebo: 142/746 ; median: 17.8 **RR: 2.04 (95 % CI: 1.72 to 2.42)** **SS in favour of APC** I^2: 0%	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
No/little functional disability at 2 h	1691 (4 studies)	APC: 542/975 Placebo: 237/716 **RR: 1.74 (95% CI: 1.53 to 1.98)** **SS in favour or APC** I^2: 0%	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
No nausea at 2h	1587 (4 studies)	APC: 552/850 Placebo: 426/737 **RR:1.10 (95% CI:1.00 to 1.20)**	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok

		p = 0.04 **SS** I^2: 26 %	Imprecision: ok
No photophobia at 2h	1587 (4 studies)	APC: 328/849; median: 30.1% (95% CI: 20.6–44.2) Placebo: 153/738 ; median: 17.0% **RR: 1.77 (1.21 to 2.60)** **SS in favour of APC** I^2: 81%	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: -1 Directness: ok Imprecision: ok
No phonophobia at 2h	1586 (4 studies)	APC: 351/849 ; median: 33.0% (95% CI: 23.9 to 45.8) Placebo: 173/737 ; median:19.9% **RR: 1.66 (95% CI: 1.20 to 2.30)** **SS in favour of APC** I^2: 78%	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: -1 Directness: ok Imprecision: ok
Use of rescue medication	1323 (4 studies)	No pooled data: <u>Lipton 1998: (3 studies)</u> APC: 12.5% Placebo: 27.2% *p* < 0.001 **SS in favour of APC** <u>Goldstein 2005: 1 study</u> APC: 1.5% Placebo: 14.3% *p* = 0.043 **SS in favour of APC**	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: na
Adverse events	3202 (6 studies)	APC: 226/2078 ; median: 18.5% (95%-CI: 14.5 to 23.48) Placebo: 88/1124 ; median: 10.8% **RR: 1.71 (95%CI: 1.3 to 2.2)** RD: 7.7% (95%-CI: 3.7–12.6) **SS in favour of placebo** I^2: 0%	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok

Table 18

This systematic review by Diener 2022 searched for RCTs comparing a combination of paracetamol, acetylsalicylic acid (ASA) and caffeine *("APC")* to placebo to treat a migraine attack with at least a moderate headache intensity.

Seven RCTs comparing APC to placebo were found.
In all studies, medications were taken when the pain of the treated migraine attack was moderate or severe. The studies investigated two tablets of usual APC combinations, corresponding to 500/400/100 mg aspirin/paracetamol/caffeine, or 500/500/130 mg.

The included studies, as assessed by Diener 2022, are of a fair methodological quality. One study had a very small sample size in the placebo group.

In **adults with migraine**, **APC** resulted in **more pain freedom at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **APC** resulted in **more pain relief at 2h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **APC** resulted in **more pain freedom at 1h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **APC** resulted in **more pain relief at 1h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **APC** resulted in **more participants with no/little functional disability** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **APC** resulted in **more participants with no nausea at 2h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **APC** resulted in **more participants with no photophobia 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **APC** resulted in **more participants with no phonophobia 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **APC** resulted in **less use of rescue medication** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **APC** resulted in **more adverse events** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

6.4.2 Paracetamol + ASA + caffeine vs paracetamol + ASA

APC vs paracetamol + ASA for the treatment of a migraine attack in adults			
Bibliography: RCT Diener 2005(45)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Time to 50% pain relief (PO) (pain intensity recorded on a 100 mm visual analogue scale)	980 (1 study)	PAR+ASA+CAF: 1h5min PAR+ASA: 1h13min p = 0.0181 **SS in favour of PAR+ASA+CAF**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 single study with high risk of incomplete outcomes, selective reporting, and unclear allocation concealment and blinding of assessors Consistency: na Directness: -1 Imprecision: na
Time until reduction of pain intensity to 10 mm VAS (PO).	980 (1 study)	PAR+ASA+CAF: 1h56min PAR+ASA: 2h25min **SS in favour of PAR+ASA+CAF**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 single study with high risk of incomplete outcomes, selective reporting, and unclear allocation concealment and blinding of assessors Consistency: na Directness: -1 Imprecision: na
Pain intensity difference at 2h relative to baseline (mm on a 100 mm visual analogue scale)	980 (1 study)	PAR+ASA+CAF: 44.7 PAR+ASA: 40.2 **Difference: -4.6 (-7.4 to -1.7)** ***p* = 0.0019** **SS in favour of PAR+ASA+CAF**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 single study with high risk of incomplete outcomes, selective reporting, and unclear allocation concealment and blinding of assessors Consistency: na Directness: -1 Imprecision: na

% patients with impairment of daily activities at 2h (somewhat, greatly, impossible activity)	980 (1 study)	PAR+ASA+CAF: 34.6%, 10.6%, 0.8% PAR+ASA: 39.4%, 10%, 1.2% p = 0.0813 NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 single study with high risk of incomplete outcomes, selective reporting, and unclear allocation concealment and blinding of assessors Consistency: na Directness: -1 Imprecision: na
% of patients with any adverse events	980 (1 study)	PAR+ASA+CAF: 8% PAR+ASA: 7.8% No statistics provided	Insufficient data
% patients with palpitations	980 (1 study)	PAR+ASA+CAF: 0.4% PAR+ASA: 0.2% No statistics provided	Insufficient data

Table 19

We found one RCT (Diener 2005) comparing a combination of paracetamol, acetylsalicylic acid (ASA) and caffeine *("APC")* to a combination of paracetamol and ASA.

The headache had to be of at least moderate intensity for patients to be included. Paracetamol 400mg + acetylsalicylic acid 500mg + caffeine 100mg was compared to paracetamol 400mg + acetylsalicylic acid 500mg.

There are some methodological problems that limit our confidence in the estimate of the results: this is a single trial with unclear risk of bias pertaining to allocation concealment and blinding of assessors. There was a high risk of bias pertaining to incomplete data assessment and selective reporting. Level of evidence was also downgraded for directness as 13% of the patients suffered from episodic tension-type headache and 3% could not be classified as having migraine according to the IHS.

In **adults with migraine**, **APC** resulted in **a shorter time to 50% pain relief** compared to paracetamol + ASA.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

In **adults with migraine**, **APC** resulted in **a shorter time until reduction of pain intensity to 10 mm VAS** compared to paracetamol + ASA.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

In **adults with migraine**, **APC** resulted in **a greater pain intensity difference at 2h relative to baseline** compared to paracetamol + ASA.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between APC and paracetamol + ASA for **% of patients with impairment of daily activities at 2h** in **adults with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

We have **insufficient data** to compare the **% of patients with any adverse events** in APC versus paracetamol + ASA.

We have **insufficient data** to compare the **% of patients with palpitations** in APC versus paracetamol + ASA.

6.4.3 Paracetamol + ASA + caffeine vs paracetamol

APC vs paracetamol for the treatment of a migraine attack in adults			
Bibliography: RCT Diener 2005(45)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Time to 50% pain relief (PO) (pain intensity recorded on a 100 mm visual analogue scale)	733 (1 study)	PAR+ASA+CAF: 1h5min PAR: 1h21min p = 0.0016 **SS in favour of PAR+ASA+CAF**	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 single study with high risk of incomplete outcomes, selective reporting, and unclear allocation concealment and blinding of assessors Consistency: na Directness: -1 Imprecision: na
Time until reduction of pain intensity to 10 mm VAS (PO).	733 (1 study)	PAR+ASA+CAF: 1h56min PAR: 2h35min **SS in favour of PAR+ASA+CAF**	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 single study with high risk of incomplete outcomes, selective reporting, and unclear allocation concealment and blinding of assessors Consistency: na Directness: -1 Imprecision: na
Pain intensity difference at 2h relative to baseline (mm on a 100 mm visual analogue scale)	733 (1 study)	PAR+ASA+CAF: 44.7 PAR: 39.5 **Difference: -5.2 (-8.7 to -1.7)** **p = 0.0032** **SS in favour of PAR+ASA+CAF**	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 single study with high risk of incomplete outcomes, selective reporting, and unclear allocation concealment and blinding of assessors Consistency: na Directness: -1 Imprecision: na

% patients with impairment of daily activities at 2h (somewhat, greatly, impossible activity)	733 (1 study)	PAR+ASA+CAF: 34.6%, 10.6%, 0.8% PAR : 39%, 11.2%, 1.2% p = 0.0765 NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 single study with high risk of incomplete outcomes, selective reporting, and unclear allocation concealment and blinding of assessors Consistency: na Directness: -1 Imprecision: na
% of patients with any adverse events	733 (1 study)	PAR+ASA+CAF: 8% PAR: 5.8% No statistics provided	Insufficient data
% patients with palpitations	733 (1 study)	PAR+ASA+CAF: 0.4% PAR: / No statistics provided	Insufficient data

Table 20

We found one RCT (Diener 2005) comparing a combination of paracetamol, acetylsalicylic acid (ASA) and caffeine *("APC")* to paracetamol.

The headache had to be of at least moderate intensity for patients to be included. Paracetamol 400mg + acetylsalicylic acid 500mg + caffeine 100mg was compared to acetylsalicylic acid 1000mg.

There are some methodological problems that limit our confidence in the estimate of the results: this is a single trial with unclear risk of bias pertaining to allocation concealment and blinding of assessors. There was a high risk of bias pertaining to incomplete data assessment and selective reporting.
Level of evidence was also downgraded for directness as 13% of the patients suffered from episodic tension-type headache and 3% could not be classified as having migraine according to the IHS.

In **adults with migraine**, **APC** resulted in **a shorter time to 50% pain relief** compared to paracetamol.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

In **adults with migraine**, **APC** resulted in **a shorter time until reduction of pain intensity to 10 mm VAS** compared to paracetamol.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

In **adults with migraine**, **APC** resulted in **a greater pain intensity difference at 2h relative to baseline** compared to paracetamol.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between APC and paracetamol for **% of patients with impairment of daily activities at 2h** in **adults with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

We have **insufficient data** to compare the **% of patients with any adverse events** in APC versus paracetamol.

We have **insufficient data** to compare the **% of patients with palpitations** in APC versus paracetamol.

6.4.4 Paracetamol + ASA + caffeine vs ASA

APC vs ASA for the treatment of a migraine attack in adults			
Bibliography: RCT Diener 2005(45)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Time to 50% pain relief (PO) (pain intensity recorded on a 100 mm visual analogue scale)	734 (1 study)	PAR+ASA+CAF: 1h5min ASA: 1h19min p = 0.0398 **SS in favour of PAR+ASA+CAF**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 single study with high risk of incomplete outcomes, selective reporting, and unclear allocation concealment and blinding of assessors Consistency: na Directness: -1 Imprecision: na
Time until reduction of pain intensity to 10 mm VAS (PO).	734 (1 study)	PAR+ASA+CAF: 1h56min ASA: 2h31min **SS in favour of PAR+ASA+CAF**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 single study with high risk of incomplete outcomes, selective reporting, and unclear allocation concealment and blinding of assessors Consistency: na Directness: -1 Imprecision: na
Pain intensity difference at 2h relative to baseline (mm on a 100 mm visual analogue scale)	734 (1 study)	PAR+ASA+CAF: 44.7 PAR: 40.7 **Difference: -4.0 (-7.5 to -0.6)** **p = 0.0228** **SS in favour of PAR+ASA+CAF**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 single study with high risk of incomplete outcomes, selective reporting, and unclear allocation concealment and blinding of assessors Consistency: na Directness: -1 Imprecision: na

% patients with impairment of daily activities at 2h (somewhat, greatly, impossible activity)	734 (1 study)	PAR+ASA+CAF: 34.6%, 10.6%, 0.8% ASA: 37.3%, 12.7%, 1.6% p = 0.0446 **SS in favour of PAR+ASA+CAF (less with PAR + ASA + CAF)**	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 single study with high risk of incomplete outcomes, selective reporting, and unclear allocation concealment and blinding of assessors Consistency: na Directness: -1 Imprecision: na
% of patients with any adverse events	734 (1 study)	PAR+ASA+CAF: 8% ASA: 9.7% No statistics provided	Insufficient data
% patients with palpitations	734 (1 study)	PAR+ASA+CAF: 0.4% ASA: / No statistics provided	Insufficient data

Table 21

We found one RCT (Diener 2005) comparing a combination of paracetamol, acetylsalicylic acid (ASA) and caffeine *("APC")* to ASA.

The headache had to be of at least moderate intensity for patients to be included. Paracetamol 400mg + acetylsalicylic acid 500mg + caffeine 100mg was compared to acetylsalicylic acid 1000mg.

There are some methodological problems that limit our confidence in the estimate of the results: this is a single trial with unclear risk of bias pertaining to allocation concealment and blinding of assessors. There was a high risk of bias pertaining to incomplete data assessment and selective reporting.
Level of evidence was also downgraded for directness as 13% of the patients suffered from episodic tension-type headache and 3% could not be classified as having migraine according to the IHS.

In **adults with migraine**, **APC** resulted in **a shorter time to 50% pain relief** compared to ASA.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **APC** resulted in **a shorter time until reduction of pain intensity to 10 mm VAS** compared to ASA.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

In **adults with migraine**, **APC** resulted in **a greater pain intensity difference at 2h relative to baseline** compared to ASA.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

In **adults with migraine**, **APC** resulted in **a smaller % of patients with impairment of daily activities at 2h** compared to ASA.

GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

We have **insufficient data** to compare the **% of patients with any adverse events** in APC versus ASA.

We have **insufficient data** to compare the **% of patients with palpitations** in APC versus ASA.

6.4.5 Paracetamol + ASA + caffeine vs ibuprofen

APC vs ibuprofen for the treatment of a migraine attack in adults			
Bibliography: RCT Goldstein 2006(46)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Sum of pain relief score at 2 h (PO) (on a 5-point scale (0 = no relief; 1 = a little relief; 2 = some relief; 3 = a lot of relief; and 4 = complete relief))	1335 (1 study)	PAR +ASA +CAF: 2.7 Ibuprofen: 2.4 P < 0.03 **SS in favour of PAR + ASA + CAF**	⊕⊕⊖⊖ **LOW** Study quality: -2 single study with high risk of selective reporting, unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: na
Time to meaningful pain relief	1335 (1 study)	PAR +ASA +CAF: 128.4 min Ibuprofen: 147.9 min p = 0.036 **SS in favour of PAR + ASA + CAF**	⊕⊕⊖⊖ **LOW** Study quality: -2 single study with high risk of selective reporting, unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: na
Sum of pain intensity difference relative to baseline at 2h (on a 4-point scale (0 = no pain; 1 = mild pain; 2 = moderate pain; and 3 = severe pain))	1335 (1 study)	PAR +ASA +CAF: 1.5 Ibuprofen: 1.4 P < 0.045 **SS in favour of PAR + ASA + CAF**	⊕⊕⊖⊖ **LOW** Study quality: -2 single study with high risk of selective reporting, unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: na
% patients with pain reduced to mild or none at 2h	1335 (1 study)	PAR +ASA +CAF: 67% Ibuprofen: 62% p < 0.046 **SS in favour of PAR + ASA + CAF**	⊕⊕⊖⊖ **LOW** Study quality: -2 single study with high risk of selective reporting, unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: na

Functional disability	1335 (1 study)	Quantitative data not reported NS	⊕⊕⊖⊖ **LOW** Study quality: -2 single study with high risk of selective reporting, unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: na
Associated nausea	1335 (1 study)	Quantitative data not reported NS	⊕⊕⊖⊖ **LOW** Study quality: -2 single study with high risk of selective reporting, unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: na
Associated vomiting	1335 (1 study)	Quantitative data not reported NS	⊕⊕⊖⊖ **LOW** Study quality: -2 single study with high risk of selective reporting, unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: na
Associated photophobia	1335 (1 study)	Quantitative data not reported NS	⊕⊕⊖⊖ **LOW** Study quality: -2 single study with high risk of selective reporting, unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: na
Associated phonophobia	1335 (1 study)	Quantitative data not reported NS	⊕⊕⊖⊖ **LOW** Study quality: -2 single study with high risk of selective reporting, unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: na
% patients with any adverse events	1335 (1 study)	PAR +ASA +CAF: 9.7% Ibuprofen: 5.1% No statistic provided	Insufficient evidence
% patients with cardiovascular event (palpitation or tachycardia)	1335 (1 study)	PAR +ASA +CAF: 0.3% Ibuprofen: no event No statistic provided	Insufficient evidence

Table 22

We found one RCT by Goldstein 2006 comparing a combination of paracetamol, acetylsalicylic acid (ASA) and caffeine *("APC")* to ibuprofen 400 mg.

Paracetamol 500mg+ acetylsalicylic acid 500mg + caffeine 130 mg was compared to ibuprofen 400mg The headache had to be of at least moderate intensity at the dosing.

There are some methodological problems that limit our confidence in the estimate of the results: it is a single study with unclear randomization and allocation concealment, and a high risk of selective reporting.

In **adults with migraine**, **APC** resulted in **a better score of pain relief at 2h** compared to ibuprofen.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **APC** resulted in **less time to meaningful pain relief** compared to ibuprofen.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **APC** resulted in **greater pain intensity difference relative to baseline at 2h** compared to ibuprofen.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **APC** resulted in **a greater % of patients with pain reduced to mild or none at 2h** compared to ibuprofen.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between APC and ibuprofen for **functional disability** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between APC and ibuprofen for **associated nausea** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between APC and ibuprofen for **associated vomiting** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between APC and ibuprofen for **associated photophobia** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between APC and ibuprofen for **associated phonophobia** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

We have **insufficient data** to compare the **% of patients with any adverse events** in APC versus ibuprofen.

We have **insufficient data** to compare the **% of patients with palpitations or tachycardia** in APC versus ibuprofen.

6.4.6 Paracetamol + ASA + caffeine vs sumatriptan

APC vs sumatriptan for the treatment of a migraine attack in adults			
Bibliography: RCT Goldstein 2005(44)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
pain intensity difference relative to baseline at 2h (on a 4-point scale (0 = no pain; 1 = mild pain; 2 = moderate pain; and 3 = severe pain))	170 (1 study)	PAR +ASA +CAF: 1.1 Sumatriptan: 0.6 p < 0.05 **SS in favour of PAR + ASA + CAF**	⊕⊕⊖⊖ **LOW** Study quality: -2 single study with unclear randomization, allocation concealment and unclear risk of selective reporting Consistency: na Directness: ok Imprecision: na
Pain relief score at 2 h (on a 5-point scale (0 = no relief; 1 = a little relief; 2 = some relief; 3 = a lot of relief; and 4 = complete relief))	170 (1 study)	PAR +ASA +CAF: 2.5 Sumatriptan: 1.9 p < 0.05 **SS in favour of PAR + ASA + CAF**	⊕⊕⊖⊖ **LOW** Study quality: -2 single study with unclear randomization, allocation concealment and unclear risk of selective reporting Consistency: na Directness: ok Imprecision: na
% **patients with pain reduced to mild or none at 30 min**	170 (1 study)	PAR +ASA +CAF: 6% Sumatriptan: 29% P = 0.012 **In favour of sumatriptan**	⊕⊕⊖⊖ **LOW** Study quality: -2 single study with unclear randomization, allocation concealment and unclear risk of selective reporting Consistency: na Directness: ok Imprecision: na
% patients with pain reduced to mild or none at 2h	170 (1 study)	PAR +ASA +CAF: 84% Sumatriptan: 65% P≤.027 **SS in favour of PAR + ASA + CAF**	⊕⊕⊖⊖ **LOW** Study quality: -2 single study with unclear randomization, allocation concealment and unclear risk of selective reporting Consistency: na Directness: ok Imprecision: na
Pain recurrence after 2h	170 (1 study)	PAR +ASA +CAF: 10% Sumatriptan: 6.5% NS	⊕⊕⊖⊖ **LOW** Study quality: -2 single study with unclear randomization,

			allocation concealment and unclear risk of selective reporting Consistency: na Directness: ok Imprecision: na
Use of rescue medication at 4h	170 (1 study)	PAR +ASA +CAF: 1.5% Sumatriptan: 11.9% **SS in favour of PAR + ASA + CAF (less with PAR + ASA + CAF)**	⨁⨁⨀⨀ **LOW** Study quality: -2 single study with unclear randomization, allocation concealment and unclear risk of selective reporting Consistency: na Directness: ok Imprecision: na
% patient without functional disability at 4h	170 (1 study)	PAR +ASA +CAF: 81% Sumatriptan: 62% P = 0.044 **SS in favour of PAR +ASA +CAF**	⨁⨁⨀⨀ **LOW** Study quality: -2 single study with unclear randomization, allocation concealment and unclear risk of selective reporting Consistency: na Directness: ok Imprecision: na
Associated nausea	170 (1 study)	Raw data not reported NS	⨁⨁⨀⨀ **LOW** Study quality: -2 single study with unclear randomization, allocation concealment and unclear risk of selective reporting Consistency: na Directness: ok Imprecision: na
Associated vomiting	170 (1 study)	Raw data not reported NS	⨁⨁⨀⨀ **LOW** Study quality: -2 single study with unclear randomization, allocation concealment and unclear risk of selective reporting Consistency: na Directness: ok Imprecision: na
Associated photophobia at 90 min	170 (1 study)	Raw data not reported P ≤ .015 **SS in favour of PAR +ASA +CAF**	⨁⨁⨀⨀ **LOW** Study quality: -2 single study with unclear randomization, allocation concealment and unclear risk of selective reporting Consistency: na Directness: ok Imprecision: na
Associated phonophobia at 2 h	170 (1 study)	Raw data not reported P ≤ .044 **SS in favour of PAR +ASA +CAF**	⨁⨁⨀⨀ **LOW** Study quality: -2 single study with unclear randomization, allocation concealment and unclear risk of selective reporting Consistency: na Directness: ok Imprecision: na
% patients with cardiovascular events (palpitation or tachycardia)	170 (1 study)	No events	Insufficient evidence

Table 23

We found one RCT by Goldstein 2006 comparing a combination of paracetamol, acetylsalicylic acid (ASA) and caffeine *("APC")* to sumatriptan 50 mg.

The study medication had to be taken when the first symptoms usually recognized as the beginning of a migraine attack occurred. 72% of subjects reported moderate or severe pain intensity at dosing. Paracetamol 500mg+ acetylsalicylic acid 500mg + caffeine 130 mg was compared to sumatriptan 50 mg.

There are some methodological problems that limit our confidence in the estimate of the results: it is a single study with unclear blinding of personnel and assessors and an unclear risk of bias pertaining to selective reporting.

In **adults with migraine**, **APC** resulted in **more pain intensity difference relative to baseline at 2h** compared to sumatriptan.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **APC** resulted in **a better score for pain relief at 2h** compared to sumatriptan.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **APC** resulted in **a lower % of patients with pain reduced to mild or none at 30 minutes** compared to sumatriptan.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **APC** resulted in **a higher % of patients with pain reduced to mild or none at 2h** compared to sumatriptan.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between APC and sumatriptan for **pain recurrence after 2h** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **APC** resulted in **less use of rescue medication at 4h** compared to sumatriptan.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **APC** resulted in **a higher % of patients without functional disability at 4h** compared to sumatriptan.

GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between APC and sumatriptan for **associated nausea** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between APC and sumatriptan for **associated vomiting** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **APC** resulted in **less associated photophobia at 90 minutes** compared to sumatriptan.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **APC** resulted in **less associated phonophobia at 90 minutes** compared to sumatriptan.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

We have **insufficient data** to compare the % of patients with palpitations or tachycardia in APC versus sumatriptan.
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6.4.7 Paracetamol + caffeine vs sumatriptan

Paracetamol + caffeine vs sumatriptan for the treatment of a migraine attack in adults			
Bibliography: RCT Pini 2012(48)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain intensity difference at 4h (between pre and post dose) (on a 4-point scale: 0 'absent', 1 'mild', 2 'moderate', 3 'severe')	92 (1 study)	Paracetamol + caffeine: 3.2 ± 3.8 Sumatriptan: 3.2 ± 3.7 p = 0.88 NS	⨁⨁⨀⨀ **LOW** Study quality: -2 single small study with unclear blinding of personnel and assessors Consistency: na Directness: ok Imprecision: na
Total pain relief at 4h (sum of hourly assessments)	92 (1 study)	Paracetamol + caffeine: 7.0 ± 3.6 Sumatriptan: 7.4 ± 3.6 p = 0.48	⨁⨁⨀⨀ **LOW** Study quality: -2 single small study with unclear blinding of personnel and assessors

(on a 5-point scale: 0 'no relief', 1 'little relief', 2 'some relief', 3 'much relief', 4 'complete relief')		NS	Consistency: na Directness: ok Imprecision: na
% patients with complete relief at 4h	92 (1 study)	Paracetamol + caffeine: 74.1% Sumatriptan: 72.2% NS	⊕⊕⊖⊖ **LOW** Study quality: -2 single small study with unclear blinding of personnel and assessors Consistency: na Directness: ok Imprecision: na
% patients with no adverse event	92 (1 study)	Paracetamol + caffeine: 52.7% Sumatriptan: 42.1% NS	⊕⊕⊖⊖ **LOW** Study quality: -2 single small study with unclear blinding of personnel and assessors Consistency: na Directness: ok Imprecision: na
Palpitations	92 (1 study)	Paracetamol + caffeine: 9.1% Sumatriptan: 11.6% NS	⊕⊕⊖⊖ **LOW** Study quality: -2 single small study with unclear blinding of personnel and assessors Consistency: na Directness: ok Imprecision: na

Table 24

We found one RCT by Pini 2012 comparing a combination of paracetamol and caffeine to sumatriptan 50 mg.

The trial medication was to be taken when the headache occurred, and when the patients would normally have taken their usual analgesic. Paracetamol 1000 mg + caffeine 130 mg was compared to sumatriptan 50 mg

There are some methodological problems that limit our confidence in the estimate of the results: it is a single small study with unclear blinding of personnel and assessors.

Note: we have reported the outcomes at 4 hours as this was the only timepoint evaluated.

There was **no difference** between paracetamol + caffeine and sumatriptan for **pain intensity difference at 4h** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between paracetamol + caffeine and sumatriptan for **total pain relief at 4h** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between paracetamol + caffeine and sumatriptan for **% of patients with complete relief at 4h** in **adults with migraine**.

GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between paracetamol + caffeine and sumatriptan for **% of patients with no adverse events** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between paracetamol + caffeine and sumatriptan for **palpitations** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

6.5 Anti-emetics

6.5.1 Metoclopramide vs placebo

Metoclopramide vs placebo for the acute treatment of migraine in adults			
Bibliography: VanderPluym 2021(1) Including Coppola 1995(49), Dogan 2019(50), Jones 1996(51), Tek 1990(52)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain relief (2h) (Improvement of pain from moderate to severe at baseline to mild or none or pain scale improved at least 50% from baseline at defined assessment time)	268 (3 studies)	Metoclopramide: 85/122 Placebo: 45/124 **RR (95% CI): 1.91 (1.47 to 2.48)** **SS in favour of metoclopramide** I^2=67.30%	⨁⊖⊖⊖ **VERY LOW** Study quality: -2; very small studies Consistency: -1 Directness: -1 ;emergency department setting, IV in 3 RCTs Imprecision: ok
Pain scale	198 (2 studies)	SMD (95% CI): -0.12 (-0.40 to 0.17) NS I^2=90.46%	⨁⊖⊖⊖ **VERY LOW** Study quality: -2; very small studies Consistency: -1 Directness: -1 ;emergency department setting, IV in 3 RCTs Imprecision: ok
Total adverse events	124 (2 studies)	Rate Ratio: 1.21 95% CI: 0.37 to 4.03 NS I^2=N/A	⨁⊖⊖⊖ **VERY LOW** Study quality: -2; very small studies Consistency: na Directness: -1 ;emergency department setting, IV in 3 RCTs Imprecision: -1

Table 25

This systematic review by VanderPluym 2021 searched for RCTs comparing abortive pharmacologic or noninvasive nonpharmacologic therapy with placebo, usual care, another pharmacologic therapy, noninvasive nonpharmacologic therapy, wait list, no treatment, or attention control in adults with migraine.

4 RCTs comparing metoclopramide vs placebo were found.

There are some methodological problems that severely limit our confidence in the estimate of the results: all four RCTs were very small in size (sample size did not meet our inclusion criteria), but we did report the pooled results if the pooled sample size met our criteria. Moreover, all RCTs reported were realized in an emergency department setting, and 3 RCTs examined an intravenous administration of metoclopramide.

In **adults with migraine**, **metoclopramide** resulted in **more pain relief at 2h** compared to placebo.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between metoclopramide and placebo for **pain scale** in **adults with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between metoclopramide and placebo for **total adverse events** in **adults with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

6.5.2 Metoclopramide vs paracetamol

A systematic review by VanderPluym 2021 searched for RCTs comparing abortive pharmacologic or noninvasive nonpharmacologic therapy with placebo, usual care, another pharmacologic therapy, noninvasive nonpharmacologic therapy, wait list, no treatment, or attention control in adults with migraine.

One study was found, evaluating paracetamol vs metoclopramide in 98 patients. The study only used I.V. formulations for both drugs and therefore does not meet our inclusion criteria.

6.6 Triptans

6.6.1 Almotriptan vs placebo

Almotriptan 12.5 mg versus placebo for acute migraine attacks of in adults			
Bibliography: SR Chen 2007(53) Including Pascual 2000(54), Dahlof 2001(55), Dowson 2002(56), Diener 2005(57), Mathew 2007(58)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2 h (PO)	1590 (5 studies)	Almotriptan: 351/981 Placebo: 102/609 **RR (95% CI): 2.15 (1.64 to 2.80)** NNT (95%CI): 5.2 (4.0, 7.2) **SS in favour of almotriptan** I^2: 40%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; 3 studies with moderate risk of bias Consistency: ok Directness: ok Imprecision: ok
Pain relief at 2 h (PO) Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.	1429 (5 studies)	Almotriptan: 555/880 Placebo: 195/549 **RR (95% CI): 1.68 (1.42 to 1.98)** NNT (95%CI) : 4.0 (3.2, 5.3) **SS in favour of almotriptan** I^2: 42%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; 3 studies with moderate risk of bias Consistency: ok Directness: ok Imprecision: ok
Sustained pain free over 24 h (Defined as patients who were pain free at 2 hours post-dose and did not experience any pain from 2 to 24 hours post-dose as well as no use of rescue medication.)	1617 (5 studies)	**RR (95% CI): 2.12 (1.64 to 2.75)** NNT (95% CI): 7.0 (5.6 to 9.5) **SS in favour of almotriptan**	⊕⊕⊕⊖ **MODERATE** Study quality: -1; 3 studies with moderate risk of bias Consistency: N.D. Directness: ok Imprecision: ok
Pain free at 1 h	4 studies	**RR (95% CI): 1.77 (1.19 to 2.63)** **SS in favour of almotriptan**	⊕⊕⊕⊖ **MODERATE** Study quality: -1; 3 studies with moderate risk of bias Consistency: N.D. Directness: ok Imprecision: ok
Pain relief at 1 h	4 studies	**RR (95% CI): 1.47 (1.21 to 1.79)**	⊕⊕⊕⊖ **MODERATE**

Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.		**SS in favour of almotriptan**	Study quality: -1; 3 studies with moderate risk of bias Consistency: N.D. Directness: ok Imprecision: ok
Adverse events over 24 h	1617 (5 studies)	**RR (95% CI): 1.10 (0.87 to 1.40)** NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1; 3 studies with moderate risk of bias Consistency: N.D. Directness: ok Imprecision: ok

Table 26

This systematic review by Chen searched for double-blind RCTs comparing naratriptan to placebo to treat an acute migraine headache episode in adults.

The different dosages were analyzed separately.
5 RCTs evaluated almotriptan 12.5 mg versus placebo.

There are some methodological problems that limit our confidence in the estimate of the results: only one study had a Jadad score of 5, one had a score of 4 and 3 studies had a Jadad score of 3. For several outcomes it was not reported wich study contributed to the data, it was therefore not possible to determine the number of participants, nor to accurately appraise the data for these outcomes. However, as 4 of the 5 studies were included for these outcomes, we based our appraisal on all 5 studies together.

In **adults with a migraine attack**, **almotriptan 12.5 mg** resulted in **more pain freedom at 2 h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack, almotriptan 12.5 mg** resulted in **more pain relief at 2 h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack**, **almotriptan 12.5 mg** resulted in **more sustained pain freedom over 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack**, **almotriptan 12.5 mg** resulted in **more pain freedom at 1 h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack**, **almotriptan 12.5 mg** resulted in **more pain relief at 1 h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There were **no difference** between almotriptan 12.5 mg and placebo **for adverse** events over 24 h in **adults with a migraine attack**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

6.6.2 Eletriptan vs placebo

Eletriptan 40 mg versus placebo for acute migraine attacks of in adults			
Bibliography: SR Pascual 2007(59) Including Diener 2002(60), Garcia-Ramos 2003(61), Goadsby 2000(62), Mathew 2003(63), Sakai 2004(64), Sandrini 2002(65), Sheftell 2003(66), Stark 2002(67), Steiner 2003(68)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2 h	4380 (9 studies)	**RR (95% CI): 4.83 (3.05 to 7.66)** **SS in favour of eletriptan** *P* < 0.001 for heterogeneity	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: -1 Directness: ok Imprecision: ok
Pain relief at 2 h	4096 (8 studies)	**RR (95% CI): 2.48 (1.99 to 3.11)** **SS in favour of eletriptan** *P* < 0.001 for heterogeneity	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: -1 Directness: ok Imprecision: ok
Pain free at 1 h	2647 (4 studies)	**RR (95% CI): 7.94 (2.88 to 21.87)** **SS in favour of eletriptan** p = 0.3 for heterogeneity	⨁⨁⨁⨁ **High** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Pain relief at 30 min	866 (2 studies)	**RR (95% CI): 1.17 (0.29 to 4.80)** NS	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: -1 Directness: ok Imprecision: -1 (large CI)

		p = 0.04 for heterogeneity	
Pain relief at 1 h	3247 (6 studies)	**RR (95% CI): 2.54 (1.95 to 3.31)** **SS in favour of eletriptan** p = 0.07 for heterogeneity	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: -1 Directness: ok Imprecision: ok
Recurrence of migraine (Reappearance of moderate-to-severe pain before 24 hours elapsed since response at 2 hours or at 4h)	1680 (6 studies)	**RR (95% CI): 0.72 (0.59 to 0.87)** **SS in favour of eletriptan (less with eletriptan)** p = 0.26 for heterogeneity	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Adverse events	2362 (4 studies)	**RR (95% CI): 1.01 (0.73 to 1.38)** **NS** p = 0.001 for heterogeneity	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: -1 Directness: ok Imprecision: ok

Table 27

This systematic review by Pascual 2007searched for double-blind RCTs comparing eletriptan to placebo to treat an acute migraine headache episode in adults.

9 RCTs evaluated eletriptan 40 mg versus placebo were found.

There are some methodological problems that limit our confidence in the estimate of the results: heterogeneity was found between studies for most of the outcomes. Most of the studies had a Jadad quality score of 5. 2 studies had a jaded quality score of 3.

In **adults with a migraine attack**, **eletritpan 40 mg** resulted in **more pain freedom at 2 h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack, eletriptan 40 mg** resulted in **more pain relief at 2 h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack**, **eletriptan 40 mg** resulted in **more pain freedom at 1h** compared to placebo.

GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with a migraine attack**, **eletriptan 40 mg** resulted in **more pain relief at 1 h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack**, **eletriptan 40 mg** resulted in **less migraine recurrence** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

There were **no difference** between eletriptan 40 mg and placebo for **pain relief at 30 min** in **adults with a migraine attack**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There were **no difference** between eletriptan 40 mg and placebo for **adverse events** in **adults with a migraine attack**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

6.6.3 Frovatriptan vs placebo

Frovatriptan 2.5 mg versus placebo for acute migraine attacks of in adults			
Bibliography: SR Poolsup 2005(69) Including Goldstein 2002(70), Rapoport 2002(71), Ryan 2002 (Study1, Study2, and Study3)(72)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2 h	2866 (5 studies)	Frovatriptan: 209/1804 Placebo: 34/1062 **RR: 3.70 (95% CI: 2.59 to 5.29)** NNT (95% CI): 12 (10 to 15) **SS in favour of frovatriptan** Q-statistic for heterogeneity = 0.81	⨁⨁⨁⊖ **MODERATE** Study quality: -1 two studies with Jada score of 3 Consistency: ok Directness: ok Imprecision: ok
Headache response at 2 h	2866 (5 studies)	Frovatriptan: 719/1804 Placebo: 116/1062 **RR: 1.66 (95% CI: 1.47 to 1.88)**	⨁⨁⨁⊖ **MODERATE** Study quality: -1 two studies with Jada score of 3

(Headache severity changed from moderate or severe (grade 2, 3) to mild or no headache (grade 0, 1), according to International Headache Society (IHS) criteria.)		NNT (95% CI): 7 (6 to 9) **SS in favour of frovatriptan** Q-statistic for heterogeneity = 0.55	Consistency: ok Directness: ok Imprecision: ok
Pain free at 4 h	2866 (5 studies)	Frovatriptan: 526/1804 Placebo: 252/1062 **RR: 2.67 (95% CI: 2.21 to 3.22)** NNT (95% CI): 6 (5 to 7) **SS in favour of frovatriptan** Q-statistic for heterogeneity = 3.51	⊕⊕⊕⊖ **MODERATE** Study quality: -1 two studies with Jada score of 3 Consistency: ok Directness: ok Imprecision: ok
Headache response at 4 h (Headache severity changed from moderate or severe (grade 2, 3) to mild or no headache (grade 0, 1), according to International Headache Society (IHS) criteria.)	2866 (5 studies)	Frovatriptan: 1097/1804 Placebo: 352/1062 **RR: 1.83 (95% CI: 1.66 to 2.00)** NNT (95% CI): 4 (4 to 5) **SS in favour of frovatriptan** Q-statistic for heterogeneity = 2.39	⊕⊕⊕⊖ **MODERATE** Study quality: -1 two studies with Jada score of 3 Consistency: ok Directness: ok Imprecision: ok
Headache recurrence after 4 h (Headache relieved at 4 h, but subsequently recurred within 24 h of initial dose.)	1449 (5 studies)	Frovatriptan: 192/1092 Placebo: 83/352 **RR: 0.74 (95% CI: 0.59 to 0.93)** NNT (95% CI): 17 (9 to 100) **SS in favour of frovatriptan (less with frovatriptan)** Q-statistic for heterogeneity = 3.74	⊕⊕⊕⊖ **MODERATE** Study quality: -1 two studies with Jada score of 3 Consistency: ok Directness: ok Imprecision: ok
Migraine associated nausea at 2h	2866 (5 studies)	Frovatriptan: 774/1804 Placebo: 523/1062 **RR: 0.86 (95% CI: 0.80 to 0.94)** NNT (95% CI): 15 (10 to 34) **SS in favour of frovatriptan (less with frovatriptan)** Q-statistic for heterogeneity = 3.88	⊕⊕⊕⊖ **MODERATE** Study quality: -1 two studies with Jada score of 3 Consistency: ok Directness: ok Imprecision: ok

Migraine associated photophobia at 2h	2866 (5 studies)	Frovatriptan: 971/1804 Placebo: 693/1062 **RR: 0.83 (95% CI: 0.78 to 0.88**) NNT (95% CI): 10 (7 to 13) **SS in favour of frovatriptan (less with frovatriptan)** Q-statistic for heterogeneity = 0.59	⊕⊕⊕⊖ **MODERATE** Study quality: -1 two studies with Jada score of 3 Consistency: ok Directness: ok Imprecision: ok
Migraine associated phonophobia at 2h	2866 (5 studies)	Frovatriptan: 863/1804 Placebo: 598/1062 **RR: 0.86 (95% CI: 0.80 to 0.93)** NNT (95% CI): 13 (10 to 25) **SS in favour of frovatriptan (less with frovatriptan)** Q-statistic for heterogeneity = 0.90	⊕⊕⊕⊖ **MODERATE** Study quality: -1 two studies with Jada score of 3 Consistency: ok Directness: ok Imprecision: ok
Adverse events	672 (2 studies)	RR: 1.31 (95% CI: 1.07 to 1.62) NNH (95% CI): 10 (6 to 50) **SS in favour of placebo (more with frovatriptan)**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 two studies with Jada score of 3 Consistency: nd Directness: ok Imprecision: ok

Table 28

This systematic review by Poolsup 2005 searched for double-blind RCTs comparing frovatriptan to placebo to treat an acute migraine headache episode in adults.

5 RCTs evaluated frovatriptan 2.5 mg versus placebo. (3 were reported in the same publication)
Two RCTs evaluated efficacy of frovatriptan in patient having moderate or severe migraine attack. The information was not reported in the publication comprising of the 3 other studies.
Two studies were excluded from this MA: one investigated the cardiovascular effects of frovatriptan in patients at high risk of coronary artery disease. The other compared the early use of frovatriptan for mild migraine attack against dosing after the headache progressed to moderate or severe intensity.

There are some methodological problems that limit our confidence in the estimate of the results: two studies have a Jadad quality score of 3. The third study summarized the results from three trials. While the authors treated this as three separate studies in the MA they reported that the described details of these three studies were brief, and it was not possible to appraise methodological quality of these studies. Despite these studies counted for about half of the patients the level of evidence was assessed based on the risk of bias of the two other publications.

In **adults with a migraine attack**, **frovatriptan 2.5 mg** resulted in **more pain freedom at 2 h** compared to placebo.
GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack**, **frovatriptan 2.5 mg** resulted in **more pain response at 2 h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack**, **frovatriptan 2.5 mg** resulted in **more sustained pain freedom at 4 h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack**, **frovatriptan 2.5 mg** resulted in **more pain response at 4 h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack**, **frovatriptan 2.5 mg** resulted in **less headache recurrence after 4 h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.
In **adults with a migraine attack**, **frovatriptan 2.5 mg** resulted in **less migraine associated nausea at 2 h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack**, **frovatriptan 2.5 mg** resulted in **less migraine associated photophobia at 2 h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack**, **frovatriptan 2.5 mg** resulted in **less migraine associated phonophobia at 2 h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack**, **frovatriptan 2.5 mg** resulted in **more adverse events** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

6.6.4 Naratriptan vs placebo

Naratriptan 2.5 mg versus placebo for acute migraine attacks in adluts			
Bibliography: SR Ashcroft 2004(73) Including Klassen 1997(74), Mathew 1997(75), Bates 1998(76), Bomhof 1999(77), Schoenen 1999(78), Havanka 2000(79)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2 h	2358 (6 studies)	**RR (95% CI): 2.52 (1.78–3.57**) **SS in favour of naratriptan**	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: N.D. Directness: ok Imprecision: ok
Pain relief at 2 h	2358 (6 studies)	**RR (95% CI): 1.81 (1.55 to 2.11)** **SS in favour of naratriptan**	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: N.D. Directness: ok Imprecision: ok
Sustained pain relief over 24 h	2358 (6 studies)	Naratriptan: 578/1302 Placebo: 196/1056 **RR (95% CI): 2.43 (2.11 to 2.80)** **SS in favour of naratriptan** I^2: 0%	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Pain free at 4 h	2358 (6 studies)	Naratriptan: 528/1302 Placebo: 162/1056 **RR (95% CI): 2.58 (1.99 to 3.35)** **SS in favour of naratriptan** I^2: 45%	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Pain relief at 4 h	2358 (6 studies)	Naratriptan: 827/1302 Placebo: 326/1056 **RR (95% CI): 2.11 (1.75 to 2.54)** **SS in favour of naratriptan** I^2: 54%	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Adverse events	2049	Naratriptan: 315/1150 Placebo: 259/899	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: N.D. Directness: ok

	RR (95% CI): 1.03 (0.89–1.18) **NS**	Imprecision: ok

Table 29

This systematic review by Ashcroft 2004 searched for double-blind RCTs comparing naratriptan to placebo or an active control to treat an acute migraine headache episode in adults.

The different dosages were analyzed separately.
6 RCTs evaluated naratriptan 2.5 mg versus placebo.

Authors used as denominator the number of patients randomised who had a migraine attack of moderate or severe intensity.

Specific studies included in the outcome adverse events were not reported. We nevertheless evaluated the level of evidence based on the mean risk af bias for all studies included in the MA.

In **adults with a migraine attack of moderate or severe baseline intensity**, **naratriptan 2.5 mg** resulted in **more pain freedom at 2 h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with a migraine attack of moderate or severe baseline intensity**, **naratriptan 2.5 mg** resulted in **more pain relief at 2 h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with a migraine attack of moderate or severe baseline intensity**, **naratriptan 2.5 mg** resulted in **more pain freedom at 4 h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with a migraine attack of moderate or severe baseline intensity**, **naratriptan 2.5 mg** resulted in **more pain relief at 4 h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with a migraine attack of moderate or severe baseline intensity**, **naratriptan 2.5 mg** resulted in **more sustained pain relief over 24h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

There was **no difference** between naratriptan 2.5 mg and placebo **for adverse events** in **adults with a migraine attack of moderate or severe baseline intensity**.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

6.6.5 Rizatriptan vs placebo

Rizatritpan 10 mg versus placebo for acute migraine attacks of in adults			
Bibliography: Ferrari 2001(80) Including Teall 1998(81), Kramer 1998(82), Tfelt-Hansen 1998(83), Merk and Co. 1999(84), Goldstein 1998(85), Ahrens 1999(86), study 52 (unpublished)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2 h	3305 (7 studies)	Rizatriptan: 41% (39 to 43) Placebo: 10% (8 to 12) P<0.001 **SS in favour of rizatriptan** Studies were homogenous	**Unable to assess**
Pain relief at 2 h (% of patients with a reduction of pain severity from moderate or severe at baseline to mild or none)	3305 (7 studies)	Rizatriptan: 71% (69 to 73) Placebo: 38% (35 to 40) P<0.001 **SS in favour of rizatriptan** Studies were homogenous	**Unable to assess**
Sustained pain free over 24 h (% of patients who had pain free at 2 h and who did not have recurrence within 2-24 h without any additional medication)	3305 (7 studies)	Rizatriptan: 25% (23 to 27) Placebo: 7% (5 to 8) P<0.001 **SS in favour of rizatriptan** Studies were homogenous	**Unable to assess**
Sustained pain relief up to 24h (% of patients who had pain relief at 2 h and who did not have recurrence within 2-24 hwithout any additional medication)	3305 (7 studies)	Rizatriptan: 37% (35 to 39) Placebo: 18% (16 to 20) P<0.001 **SS in favour of rizatriptan** Studies were homogenous	**Unable to assess**

Pain free at 1 h	3305 (7 studies)	Rizatriptan: 12 % (11 to 13) Placebo: 3 % (2 to 4) P<0.001 **SS in favour of rizatriptan** Studies were homogenous	**Unable to assess**
Pain relief at 1 h (% of patients with a reduction of pain severity from moderate or severe at baseline to mild or none)	3305 (7 studies)	Rizatriptan: 45% (43 to 47) Placebo: 25 % (23 to 28) P<0.001 **SS in favour of rizatriptan** Studies were homogenous	**Unable to assess**
Relief of disability at 2 h (% of patients with no functional disability (grade 0 on the 4 grade scale in the group of patient who had disability grade 1,2 or 3)	3168 (studies nd)	Rizatriptan: 44% (42 to 47) Placebo: 19% (17 to 21) P<0.001 **SS in favour of rizatriptan** Studies were homogenous	**Unable to assess**
Relief of nausea at 2 h	1915 (studies nd)	Rizatriptan: 66% (63 to 68) Placebo: 45% (41 to 49) P<0.001 **SS in favour of rizatriptan** Studies were homogenous	**Unable to assess**
Relief of photophobia at 2h	1708 (studies nd)	Rizatriptan: 52% (50 to 55) Placebo: 24 % (21 to 26) P<0.001 **SS in favour of rizatriptan** Studies were homogenous	**Unable to assess**
Relief of phonophobia at 2h	2442 (studies nd)	Rizatriptan: 56% (54 to 59) Placebo: 30 % (27 to 33) P<0.001 **SS in favour of rizatriptan** Studies were homogenous	**Unable to assess**

Adverse events over 24 h	3305 (7 studies)	Rizatriptan: 43% Placebo: 30% **No analysis provided**	No enough evidence

Table 30

This systematic review by Ferrari synthesized all double-blind RCTs conducted by Merk and Co comparing rizatriptan 10 mg to placebo to treat an acute migraine headache episode in adults.

7 RCTs were included comparing rizatriptan 10 mg to placebo.
In all studies patients were instructed to take medication when they developed moderate or severe migraine headache.

5 studies used tablets formulation while 2 studies used the wafer formulation.

There are some methodological problems that limit our confidence in the estimate of the results: this review is not a SR, rather only studies funded by Merk and Co were synthesized. No details were reported for individual studies. Details of which studies contributed to pooled data were only given for outcomes pain free at 2 h and pain relief at 2 h, no details were provided for the other outcomes, nevertheless we extrapolated that the same studies contributed to the data each time that the same number of participants was reported. No statistics were provided regarding heterogeneity, the authors stated that there were not heterogeneity for different outcomes. We had no enough information to determine level of evidence for these data

In **adults with migraine**, **rizatriptan 10 mg** resulted in **more pain freedom at 2 h** compared to placebo.
GRADE: Unable to assess

In **adults with migraine**, **rizatriptan 10 mg** resulted in **more pain relief at 2 h** compared to placebo.
GRADE: Unable to assess

In **adults with migraine**, **rizatriptan 10 mg** resulted in **more sustained pain freedom over 24h** compared to placebo.
GRADE: Unable to assess

In **adults with migraine**, **rizatriptan 10 mg** resulted in **more sustained pain relief over 24h** compared to placebo.
GRADE: Unable to assess

In **adults with migraine attack**, **rizatriptan 10 mg** resulted in **more pain freedom at 1 h** compared to placebo.
GRADE: Unable to assess

In **adults with migraine**, **rizatriptan 10 mg** resulted in **more pain relief at 1 h** compared to placebo.

GRADE: Unable to assess

In **adults with migraine**, **rizatriptan 10 mg** resulted in **more disability relief at 2 h** compared to placebo.
GRADE: Unable to assess

In **adults with migraine, rizatriptan 10 mg** resulted in **more nausea relief at 2 h** compared to placebo.
GRADE: Unable to assess

In **adults with migraine**, **rizatriptan 10 mg** resulted in **more photophobia relief at 2 h** compared to placebo.
GRADE: Unable to assess

In **adults with migraine**, **rizatriptan 10 mg** resulted in **more phonophobia relief at 2 h** compared to placebo.
GRADE: Unable to assess

We have **insufficient data** for **adverse event** for the comparison rizatriptan 10 mg to placebo in adults with migraine.

6.6.6 Sumatriptan (oral) vs placebo

6.6.6.1 Sumatriptan 50 mg versus placebo for acute migraine attacks of moderate or severe baseline pain intensity in adults

Sumatriptan 50 mg (oral route of administration) versus placebo for acute migraine attacks of moderate or severe baseline pain intensity in adults			
Bibliography: SR Derry 2012(87) Including 160-104(88), Bussone 2000(89), Carpay 2004(90), Cutler 1995(91), Dahlof 2009(92), Diener 2004a(18), Diener 2004b(19), Goldstein 1998(85), Goldstein 2005(93), Ishkanian 2007(94), Jelinski 2006(95), Kolodny 2004(96), Kudrow 2005(97), Lines 2001(98), Lipton 2000(99), Nett 2003(100), Pfaffenrath 1998(101), Pini 1999(102), Sandrini 2002(65), Sargent 1995(103), Savani 1999(104), Sheftell 2005a(105), Sheftell 2005b(105), Smith 2005(39), Tfelt-Hansen 2006(106), Winner 2003a(107), Winner 2003b(107)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2 h (PO)	6447 (13 studies)	Sumatriptan: 28% (1080/3922) Placebo: 11% (282/2525)	⨁⨁⨁⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation

		RR (95% CI): 2.7 (2.4 to 3.1) NNT (95%CI): 6.1 (5.5 to 6.9) **SS in favour of sumatriptan** I^2: 53%	concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok
Pain relief at 2 h (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	8102 (19 studies)	Sumatriptan: 57% (2822/4955) Placebo: 32% (1007/3147) **RR (95% CI): 1.8 (1.7 to 1.9)** NNT (95%CI): 4.0 (3.7 to 4.4) **SS in favour of sumatriptan** I^2: 52%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok
Sustained pain-free over 24 h (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	2526 (4 studies)	Sumatriptan: 17% (226/1309) Placebo: 7% (82/1217) **RR (95% CI): 2.6 (2.1 to 3.4)** NNT (95%CI): 9.5 (7.7 to 12) **SS in favour of sumatriptan** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok
Sustained pain relief over 24 h (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.)	2526 (4 studies)	Sumatriptan: 35% (454/1309) Placebo: 18% (220/1217) **RR (95% CI): 1.9 (1.7 to 2.2)** NNT (95%CI): 6.0 (5.0 to 7.6) **SS in favour of sumatriptan** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok
Pain free at 1 h	1735 (5 studies)	Sumatriptan: 5% (45/902) Placebo: 2% (16/833) **RR (95% CI): 2.6 (1.5 to 4.6)** NNT (95%CI): 33 (21 to 73) **SS in favour of sumatriptan** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok
Pain relief at 1 h (Headache relief was defined as a decrease from an initial moderate or severe	2766 (9 studies)	Sumatriptan: 454/1655 Placebo: 157/1111 **RR (95% CI): 1.8 (1.52 to 2.13)** **SS in favour of sumatriptan**	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok

headache to mild or none.)		I^2: 18%	Directness: ok Imprecision: ok
Relief of nausea at 2 h	1063 (7 studies)	Sumatriptan: 268/596 Placebo: 123/377 **RR (95% CI): 1.38 (1.16 to 1.65)** **SS in favour of sumatriptan** I^2: 45%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok
Relief of photophobia at 2 h	1144 (6 studies)	Sumatriptan: 284/638 Placebo: 160/506 **RR (95% CI): 1.42 (1.22 to 1.65)** **SS in favour of sumatriptan** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok
Relief of phonophobia at 2 h	852 (4 studies)	Sumatriptan: 244/490 Placebo: 134/362 **RR (95% CI): 1.37 (1.16 to 1.6)** **SS in favour of sumatriptan** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok
Improvement of functional disability	607 (4 studies)	Sumatriptan: 49% (186/378) Placebo: 31% (72/229) **RR (95% CI): 1.5 (1.2 to 1.8)** NNT (95% CI): 5.6 (3.9 to 10) **SS in favour of sumatriptan** I^2: 46%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok
Use of rescue medication up to 24 h	2079 (4 studies)	Sumatriptan: 20% (266/1339) Placebo: 42% (309/740) **RR (95% CI): 0.77 (0.68 to 0.87)** NNT to prevent (95% CI): 4.6 (3.8 to 5.6) **SS in favour of sumatriptan** I^2: 40%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok
Use of rescue medication up to 4 h	2098 (5 studies)	Sumatriptan: 23% (296/1278) Placebo: 45% (366/820) **RR (95% CI): 0.56 (0.49 to 0.63)**	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok

		NNT to prevent (95% CI): 4.7 (3.9 to 5.8) **SS in favour of sumatriptan** I^2: 50%	Directness: ok Imprecision: ok
Adverse events over 24 h	3728 (10 studies)	Sumatriptan: 32% (667/2114) Placebo: 24% (389/1614) **RR (95% CI): 1.3 (1.2 to 1.4)** NNH (95% CI): 13 (9.7 to 22) **SS in favour of placebo** I : 31%	⨁⨁⨁⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok

Table 31

This systematic review by Derry 2012 searched for double-blind RCTs comparing oral sumatriptan to placebo or an active control to treat an acute migraine headache episode in adults.

27 RCTs evaluated sumatriptan 50 mg and 29 RCTs evaluated sumatriptan 100 mg versus placebo. The different dosages were analyzed separately.

Authors analyzed studies performed in established pain of at least moderate intensity separately from studies in which medication was taken before pain became well established or in which a second dose of medication was permitted.

There are some methodological problems that limit our confidence in the estimate of the results: the majority of included studies had an unclear risk of bias pertaining to allocation concealment, randomization or blinding.

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 50 mg** resulted in **more pain freedom at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 50 mg** resulted in **more pain relief at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 50 mg** resulted in **more sustained pain freedom over 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 50 mg** resulted in **more sustained pain relief over 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 50 mg** resulted in **more pain freedom at 1h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 50 mg** resulted in **more pain relief at 1h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 50 mg** resulted in **more relief of nausea at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 50 mg** resulted in **more relief of photophobia at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 50 mg** resulted in **more relief of phonophobia at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 50 mg** resulted in **more improvement of functional disability** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 50 mg** resulted in **less use of rescue medication up to 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 50 mg** resulted in **less use of rescue medication up to 4h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 50 mg** resulted in **more adverse events over 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate

6.6.6.2 Sumatriptan 50 mg versus placebo for acute migraine attacks of mild baseline pain intensity in adults

Sumatriptan 50 mg (oral route of administration) versus placebo for acute migraine attacks of mild baseline pain intensity in adults			
Bibliography: SR Derry 2012(87) Including 160-104(88), Bussone 2000(89), Carpay 2004(90), Cutler 1995(91), Dahlof 2009(92), Diener 2004a(18), Diener 2004b(19), Goldstein 1998(85), Goldstein 2005(93), Ishkanian 2007(94), Jelinski 2006(95), Kolodny 2004(96), Kudrow 2005(97), Lines 2001(98), Lipton 2000(99), Nett 2003(100), Pfaffenrath 1998(101), Pini 1999(102), Sandrini 2002(65), Sargent 1995(103), Savani 1999(104), Sheftell 2005a(105), Sheftell 2005b(105), Smith 2005(39), Tfelt-Hansen 2006(106), Winner 2003a(107), Winner 2003b(107)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2h	1514 (7 studies)	Sumatriptan: 46% (357/783) Placebo: 23% (168/731) **RR (95% CI): 2.0 (1.7 to 2.4)** NNT (95% CI): 4.4 (3.8 to 5.7) **SS in favour of sumatriptan** I^2: 7%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; half of included studies with unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok
Sustained pain-free over 24 h (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	866 (4 studies)	Sumatriptan: 28% (124/436) Placebo: 10% (44/430) **RR (95% CI): 2.8 (2.1 to 3.9)** NNT (95% CI): 5.5 (4.3 to 7.6) **SS in favour of sumatriptan** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; half of included studies with unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok
Pain free at 1 h	1246 (5 studies)	Sumatriptan: 26% (161/624) Placebo: 14% (87/622) **RR (95% CI): 1.9 (1.5 to 2.4)** NNT (95% CI): 8.5 (6.2 to 13)	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok

		SS in favour of sumatriptan I^2: 0%	
Relief of nausea at 2h	280 (2 studies)	Sumatriptan: 78/145 Placebo: 10/135 **RR (95% CI): 6.88 (3.78 to 12.51)** **SS in favour of sumatriptan** I^2: 82%	⊕⊕⊖⊖ **LOW** Study quality: -1; 1 study with unclear allocation concealment, randomization and blinding Consistency: -1 Directness: ok Imprecision: ok
Relief of photophobia at 2h	483 (2 studies)	Sumatriptan: 135/237 Placebo: 44/246 **RR (95% CI): 2.95 (2.2 to 3.97)** **SS in favour of sumatriptan** I^2: 80%	⊕⊕⊖⊖ **LOW** Study quality: -1; 1 study with unclear allocation concealment, randomization and blinding Consistency: -1 Directness: ok Imprecision: ok
Relief of phonophobia at 2h	413 (2 studies)	Sumatriptan: 105/202 Placebo: 37/211 **RR (95% CI): 2.99 (2.15 to 4.16)** **SS in favour of sumatriptan** I^2: 85%	⊕⊕⊖⊖ **LOW** Study quality: -1; 1 study with unclear allocation concealment, randomization and blinding Consistency: -1 Directness: ok Imprecision: ok
Use of rescue medication up to 24 h	384 (2 studies)	Sumatriptan: 30% (66/221) Placebo: 58% (94/163) **RR (95% CI): 0.54 (0.42 to 0.68)** NNTp (95% CI): 3.6 (2.7 to 5.5) **SS in favour of sumatriptan** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; 1 study with unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok
Adverse events over 24 h	1242 (6 studies)	Sumatriptan: 16% (104/642) Placebo: 7% (43/600) **RR (95% CI): 2.3 (1.6 to 3.2)** NNH (95% CI): 11 (8.0 to 18)	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok

	SS in favour of placebo I^2: 18%

Table 32

This systematic review by Derry 2012 searched for double-blind RCTs comparing oral sumatriptan to placebo or an active control to treat an acute migraine headache episode in adults.

27 RCTs evaluated sumatriptan 50 mg and 29 RCTs evaluated sumatriptan 100 mg versus placebo. The different dosages were analyzed separately.

Authors analyzed studies performed in established pain of at least moderate intensity separately from studies in which medication was taken before pain became well established or in which a second dose of medication was permitted.

There are some methodological problems that limit our confidence in the estimate of the results: the majority of included studies had an unclear risk of bias pertaining to allocation concealment, randomization or blinding.

In **adults with a migraine attack of mild baseline intensity**, **sumatriptan 50 mg** resulted in **more pain freedom at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of mild baseline intensity**, **sumatriptan 50 mg** resulted in **more sustained pain freedom over 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of mild baseline intensity** , **sumatriptan 50 mg** resulted in **more pain freedom at 1h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with a migraine attack of mild baseline intensity** , **sumatriptan 50 mg** resulted in **more relief of nausea at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with a migraine attack of mild baseline intensity** , **sumatriptan 50 mg** resulted in **more relief of photophobia at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with a migraine attack of mild baseline intensity** , **sumatriptan 50 mg** resulted in **more relief of phonophobia at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with a migraine attack of mild baseline intensity**, **sumatriptan 50 mg** resulted in **less use of rescue medication up to 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of mild baseline intensity**, **sumatriptan 50 mg** resulted in **more adverse events over 24h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

6.6.6.3 Sumatriptan 100 mg versus placebo for acute migraine attacks of moderate or severe baseline pain intensity in adults

Sumatriptan 100 mg (oral route of administration) versus placebo for acute migraine attacks of moderate or severe baseline pain intensity in adults			
Bibliography: SR Derry 2012(87) Including: Carpay 2004(90), Cutler 1995(91), Dahlof 1991(108), DKSMSG 1999(24), Dodick 2002(109), Dowson 2002(56), Ensink 1991(110), Geraud 2000(111), Goadsby 1991(112), Goadsby 2000(62), Havanka 2000(79), Jelinski 2006(95), Kaniecki 2006, Mathew 2003(113), Myllyla 1998(114), Nappi 1994(115), Nett 2003(100), Patten 1991(116), Pfaffenrath 1998(101), Pini 1995(117), Sandrini 2002(65), Sargent 1995(103), Sheftell 2005a(105), Sheftell 2005b(105) , Tfelt-Hansen 1995(118), Tfelt-Hansen 1998(83), Visser 1996(119), Winner 2003a (107), Winner 2003b(107)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2 h	6571 (16 studies)	Sumatriptan: 32% (1291/4017) Placebo: 11% (272/2554) **RR (95% CI): 3.2 (2.8 to 3.6)** NNT (95% CI): 4.7 (4.3 to 5.1) **SS in favour of sumatriptan** I^2: 37%	⨁⨁⨁⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok

Pain relief at 2 h (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	7811 (21 studies)	Sumatriptan: 61% (2877/4751) Placebo: 32% (967/3060) **RR (95% CI): 1.9 (1.8 to 2.0)** NNT (95% CI): 3.5 (3.2 to 3.7) **SS in favour of sumatriptan** I^2: 67%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok
Sustained pain-free over 24h (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	2891 (6 studies)	Sumatriptan: 24% (374/1590) Placebo: 8% (106/1301) **RR (95% CI): 2.8 (2.4 to 3.5)** NNT (95%CI): 6.5 (5.6 to 7.8) **SS in favour of sumatriptan** I^2: 31%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok
Sustained pain relief over 24 h (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.)	4116 (6 studies)	Sumatriptan: 36% (922/2538) Placebo: 17% (270/1578) **RR (95% CI): 2.1 (1.9 to 2.4)** NNT (95% CI): 5.2 (4.6 to 6.0) **SS in favour of sumatriptan** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok
Pain free at 1h	3176 (6 studies)	Sumatriptan: 7% (158/2216) Placebo: 2% (15/960) **RR (95% CI): 4.0 (2.3 to 6.8)** NNT (95% CI): 18 (15 to 24) **SS in favour of sumatriptan** I^2: 38%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok

Pain relief at 1 h (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none)	3983 (10 studies)	Sumatriptan: 795/2709 Placebo: 317/1041 **RR (95% CI): 1.52 (1.37 to 1.69)** **SS in favour of sumatriptan** I^2: 11%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok
Relief of nausea at 2 h	2996 (14 studies)	Sumatriptan: 880/1955 Placebo: 187/1274 **RR (95% CI): 1.88 (1.62 to 2.18)** **SS in favour of sumatriptan** I^2: 31%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok
Relief of photophobia at 2 h	2494 (9 studies)	Sumatriptan: 834/1703 Placebo: 201/791 **RR (95% CI): 1.85 (1.63 to 2.11)** **SS in favour of sumatriptan** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok
Relief of phonophobia at 2 h	2128 (7 studies)	Sumatriptan: 736/1492 Placebo: 164/626 **RR (95% CI): 1.83 (1.59 to 2.11)** **SS in favour of sumatriptan** I^2: 33%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok
Improvement of functional disability	1827 (6 studies)	Sumatriptan: 58% (651/1113) Placebo: 31% (220/714) **RR (95% CI): 1.9 (1.7 to 2.1)** NNT (95% CI): 3.6 (3.1 to 4.3)	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok

		SS in favour of sumatriptan I^2: 0%	
Use of rescue medication up to 24 h	2810 (6 studies)	Sumatriptan: 33% (621/1877) Placebo: 58% (543/933) **RR (95% CI): 0.57 (0.52 to 0.62)** NNTp (95% CI): 4.0 (3.5 to 4.7) **SS in favour of sumatriptan** I^2: 79%	⊕⊕⊖⊖ **LOW** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: -1 Directness: ok Imprecision: ok
Use of rescue medication up to 4 h	1027 (3 studies)	Sumatriptan: 27% (179/675) Placebo: 54% (189/352) **RR (95% CI): 0.55 (0.47 to 0.65)** NNTp (95% CI): 3.7 (3.0 to 4.8) **SS in favour of sumatriptan** I^2: 15%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok
Adverse events over 24 h	3257 (12 studies)	Sumatriptan: 43% (931/2171) Placebo: 23% (255/1086) **RR (95% CI): 1.7 (1.5 to 1.9)** NNH (95%CI): 5.2 (4.4 to 6.2) **SS in favour of placebo** I^2: 75%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: -1 Directness: ok Imprecision: ok
Palpitation/tachycardia	261 (1 study)	Sumatriptan: 7/130 Placebo: 2/131 RR (95% CI): 3.53 (0.75 to 16.66) NS	⊕⊕⊖⊖ **LOW** Study quality: -1; single study with unclear blinding Consistency: na Directness: ok Imprecision: -1

Table 33

This systematic review by Derry 2012 searched for double-blind RCTs comparing oral sumatriptan to placebo or an active control to treat an acute migraine headache episode in adults.

27 RCTs evaluated sumatriptan 50 mg and 29 RCTs evaluated sumatriptan 100 mg versus placebo. The different dosages were analyzed separately.

Authors analyzed studies performed in established pain of at least moderate intensity separately from studies in which medication was taken before pain became well established or in which a second dose of medication was permitted.

There are some methodological problems that limit our confidence in the estimate of the results: the majority of included studies had an unclear risk of bias pertaining to allocation concealment, randomization or blinding.

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 100 mg** resulted in **more pain freedom at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 100 mg** resulted in **more pain relief at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 100 mg** resulted in **more sustained pain freedom over 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 100 mg** resulted in **more sustained pain relief over 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 100 mg** resulted in **more pain freedom at 1h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 100 mg** resulted in **more pain relief at 1h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 100 mg** resulted in **more relief of nausea at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 100 mg** resulted in **more relief of photophobia at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 100 mg** resulted in **more relief of phonophobia at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 100 mg** resulted in **more improvement of functional disability** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 100 mg** resulted in **less use of rescue medication up to 24h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 100 mg** resulted in **less use of rescue medication up to 4h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **sumatriptan 100 mg** resulted in **more adverse events over 24h** compared to placebo.
GRADE: MODERATE quality of evidence

There was **no difference** between **sumatriptan 100 mg** and placebo for **palpitations/tachycardia** in **adults with a migraine attack of moderate or severe baseline intensity**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

6.6.6.4 Sumatriptan 100 mg versus placebo for acute migraine attacks of mild baseline pain intensity in adults

Sumatriptan 100 mg (oral route of administration) versus placebo for acute migraine attacks of mild baseline pain intensity in adults

Bibliography: SR Derry 2012(87)

Including: Carpay 2004(90), Cutler 1995(91), Dahlof 1991(92), DKSMSG 1999(24), Dodick 2002(109), Dowson 2002(56), Ensink 1991(110), Geraud 2000(111), Goadsby 1991(112), Goadsby 2000(62), Havanka 2000(79), Jelinski 2006(95), Kaniecki 2006(120), Mathew 2003(113), Myllyla 1998(114), Nappi 1994(115), Nett 2003(100), Patten 1991(116), Pfaffenrath 1998(101), Pini 1995(117), Sandrini 2002(65), Sargent 1995(103), Sheftell 2005a(105), Sheftell 2005b(105), Tfelt-Hansen 1995(118), Tfelt-Hansen 1998(83), Visser 1996(119), Winner 2003a(107)

Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Pain free at 2 h	1240 (5 studies)	Sumatriptan: 58% (358/618) Placebo: 24% (151/622) **RR (95% CI): 2.4 (2.1 to 2.8)** NNT (95%CI): 3.0 (2.6 to 3.5) **SS in favour of sumatriptan** I^2: 64%	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Sustained pain-free over 24 h (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	771 (3 studies)	Sumatriptan: 33% (127/389) Placebo: 10% (39/382) **RR (95% CI): 3.2 (2.3 to 4.5)** NNT (95%CI): 4.5 (3.6 to 5.9) **SS in favour of sumatriptan** I^2: 40%	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Pain free at 1 h	1240 (5 studies)	Sumatriptan: 31% (189/618) Placebo: 14% (87/622) **RR (95% CI): 2.2 (1.8 to 2.8)** NNT (95%CI): 6.0 (4.7 to 8.3)	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok

		SS in favour of sumatriptan I^2: 0%	
Relief of nausea at 2 h	265 (3 studies)	Sumatriptan: 58/130 Placebo: 10/135 **RR (95% CI): 5.89 (3.18 to 10.91)** **SS in favour of sumatriptan** I^2: 77%	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: -1 Directness: ok Imprecision: ok
Relief of photophobia at 2 h	475 (3 studies)	Sumatriptan: 131/229 Placebo: 44/246 **RR (95% CI): 3.23 (2.41 to 4.33)** **SS in favour of sumatriptan** I^2: 78%	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: -1 Directness: ok Imprecision: ok
Relief of phonophobia at 2 h	400 (3 studies)	Sumatriptan: 120/189 Placebo: 37/211 **RR (95% CI): 3.7 (2.69 to 5.08)** **SS in favour of sumatriptan** I^2: 63%	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Adverse events over 24 h	941 (4 studies)	Sumatriptan: 19% (89/471) Placebo: 7% (32/470) **RR (95% CI): 2.8 (1.9 to 4.1)** NNT (95%CI): 8.3 (6.1 to 13) **SS in favour of placebo** I^2: 0%	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Palpitation/tachycardia	238 (1 study)	No events Not estimable	Insufficient data

Table 34

This systematic review by Derry 2012 searched for double-blind RCTs comparing oral sumatriptan to placebo or an active control to treat an acute migraine headache episode in adults.

27 RCTs evaluated sumatriptan 50 mg and 29 RCTs evaluated sumatriptan 100 mg versus placebo. The different dosages were analyzed separately.

Authors analyzed studies performed in established pain of at least moderate intensity separately from studies in which medication was taken before pain became well established or in which a second dose of medication was permitted.

There are some methodological problems that limit our confidence in the estimate of the results: the majority of included studies had an unclear risk of bias pertaining to allocation concealment, randomization or blinding.

In **adults with a migraine attack of mild baseline intensity**, **sumatriptan 100 mg** resulted in **more pain freedom at 2h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with a migraine attack of mild baseline intensity**, **sumatriptan 100 mg** resulted in **more sustained pain freedom over 24h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with a migraine attack of mild baseline intensity**, **sumatriptan 100 mg** resulted in **more pain freedom over 1h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with a migraine attack of mild baseline intensity**, **sumatriptan 100 mg** resulted in **more relief of nausea at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of mild baseline intensity**, **sumatriptan 100 mg** resulted in **more relief of photophobia at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of mild baseline intensity**, **sumatriptan 100 mg** resulted in **more relief of phonophobia at 2h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with a migraine attack of mild baseline intensity**, **sumatriptan 100 mg** resulted in **more adverse events** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

We have **insufficient data** to compare the risk of **palpitations/tachycardia** in sumatriptan 100 mg versus placebo.

6.6.7 Sumatriptan (sc) vs placebo

Sumatriptan 6 mg (subcutaneous route of administration) for acute migraine of moderate or severe baseline pain intensity attacks in adults.			
Bibliography: SR Derry 2012sc(121) Including: Akpunonu 1995(122), Bates 1994(123), Bousser 1993(124), Cady 1991 (study 1 and 2)(125), Cady 1993(126), Cady 1998(127), Dahlof 1998(128), Diener 1999(129), Diener 2001(130), Facchinetti 1995(131), Ferrari 1991(132), Gross 1994(133), Henry 1993(134), Jensen 1995(135), Mathew 1992(136), Mushet 1996 (study 1 and 2)(137), Pfaffenrath 1991(138), Russell 1994(139), S2BM03(140), Sang 2004(141), Schulman 2000(142), SUM40286(143), SUM40287(143), Winner 2006 (study 1 and 2)(144)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2h	2522 (13 studies)	Sumatriptan s.c.: 59% (799/1351) Placebo: 15% (174/1171) **RR (95% CI): 3.9 (3.3 to 4.5)** NNT (95% CI): 2.3 (2.1 to 2.4) **SS in favour of sumatriptan s.c.** I^2: 62%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding or very small size Consistency: ok Directness: ok Imprecision: ok
Pain relief at 2 h (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	2738 (14 studies)	Sumatriptan s.c.: 79% (1152/1459) Placebo: 31% (395/1279) **RR (95% CI): 2.5 (2.3 to 2.7)** NNT (95% CI): 2.1 (2.0 to 2.2) **SS in favour of sumatriptan s.c.** I^2: 75%	⊕⊕⊖⊖ **LOW** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding or very small size Consistency: -1 Directness: ok Imprecision: ok
Pain free at 1 h	3592 (16 studies)	Sumatriptan s.c.: 41% (905/2198) Placebo: 7% (99/1394) **RR (95% CI): 5.6 (4.6 to 6.8)** NNT (95% CI): 2.9 (2.7 to 3.2)	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding or very small size Consistency: ok

		SS in favour of sumatriptan s.c. I^2: 35%	Directness: ok Imprecision: ok
Pain relief at 1 h (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	5177 (24 studies)	Sumatriptan s.c.: 71% (2229/3139) Placebo: 26% (532/2038) **RR (95% CI): 2.7 (2.5 to 2.9)** NNT (95% CI): 2.2 (2.1 to 2.4) **SS in favour of sumatriptan s.c.** I^2: 68%	⊕⊕⊖⊖ **LOW** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding or very small size Consistency: -1 Directness: ok Imprecision: ok
Sustained pain free over 24h (Headache relief at 2 hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication)	1336 (5 studies)	Sumatriptan s.c.: 31% (222/713) Placebo: 15% (91/623) **RR (95% CI): 2.2 (1.8 to 2.8)** NNT (95% CI): 6.1 (4.8 to 8.2) **SS in favour of sumatriptan s.c.** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding Consistency: ok Directness: ok Imprecision: ok
Relief of nausea at 1 h	1461 (8 studies)	**RR (95% CI): 1.9 (1.7 to 2.2)** NNT (95% CI): 3.1 (2.7 to 3.7) **SS in favour of sumatriptan s.c.** I^2: not provided	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization, blinding, or very small size Consistency: na Directness: ok Imprecision: ok
Relief of nausea at 2 h	667 (5 studies)	Sumatriptan s.c.: 76% (276/364) Placebo: 34% (103/303) **RR (95% CI): 2.2 (1.9 to 2.6)** NNT (95% CI): 2.4 (2.1 to 2.9) **SS in favour of sumatriptan s.c.** I^2: 80%	⊕⊕⊖⊖ **LOW** Study quality: -1; majority of studies with unclear allocation concealment, randomization, blinding Consistency: -1 Directness: ok Imprecision: ok
Relief of photophobia at 1 h	1460 (6 studies)	**RR (95% CI): 3.0 (2.5 to 3.7)** NNT (95% CI): 2.7 (2.4 to 3.1) **SS in favour of sumatriptan s.c.** I^2: not provided	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization, blinding, or very small size Consistency: na Directness: ok Imprecision: ok
Relief of photophobia at 2 h	631 (3 studies)	Sumatriptan s.c.: 71% (245/343) Placebo: 36% (105/288) **RR (95% CI): 1.9 (1.6 to 2.2)** NNT (95% CI): 2.9 (2.4 to 3.6) **SS in favour of sumatriptan s.c.** I^2: 0%	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok

Relief of phonophobia at 1 h	300 (3 studies)	Sumatriptan s.c.: Placebo: **RR (95% CI): 2.6 (1.8 to 3.7)** NNT (95% CI): 2.4 (1.9 to 3.3) **SS in favour of sumatriptan s.c.** I^2: not provided	⊕⊕⊕⊖ **MODERATE** Study quality: -1;1 RCT with unclear allocation concealment, 2 with very small size Consistency: na Directness: ok Imprecision: ok
Relief of phonophobia at 2 h	572 (3 studies)	Sumatriptan s.c.: 72% (223/310) Placebo: 39% (101/262) **RR (95% CI): 1.8 (1.5 to 2.2)** NNT (95% CI): 3.0 (2.4 to 3.9) **SS in favour of sumatriptan s.c.** I^2: not provided	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: na Directness: ok Imprecision: ok
Partial relief of functional disability at 1 h (Moderate or severe functional disability to mild or none)	1328 (4 studies)	Sumatriptan s.c.: 72% (649/899) Placebo: 22% (96/429) **RR (95% CI): 3.2 (2.7 to 3.8)** NNT (95% CI): 2.0 (1.8 to 2.2) **SS in favour of sumatriptan s.c.** I^2: 49%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization, blinding Consistency: ok Directness: ok Imprecision: ok
Relief of functional disability at 2 h (Any functional disability at baseline to none)	750 (3 studies)	Sumatriptan s.c.: 56% (213/377) Placebo: 17% (62/373) **RR (95% CI): 3.4 (2.7 to 4.4)** NNT (95% CI): 2.5 (2.2 to 3.3) **SS in favour of sumatriptan s.c.** I^2: 92%	⊕⊕⊖⊖ **LOW** Study quality: -1; 1 study with unclear allocation concealment, randomization and blinding Consistency: -1 Directness: ok Imprecision: ok
Use of rescue medication (up to 24h)	987 (5 studies)	Sumatriptan s.c.: 168/621 Placebo: 176/366 **RR (95% CI): 0.52 (0.45 to 0.60)** **SS in favour of sumatriptan s.c.** I^2: 77%	⊕⊕⊖⊖ **LOW** Study quality: -1; majority of studies with unclear allocation concealment or blinding Consistency: -1 Directness: ok Imprecision: ok
Adverse events	1342 (9 studies)	Sumatriptan s.c.: 44% (341/767) Placebo: 24% (137/575) **RR (95% CI): 2.1 (1.8 to 2.5)** NNH (95% CI): 4.9 (3.9 to 6.4) **SS in favour of placebo** I^2: 49%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization or blinding, or very small sample size Consistency: ok Directness: ok Imprecision: ok

Table 35

This systematic review by Derry 2012sc searched for double-blind RCTs comparing subcutaneous sumatriptan to placebo or an active control to treat an acute migraine headache episode in adults.

27 RCTs were found that compared subcutaneous sumatriptan versus placebo.

Authors analysed studies using a single dose of sumatriptan in established pain of at least moderate intensity separately from studies in which medication was taken before pain was well established or in which a second dose of medication was permitted. Most studies were performed in migraine attacks with pain of at least moderate intensity. The other studies were dominated by participants with moderate or severe migraine attacks at the time of dosing.

Not all studies reported baseline incidence of associated symptoms from which relief could be calculated. These studies were not pooled in the analysis. Five of the studies providing data on relief of associated symptoms (Cady 1993; Facchinetti 1995; Pfaffenrath 1991; Wendt 2006; Winner 2006 Study 1) included a small number (< 10%) of participants with mild baseline pain intensity.

There are some methodological problems that limit our confidence in the estimate of the results: the majority of included studies had an unclear risk of bias pertaining to allocation concealment, randomization, blinding, or very small sample size.

In **adults with migraine of moderate or severe baseline pain intensity**, **sumatriptan 6 mg SC** resulted in **more pain freedom at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate or severe baseline pain intensity**, **sumatriptan 6 mg SC** resulted in **more pain relief at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine of moderate or severe baseline pain intensity**, **sumatriptan 6 mg SC** resulted in **more pain freedom at 1h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate or severe baseline pain intensity**, **sumatriptan 6 mg SC** resulted in **more pain relief at 1h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine of moderate or severe baseline pain intensity**, **sumatriptan 6 mg SC** resulted in **more sustained pain freedom over 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate or severe baseline pain intensity**, **sumatriptan 6 mg SC** resulted in **more relief of nausea at 1h** compared to placebo.

GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate or severe baseline pain intensity**, **sumatriptan 6 mg SC** resulted in **more relief of nausea at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine of moderate or severe baseline pain intensity**, **sumatriptan 6mg SC** resulted in **more relief of photophobia at 1h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate or severe baseline pain intensity**, **sumatriptan 6 mg SC** resulted in **more relief of photophobia at 2h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine of moderate or severe baseline pain intensity**, **sumatriptan 6 mg SC** resulted in **more relief of phonophobia at 1h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate or severe baseline pain intensity**, **sumatriptan 6 mg SC** resulted in **more relief of phonophobia at 2h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine of moderate or severe baseline pain intensity**, **sumatriptan 6 mg SC** resulted in **more partial relief of functional disability at 1h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate or severe baseline pain intensity**, **sumatriptan 6 mg SC** resulted in **more relief of functional disability at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine of moderate or severe baseline pain intensity**, **sumatriptan 6 mg SC** resulted in **less use of rescue medication up to 24h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine of moderate or severe baseline pain intensity**, **sumatriptan 6mg SC** resulted in **more adverse events** compared to placebo.

GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

6.6.8 Sumatriptan (nasal) vs placebo

Nasal sumatriptan vs placebo for cute migraine attacks in adults			
Bibliography: SR Menshawy 2018(145) Including: Rao 2016(146), Cady 2014(147), Djupesland 2010(148), Wang 2007(149), Winner 2006(150), Ahonen 2004(151), S2B-340(152), Peikert 1999(153), Diamond 1998(154), Ryan 1997 (study 1 and study 2)(155), Salonen 1994(156), Salonen 1991(157)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2h	ND	**RR = 1.70, 95% CI [1.31 to 2.21]** p < 0.0001 **SS in favour of intranasal sumatriptan** I^2: 53%	⨁⨁⨀⨀ **LOW** Study quality: -1; unclear allocation concealment in several RCTs, unclear randomization, allocation concealment, blinding, incomplete outcome data, reporting in one RCT Consistency: ok Directness: -1 , 2 studies including adolescents and children Imprecision: ok
Pain free at 1h	ND	**RR = 1.56, 95% CI [1.10, 2.21]** p = 0.01 **SS in favour of intranasal sumatriptan** I^2: 35%	⨁⨁⨀⨀ **LOW** Study quality: -1; unclear allocation concealment in several RCTs, unclear randomization, allocation concealment, blinding, incomplete outcome data, reporting in one RCT Consistency: ok Directness: -1 , 2 studies including adolescents and children Imprecision: ok
Sustained pain-free over 24h	310 (2 studies) (Cady 2014, Rao 2016)	Sumatriptan: 41/157 Placebo: 18/153 RR = 2.21, 95% CI [1.33, 3.68] p = 0.002 **SS in favour of intranasal sumatriptan** I^2: 0%	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: ok Directness: ok Imprecision: -1 (low number of events, ans study sizes)
Headache relief at 1h	ND	RR = 1.47, 95%CI [1.24, 1.73] p < 0.00001 **SS in favour of intranasal sumatriptan**	⨁⨁⨀⨀ **LOW** Study quality: -1; unclear allocation concealment in several RCTs, unclear randomization, allocation concealment, blinding, incomplete outcome data, reporting in one RCT

		I^2: 59%	Consistency: ok Directness: -1 , 2 studies including adolescents and children Imprecision: ok
Headache relief at 2 h	ND	RR = 1.58, 95%CI [1.35, 1.84] p < 0.00001 **SS in favour of intranasal sumatriptan** I^2: 69%	⊕⊖⊖⊖ **VERY LOW** Study quality: -1; unclear allocation concealment in several RCTs, unclear randomization, allocation concealment, blinding, incomplete outcome data, reporting in one RCT Consistency: -1 Directness: -1 , 2 studies including adolescents and children Imprecision: ok
Meaningful relief	ND	RR = 1.66, 95% CI [1.41, 1.95] p < 0.00001 **SS in favour of intranasal sumatriptan** I^2: 0%	⊕⊕⊖⊖ **LOW** Study quality: -1; unclear allocation concealment in several RCTs, unclear randomization, allocation concealment, blinding, incomplete outcome data, reporting in one RCT Consistency: ok Directness: -1 , 2 studies including adolescents and children Imprecision: ok
Disability-free patients at 1h	ND	RR = 1.17, 95% CI [0.98, 1.41] p = 0.08 NS I^2: 69%	⊕⊖⊖⊖ **VERY LOW** Study quality: -1; unclear allocation concealment in several RCTs, unclear randomization, allocation concealment, blinding, incomplete outcome data, reporting in one RCT Consistency: -1 Directness: -1 , 2 studies including adolescents and children Imprecision: ok
Disability-free patients at 2 h	ND	RR = 1.38, 95% CI [1.20, 1.60] p < 0.00001 **SS in favour of intranasal sumatriptan** I^2: 45%	⊕⊕⊖⊖ **LOW** Study quality: -1; unclear allocation concealment in several RCTs, unclear randomization, allocation concealment, blinding, incomplete outcome data, reporting in one RCT Consistency: ok Directness: -1 , 2 studies including adolescents and children Imprecision: ok
Use of rescue medication at 2h	ND	RR = 0.75, 95%CI [0.60, 0.94] p = 0.01 **SS in favour of intranasal sumatriptan (less with intranasal sumatriptan)**	⊕⊕⊖⊖ **LOW** Study quality: -1; unclear allocation concealment in several RCTs, unclear randomization, allocation concealment, blinding, incomplete outcome data, reporting in one RCT Consistency: ok

		I^2: 35%	Directness: -1 , 2 studies including adolescents and children Imprecision: ok
Adverse events	ND	RR = 2.54, 95% CI [1.66, 378] p < 0.0001 **SS in favour of placebo (less with placebo)** I^2: 64%	⊕⊕⊖⊖ **LOW** Study quality: -1; unclear allocation concealment in several RCTs, unclear randomization, allocation concealment, blinding, incomplete outcome data, reporting in one RCT Consistency: ok Directness: -1 , 2 studies including adolescents and children Imprecision: ok

Table 36

This systematic review by Menshawy 2018 searched for RCTs comparing intranasal sumatriptan to placebo or an active control nasal spray to treat an acute migraine headache episode.

13 RCTs were found that compared intranasal sumatriptan versus placebo.

Most studies included patients having migraine headache without aura of a moderate-to-severe degree.

These results are from pooled studies using different sumatriptan dosages going from 1mg to 40mg. Different delivery system were also pooled.

There are some methodological problems that limit our confidence in the estimate of the results: the majority of included studies had an unclear risk of bias pertaining to allocation concealment, randomization, blinding, or very small sample size.

No details were provided on the studies contributing to each pooled outcome. It was therefore not possible to determine the number of patients included in the analysis, nor to appropriately evaluate the risk of bias and the final quality of evidence. The final quality of evidence was evaluated based on all 13 RCTs together.

One large study only included patients aged 12 to 17 years and one small study only used children and adolescents ages 8 to 17 years. As no detail were provided on the exact contribution of these studies for each outcome, and because this represents more than 10% of all the included patients, the level of evidence were downgraded for directness for all the outcomes.

In **adults with migraine** , **intranasal sumatriptan** resulted in **more pain freedom at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine** , **intranasal sumatriptan** resulted in **more pain freedom at 1h** compared to placebo.
GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine** , **intranasal sumatriptan** resulted in **more sustained pain freedom at 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine** , **intranasal sumatriptan** resulted in **more headache relief at 1h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine** , **intranasal sumatriptan** resulted in **more headache relief at 2h** compared to placebo.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

In **adults with migraine** , **intranasal sumatriptan** resulted in **more meaningful relief** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between intranasal sumatriptan and placebo for **disability-free patients at 1h** in **adults with migraine**.
GRADE:VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

In **adults with migraine**, **intranasal sumatriptan** resulted in **more disability-free patients at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **intranasal sumatriptan** resulted in **less use of rescue medication at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **intranasal sumatriptan** resulted in **more averse events** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

6.6.9 Zolmitriptan (oral) vs placebo

6.6.9.1 Zolmitriptan 2.5 mg versus placebo for acute migraine attacks of moderate or severe baseline pain intensity in adults

Zolmitriptan 2.5 mg (mainly oral route of administration) versus placebo for acute migraine attacks of moderate or severe baseline pain intensity in adults			
Bibliography: SR Bird 2014(158) Including 311CIL/0099 2000(159), Charlesworth 2003(160), Dib 2002(161), Dowson 2002(162), Klapper 2004(163), Loder 2005(164), Pascual 2000(165), Rapoport 1997(166), Ryan 2000(167), Sakai 2002(168), Solomon 1997(169), Steiner 2003(170), Tuchman 2006(171), Visser 1996(172)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2 h (PO)	5825 (11 studies)	Zolmitriptan: 30% (1030/3455) Placebo: 10% (243/2370) **RR (95% CI): 3.0 (2.6 to 3.5)** NNT (95% CI): 5.1 (4.7 to 5.7). **SS in favour of zolmitriptan** I^2: 33%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear randomization and allocation concealment, some with unclear blinding and unclear risk of attrition bias Consistency: ok Directness: ok Imprecision: ok
Pain relief at 2 h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	4904 (11 studies)	Zolmitriptan: 60% (1758/2921) Placebo: 29% (584/1983) **RR (95% CI): 2.1 (1.9 to 2.2)** NNT (95% CI): 3.3 (3.0 to 3.6). **SS in favour of zolmitriptan** I^2: 45%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear randomization and allocation concealment, some with unclear blinding and unclear risk of attrition bias Consistency: ok Directness: ok Imprecision: ok
Sustained pain-free over 24 h (PO) (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	984 (2 studies)	Zolmitriptan: 19% (129/694) Placebo: 6% (16/290) **RR (95% CI): 3.5 (2.1 to 5.8)** NNT (95% CI): 7.7 (6.0 to 11) **SS in favour of zolmitriptan** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; one study with unclear randomization, allocation concealment and binding Consistency: ok Directness: ok Imprecision: ok
Sustained pain relief over 24 h (PO) (Headache relief at two hours, sustained for 24 hours, with no use of	2059 (4 studies)	Zolmitriptan: 39% (557/1436) Placebo: 14% (85/623) **RR (95% CI): 2.9 (2.4 to 3.6)** NNT (95% CI): 4.0 (3.5 to 4.7)	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear randomization and allocation concealment, some with unclear blinding and unclear risk of attrition bias

rescue medication or a second dose of study medication.)		**SS in favour of zolmitriptan** I^2: 0%	Consistency: ok Directness: ok Imprecision: ok
Relief of nausea at 2 h	2140 (7 studies)	Zolmitriptan: 662/1250 Placebo: 322/890 **RR (95% CI): 1.53 (1.37 to 1.69)** **SS in favour of zolmitriptan** I^2: 42%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear randomization and allocation concealment, some with unclear blinding and unclear risk of attrition bias Consistency: ok Directness: ok Imprecision: ok
Relief of photophobia at 2 h	2700 (7 studies)	Zolmitriptan: 790/1558 Placebo: 300/1142 **RR (95% CI): 1.99 (1.78 to 2.23)** **SS in favour of zolmitriptan** I^2: 70%	⊕⊕⊖⊖ **LOW** Study quality: -1; majority of studies with unclear randomization and allocation concealment, some with unclear blinding and unclear risk of attrition bias Consistency: -1 Directness: ok Imprecision: ok
Relief of phonophobia at 2 h	2068 (6 studies)	Zolmitriptan: 607/1138 Placebo: 249/930 **RR (95% CI): 2.03 (1.8 to 2.3)** **SS in favour of zolmitriptan** I^2: 77%	⊕⊕⊖⊖ **LOW** Study quality: -1; majority of studies with unclear randomization and allocation concealment, some with unclear blinding and unclear risk of attrition bias Consistency: -1 Directness: ok Imprecision: ok
Use of rescue medication	5020 (11 studies)	Zolmitriptan: 1019/2960 Placebo 1308/2060 **RR (95% CI): 0.54 [0.51,0.57]** **SS in favour of zolmitriptan (less with zolmitriptan)** I^2: 74%	⊕⊕⊖⊖ **LOW** Study quality: -1; majority of studies with unclear randomization and allocation concealment, some with unclear blinding and unclear risk of attrition bias Consistency: -1 Directness: ok Imprecision: ok
Adverse events	6055 (12 studies)	Zolmitriptan: 32% (1167/3628) Placebo: 17% (422/2427) **RR (95% CI): 1.7 (1.6 to 1.9)** NNH (95% CI): 6.8 (5.9 to 7.9) **SS in favour of placebo (more with zolmitriptan)** I^2: 74%	⊕⊕⊖⊖ **LOW** Study quality: -1; majority of studies with unclear randomization and allocation concealment, some with unclear blinding and unclear risk of attrition bias Consistency: -1 Directness: ok Imprecision: ok

Vasodilation/warm feeling	2784 (6 studies)	Zolmitriptan: 38/1566 Placebo: 13/1218 **RR (95% CI): 2.23 (1.18 to 4.22)** **SS in favour of placebo (more with zolmitriptan)** I^2: 0%	⨁⨁⨀⨀ **LOW** Study quality: -1; majority of studies with unclear randomization and allocation concealment, some with unclear blinding and unclear risk of attrition bias Consistency: ok Directness: ok Imprecision: -1

Table 37

This systematic review by Bird 2014 searched for double-blind RCTs comparing zolmitriptan to placebo or an active control to treat an acute migraine headache episode in adults.

14 RCTs evaluated zolmitriptan 2.5 mg, 8 RCTs evaluated zolmitriptan 5 mg (oral route of administration), and 3 RCTs evaluated zolmitriptan 5 mg (nasal route of administration) versus placebo. The different route of administration and dosages were analyzed separately.

All the studies used oral route of administration (including both oral tablets or oral disintegrating tablets). One study used both oral and nasal routes of administration. Data have been pooled.

One small study only included participants that were required to have a diagnosis of menstrual migraine. Two studies included a small number of participants that were aged 12-18.

Authors analyzed studies performed in established pain of at least moderate intensity separately from studies in which medication was taken before pain became well established or in which a second dose of medication was permitted.

There are some methodological problems that limit our confidence in the estimate of the results: the majority of included studies had an unclear risk of bias pertaining to allocation concealment or randomization, some had an unclear risk of bias pertaining blinding or missing outcome data.

In **adults with a migraine attack of moderate or severe baseline intensity**, **zolmitriptan 2.5 mg** (mainly **oral** route of administration) resulted in **more pain freedom at 2 h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **zolmitriptan 2.5 mg** (mainly **oral** route of administration) resulted in **more pain relief at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **zolmitriptan 2.5 mg** (mainly **oral** route of administration) resulted in **more sustained pain freedom over 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **zolmitriptan 2.5 mg** (mainly **oral** route of administration) resulted in **more sustained pain relief over 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **zolmitriptan 2.5 mg** (mainly **oral** route of administration) resulted in **more relief of nausea at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity, zolmitriptan 2.5 mg** (mainly **oral** route of administration) resulted in **more relief of photophobia at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with a migraine attack of moderate or severe baseline intensity**, **zolmitriptan 2.5 mg** (mainly **oral** route of administration) resulted in **more relief of phonophobia at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with a migraine attack of moderate or severe baseline intensity**, **zolmitriptan 2.5 mg** (mainly **oral** route of administration) resulted in **less use of rescue medication** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with a migraine attack of moderate or severe baseline intensity**, **zolmitriptan 2.5 mg** (mainly **oral** route of administration) resulted in **more adverse events** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with a migraine attack of moderate or severe baseline intensity**, **zolmitriptan 2.5 mg** (mainly **oral** route of administration) resulted in **more vasodilatation or warm feeling** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

6.6.9.2 *Zolmitritpan 5mg versus placebo for acute migraine attacks of mild baseline pain intensity in adults*

Zolmitriptan 5 mg (oral route of administration) versus placebo for acute migraine attacks of moderate or severe baseline pain intensity in adults			
Bibliography: SR Bird 2014(158) Including Charlesworth 2003(160), Dahlof 1998(173), Geraud 2000(111), Ho 2008(174), Rapoport 1997(166), Ryan 2000(167), Sakai 2002(168), Spierings 2004(175), Visser 1996(172)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2h (PO)	4277 (8 studies)	Zolmitriptan: 750/2445 Placebo: 181/1832 **RR (95% CI): 3.2 (2.7 to 3.7)** NNT (95% CI): 4.8 (4.3 to 5.4) **SS in favour of zolmitriptan** I^2: 42%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; most of included studies with unclear randomization and allocation concealment randomization, some with unclear risk of attrition bias Consistency: ok Directness: ok Imprecision: ok
Pain relief at 2h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	4292 (8 studies)	Zolmitriptan: 1452/2450 Placebo: 560/1842 **RR (95% CI): 1.9 (1.8 to 2.1)** NNT (95% CI): 3.5 (3.2 to 3.9) **SS in favour of zolmitriptan** I^2: 53%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; most of included studies with unclear randomization and allocation concealment randomization, some with unclear risk of attrition bias Consistency: ok Directness: ok Imprecision: ok
Sustained pain-free over 24 h (PO) (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	693 (1 study)	Zolmitriptan: 62/345 Placebo: 17/348 **RR (95% CI): 3.68 (2.2 to 6.16)** **SS in favour of zolmitriptan**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: N.A. Directness: ok Imprecision: -1
Sustained pain relief over 24 h (PO) (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a	2827 (5 studies)	Zolmitriptan: 627/1682 Placebo: 175/1145 **RR (95% CI): 2.4 (2.0 to 2.8)** NNT (95% CI): 4.6 (4.0 to 5.3) **SS in favour of zolmitriptan** I^2: 24%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; most of included studies with unclear randomization and allocation concealment randomization, some with unclear risk of attrition bias Consistency: ok Directness: ok Imprecision: ok

second dose of study medication.)			
Pain relief at 1h (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	2310 (6 studies)	Zolmitriptan: 38% (558/1477) Placebo: 22% (183/833) **RR (95% CI): 1.8 (1.5 to 2.1)** NNT (95% CI): 6.3 (5.1 to 8.3) **SS in favour of zolmitriptan** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; most of included studies with unclear randomization and allocation concealment randomization, some with unclear risk of attrition bias Consistency: ok Directness: ok Imprecision: ok
Relief of nausea at 2h	2056 (6 studies)	Zolmitriptan: 609/1187 Placebo: 316/869 **RR (95% CI): 1.51 [1.36 to 1.68)** **SS in favour of zolmitriptan** I^2: 50%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; most of included studies with unclear randomization and allocation concealment randomization, some with unclear risk of attrition bias Consistency: ok Directness: ok Imprecision: ok
Relief of photophobia at 2h	2690 (6 studies)	Zolmitriptan: 766/1555 Placebo: 271/1135 **RR (95% CI): 2.03 (1.81 to 2.29)** **SS in favour of zolmitriptan** I^2: 63%	⊕⊕⊖⊖ **LOW** Study quality: -1; most of included studies with unclear randomization and allocation concealment randomization, some with unclear risk of attrition bias Consistency: -1 Directness: ok Imprecision: ok
Relief of phonophobia at 2h	2512 (6 studies)	Zolmitriptan: 730/1471 Placebo: 254/1041 **RR (95% CI): 2.04 (1.81 to 2.3)** **SS in favour of zolmitriptan** I^2: 67%	⊕⊕⊖⊖ **LOW** Study quality: -1; most of included studies with unclear randomization and allocation concealment randomization, some with unclear risk of attrition bias Consistency: -1 Directness: ok Imprecision: ok
Use of rescue medication	2571 (5 studies)	Zolmitriptan: 561/1539 Placebo: 596/1032 **RR (95% CI): 0.6 (0.55 to 0.65)** **SS in favour of zolmitriptan (less rescue medication with zolmitriptan)** I^2: 78%	⊕⊕⊖⊖ **LOW** Study quality: -1; most of included studies with unclear randomization and allocation concealment randomization, some with unclear risk of attrition bias Consistency: -1 Directness: ok Imprecision: ok
Adverse events	4230 (7 studies)	Zolmitriptan: 1083/2620 Placebo: 318/1610	⊕⊕⊕⊖ **MODERATE** Study quality: -1; most of included studies with unclear

		RR (95% CI): 2.0 (1.8 to 2.2) NNH (95% CI): 4.6 (4.2 to 5.3) **SS in favour of placebo (more with zolmitriptan)** I^2: 17%	randomization and allocation concealment randomization, some with unclear risk of attrition bias Consistency: ok Directness: ok Imprecision: ok
Vasodilation/warm feeling	3004 (6 studies)	Zolmitriptan: 76/1738 Placebo: 15/1268 **RR (95% CI): 2.93 (1.65 to 5.2)** **SS in favour of placebo (more with zolmitriptan)** I^2: 5%	⨁⨁⨀⨀ **LOW** Study quality: -1; most of included studies with unclear randomization and allocation concealment randomization, some with unclear risk of attrition bias Consistency: ok Directness: ok Imprecision: -1

Table 38

This systematic review by Bird 2014 searched for double-blind RCTs comparing zolmitriptan to placebo or an active control to treat an acute migraine headache episode in adults.

14 RCTs evaluated zolmitriptan 2.5 mg, 8 RCTs evaluated zolmitriptan 5 mg (oral route of administration), and 3 RCTs evaluated zolmitriptan 5 mg (nasal route of administration) versus placebo. The different route of administration and dosages were analyzed separately.

All the studies used oral route of administration, only one study used an oral disintegrating tablet formulation. The outcomes for relief of associated symptoms included studies using oral route of administration as well as one small study that used zolmitriptan 5 mg nasal spray.

One study included a small number of participants that were aged 12-18.

Authors analyzed studies performed in established pain of at least moderate intensity separately from studies in which medication was taken before pain became well established or in which a second dose of medication was permitted.

There are some methodological problems that limit our confidence in the estimate of the results: the majority of included studies had an unclear risk of bias pertaining to allocation concealment or randomization, some had an unclear risk of attrition bias (missing outcome data).

In **adults with a migraine attack of moderate or severe baseline intensity**, **zolmitriptan 5 mg** (**oral** route of administration) resulted in **more pain freedom at 2 h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity zolmitriptan 5 mg** (**oral** route of administration) resulted in **more pain relief at 2h** compared to placebo.
GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **zolmitriptan 5 mg** (**oral** route of administration) resulted in **more sustained pain freedom over 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **zolmitriptan 5 mg** (**oral** route of administration) resulted in **more sustained pain relief over 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity zolmitriptan 5 mg** (**oral** route of administration) resulted in **more pain relief at 1 h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **zolmitriptan 5 mg** (**oral** route of administration) resulted in **more relief of nausea at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity, zolmitriptan 5 mg** (**oral** route of administration) resulted in **more relief of photophobia at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with a migraine attack of moderate or severe baseline intensity**, **zolmitriptan 5 mg** (**oral** route of administration) resulted in **more relief of phonophobia at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with a migraine attack of moderate or severe baseline intensity**, **zolmitriptan 5 mg** (**oral** route of administration) resulted in **less use of rescue medication** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with a migraine attack of moderate or severe baseline intensity**, **zolmitriptan 5 mg** (**oral** route of administration) resulted in **more adverse events** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity**, **zolmitriptan 5 mg** (**oral** route of administration) resulted in **more vasodilatation or warm feeling** compared to placebo.

GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

6.6.10 Zolmitritpan (nasal) vs placebo

Zolmitriptan 5 mg (nasal route of administration) versus placebo for acute migraine attacks of moderate or severe baseline pain intensity in adults			
Bibliography: SR Bird 2014(158) Including Charlesworth 2003(160), Dodick 2005(176), Gawel 2005(177)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2h (PO)	5095 (3 studies)	Zolmitriptan: 866/2579 Placebo: 300/2516 **RR (95% CI): 2.8 (2.5 to 3.2)** NNT (95% CI): 4.6 (4.2 to 5.2). **SS in favour of zolmitriptan** I^2: 65%	⨁⨁⨀⨀ L**OW** Study quality: -1; all studies with unclear allocation concealment and 2 studies with unclear randomization Consistency: -1 Directness: ok Imprecision: ok
Pain relief at 2h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	3164 (3 studies)	Zolmitriptan: 1085/1596 Placebo: 518/1568 **RR (95% CI): 2.1 (1.9 to 2.2)** NNT (95% CI): 2.9 (2.6 to 3.2) **SS in favour of zolmitriptan** I^2: 87%	⨁⨁⨀⨀ **LOW** Study quality: -1; all studies with unclear allocation concealment and 2 studies with unclear randomization Consistency: -1 Directness: ok Imprecision: ok
Sustained pain-free over 24h (PO) (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	4298 (2 studies)	Zolmitriptan: 284/2171 Placebo: 56/2127 **RR (95% CI): 4.9 (3.7 to 6.5)** NNT (95% CI): 9.6 (8.3 to 11) **SS in favour of zolmitriptan** I^2: 85%	⨁⨁⨀⨀ **LOW** Study quality: -1; all studies with unclear allocation concealment and unclear randomization Consistency: -1 Directness: ok Imprecision: ok
Sustained pain relief over 24 h (PO)	4279 (2 studies)	Zolmitriptan: 818/2172 Placebo: 200/2107 **RR (95% CI): 4.0 (3.4 to 4.6)**	⨁⨁⨁⨀ **MODERATE** Study quality: -1; all studies with unclear allocation concealment and one study with unclear randomization

(Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.)		NNT (95% CI): 3.6 (3.3 to 3.9) **SS in favour of zolmitriptan** I^2: 0%	Consistency: ok Directness: ok Imprecision: ok
Pain relief at 1h (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	2684 (2 studies)	Zolmitriptan: 56% (763/1362) Placebo: 32% (420/1322) **RR (95% CI): 1.8 (1.6 to 1.9)** NNT (95% CI): 4.2 (3.6 to 4.9) **SS in favour of zolmitriptan** I^2: 76%	⊕⊕⊖⊖ **LOW** Study quality: -1; all studies with unclear allocation concealment and one study with unclear randomization Consistency: -1 Directness: ok Imprecision: ok
Use of rescue medication at 2h	5191 (3 studies)	Zolmitriptan: 894/2633 Placebo: 1650/2558 **RR (95% CI): 0.53 (0.5,0.56)** **SS in favour of zolmitriptan (less rescue medication with zolmitriptan)** I^2: 78%	⊕⊕⊖⊖ L**OW** Study quality: -1; all studies with unclear allocation concealment and 2 studies with unclear randomization Consistency: -1 Directness: ok Imprecision: ok
Adverse events	4842 (3 studies)	Zolmitriptan: 2101/2445 Placebo: 742/2397 **RR (95% CI): 2.4 (2.1 to 2.6)** NNH (95% CI): 4.2 (3.8 to 4.7) **SS in favour of placebo (more adverse events with zolmitriptan)** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; all studies with unclear allocation concealment and 2 studies with unclear randomization Consistency: ok Directness: ok Imprecision: ok

Table 39

This systematic review by Bird 2014 searched for double-blind RCTs comparing zolmitriptan to placebo or an active control to treat an acute migraine headache episode in adults.

14 RCTs evaluated zolmitriptan 2.5 mg, 8 RCTs evaluated zolmitriptan 5 mg (oral route of administration), and 3 RCTs evaluated zolmitriptan 5 mg (nasal route of administration) versus placebo. The different route of administration and dosages were analyzed separately.

Authors analyzed studies performed in established pain of at least moderate intensity separately from studies in which medication was taken before pain became well established or in which a second dose of medication was permitted.

There are some methodological problems that limit our confidence in the estimate of the results: all the included studies had an unclear risk of bias pertaining to allocation concealment and two of the three studies had an unclear risk of bias pertaining to randomization.

In **adults with a migraine attack of moderate or severe baseline intensity**, **zolmitriptan 5 mg** (**nasal** route of administration) resulted in **more pain freedom at 2 h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with a migraine attack of moderate or severe baseline intensity zolmitriptan 5 mg** (**nasal** route of administration) resulted in **more pain relief at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with a migraine attack of moderate or severe baseline intensity**, **zolmitriptan 5 mg** (**nasal** route of administration) resulted in **more sustained pain freedom over 24h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with a migraine attack of moderate or severe baseline intensity**, **zolmitriptan 5 mg** (**nasal** route of administration) resulted in **more sustained pain relief over 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate or severe baseline intensity zolmitriptan 5 mg** (**nasal** route of administration) resulted in **more pain relief at 1 h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with a migraine attack of moderate or severe baseline intensity**, **zolmitriptan 5 mg** (**nasal** route of administration) resulted in **less use of rescue medication** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with a migraine attack of moderate or severe baseline intensity**, **zolmitriptan 5 mg** (**nasal** route of administration) resulted in **more adverse events** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

6.6.11 Almotriptan vs zolmitriptan

Almotriptan vs zolmitriptan for acute treatment of migraine attack in adults			
Bibliography: SR Xu 2016(41) Including Goadsby 2007(178)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2 h	1062 (1 study)	OR (95% CI): 0.90 (0.73 to 1.11) NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1; single study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: ok
Pain relief at 2h	1062 (1 study)	OR (95% CI): 0.93 (0.77 to 1.12) NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1; single study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: ok
Use of rescue medication	1062 (1 study)	OR (95% CI): 0.99 (0.74 to 1.32) NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1; single study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: ok
Migraine recurrence	1062 (1 study)	OR (95% CI): 1.07 (0.8 to 1.42) NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1; single study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: ok

Table 40

In this NMA, authors performed a systematic review for double-blind RCTs that compared NSAIDs and triptans. They initially carried out a conventional pair-wise meta-analysis which directly compares each pair of treatments then the NMA was performed for each endpoint. In this document we have only reported data from direct comparisons.

One RCT comparing almotriptan to zolmitriptan was found. Almotriptan 12.5 mg was compared to zolmitriptan 2.5 mg. Medication administered when migraine headache pain was of moderate or severe intensity

There are some methodological problems that limit our confidence in the estimate of the results: it is a single study with unclear risk of bias pertaining to randomization and allocation concealment.

There was **no difference** between almotriptan and zolmitriptan for **pain freedom at 2h** in **adults with migraine**.
GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between almotriptan and zolmitriptan for **pain relief at 2h** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between almotriptan and zolmitriptan for **use of rescue medication** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between almotriptan and zolmitriptan for **migraine recurrence** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

6.6.12 Eletriptan vs zolmitriptan

Eletriptan versus zolmitriptan for acute treatment of migraine attack in adults			
Bibliography: SR Xu 2016(41) Including Steiner 2003(68)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 1h	1337 (1 study)	OR (95% CI): 1.59 (0.96 to 2.64) NS	⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: na Directness: ok Imprecision: ok
Pain relief at 1h	1337 (1 study)	**OR (95% CI): 1.39 (1.06 to 1.81)** **SS in favour of eletriptan**	⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: na Directness: ok Imprecision: ok
Pain free at 2 h	1337 (1 study)	**OR (95% CI): 1.93 (1.50 to 2.49)** **SS in favour of eletriptan**	⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: na Directness: ok Imprecision: ok
Pain relief at 2h	1337 (1 study)	OR (95% CI): 1.13 (0.93 to 1.38) NS	⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: na Directness: ok Imprecision: ok

Nausea absence at 2h	1337 (1 study)	OR (95% CI): 1.10 (0.91 to 1.34) NS	⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: na Directness: ok Imprecision: ok
Migraine recurrence	1337 (1 study)	OR (95% CI): 0.92 (0.68 to 1.23) NS	⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: na Directness: ok Imprecision: ok
Adverse events	1337 (1 study)	OR (95% CI): 1.08 (0.85 to 1.37) NS	⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: na Directness: ok Imprecision: ok

Table 41

In this NMA, authors performed a systematic review for double-blind RCTs that compared NSAIDs and triptans. They initially carried out a conventional pair-wise meta-analysis which directly compares each pair of treatments then the NMA was performed for each endpoint. In this document we have only reported data from direct comparisons.

One RCT comparing eletriptan to zolmitriptan was found. The study used zolmitriptan 2.5 mg Vs eletriptan 40 mg vs eletriptan 80 mg. Medication administered when migraine headache pain was of moderate or severe intensity

The study was judged to have a low risk of bias.

There was **no difference** between eletriptan and zolmitriptan for **pain freedom at 1h** in **adults with migraine**.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **eletriptan** resulted in **more pain relief at 1h** compared to zolmitriptan.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **eletriptan** resulted in **more pain freedom at 2h** compared to zolmitriptan.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

There was **no difference** between eletriptan and zolmitriptan for **pain relief at 2h** in **adults with migraine**.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

There was **no difference** between eletriptan and zolmitriptan for **nausea absence at 2h** in **adults with migraine**.

GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

There was **no difference** between eletriptan and zolmitriptan for **migraine recurrence** in **adults with migraine**.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

There was **no difference** between eletriptan and zolmitriptan for **adverse events** in **adults with migraine**.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

6.6.13 Naratriptan vs rizatriptan

Naratriptan versus rizatriptan for acute treatment of migraine attack in adults			
Bibliography: SR Xu 2016(41) Including Bomhof 1999(77)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 1h	522 (1 study)	**OR (95% CI): 0.35 (0.14 to 0.84)** **SS in favour of rizatriptan**	⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: na Directness: ok Imprecision: ok
Pain relief at 1h	522 (1 study)	OR (95% CI): 0.73 (0.49 to 1.08) NS	⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: na Directness: ok Imprecision: ok
Pain free at 2 h	522 (1 study)	**OR (95% CI): 0.46 (0.31, 0.69)** **SS in favour of rizatriptan**	⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: na Directness: ok Imprecision: ok
Pain relief at 2h	522 (1 study)	**OR (95% CI): 0.70 (0.51 to 0.97)** **SS in favour of rizatriptan**	⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: na Directness: ok Imprecision: ok
Nausea absence at 2h	522 (1 study)	OR (95% CI): 0.86 (0.63 to 1.18) NS	⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: na Directness: ok Imprecision: ok
Migraine recurrence	522 (1 study)	**OR (95% CI): 0.63 (0.41 to 0.96)**	⨁⨁⨁⨁ **HIGH** Study quality: ok

		SS in favour of naratriptan (less with naratriptan)	Consistency: na Directness: ok Imprecision: ok
Adverse events	522 (1 study)	OR (95% CI): 0.70 (0.44 to 1.09) NS	⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: na Directness: ok Imprecision: ok

Table 42

In this NMA, authors performed a systematic review for double-blind RCTs that compared NSAIDs and triptans. They initially carried out a conventional pair-wise meta-analysis which directly compares each pair of treatments then the NMA was performed for each endpoint. In this document we have only reported data from direct comparisons.

One RCT comparing naratriptan to rizatriptan was found. Naratriptan 2.5 mg and rizatriptan 10 mg were used.

The study was judged to have a Jadad quality score of 4 (out of 5).

In **adults with migraine**, **rizatriptan** resulted in **more pain freedom at 1h** compared to naratriptan.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

There was **no difference** between rizatriptan and naratriptan for **pain relief at 1h** in **adults with migraine**.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **rizatriptan** resulted in **more pain freedom at 2h** compared to naratriptan.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **rizatriptan** resulted in **more pain relief at 2h** compared to naratriptan.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

There was **no difference** between rizatriptan and naratriptan for **nausea absence at 2h** in **adults with migraine**.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **rizatriptan** resulted in **more migraine recurrence** compared to naratriptan.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

There was **no difference** between rizatriptan and naratriptan for **adverse events** in **adults with migraine**.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

6.6.14 Naratriptan vs sumatriptan

Naratriptan 2.5 mg versus sumatriptan 100 mg for acute treatment of migraine attack in adults			
Bibliography: SR Ashcroft 2004(73) Including Bates 1998(76), Havanka 2000(79), Gobel 2000a(179)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2 h	635 (2 studies)	**RR (95% CI): 0.69 (0.53 to 0.91)** **SS in favour of sumatriptan**	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: nd Directness: ok Imprecision: ok
Headache relief at 2 h	635 (2 studies)	RR (95% CI): 0.86 (0.74 to 1.00) NS	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: nd Directness: ok Imprecision: ok
Pain free at 4 h	635 (2 studies)	Naratriptan: 124/296 Sumatriptan: 180/339 **RR (95% CI): 0.79 (0.67 to 0.93**) **SS in favour of sumatriptan** I^2: 0%	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Headache relief at 4 h	635 (2 studies)	Naratriptan: 186/296 Sumatriptan: 251/339 **RR (95% CI): 0.85 (0.76 to 0.95)** **SS in favour of sumatriptan** I^2: 3.5%	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Sustained pain relief up to 24h	635 (2 studies)	Naratriptan: 146/296 Sumatriptan: 161/339 RR (95% CI): 1.04 (0.88 to 1.22) NS	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok

		I^2: 0%	
Adverse events	635 (2 studies)	Naratriptan: 81/285 Sumatriptan: 131/318 **RR (95% CI): 0.68 (0.55 to 0.86)** **SS in favour or naratriptan (less adverse events with naratriptan)**	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: nd Directness: ok Imprecision: ok

Table 43

This systematic review by Ashcroft 2004 searched for RCTs of naratriptan for the acute treatment of migraine attacks in adults.

Three RCTs comparing naratriptan to sumatriptan were found. One RCT was performed in patients with a history of frequent headache recurrence. The results of this population was not reported in the present document as they are not part of the general population of patient with migraine.

Given that migraine trials often include patients who are randomised to treatment but who do not have a migraine attack during the study period, the denominator was the number of patients randomised who had a migraine attack of moderate or severe intensity.

All three studies were judged to have a low risk of bias.

In **adults with migraine**, **naratriptan 2.5 mg** resulted in **less pain freedom at 2h** compared to sumatriptan 100 mg.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

There was **no difference** between naratriptan 2.5 mg and sumatriptan 100 mg for **headache relief at 2h** in **adults with migraine**.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **naratriptan 2.5 mg** resulted in **less pain freedom at 4h** compared to sumatriptan 100 mg.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **naratriptan** 2.5 mg resulted in **less headache relief at 4h** compared to sumatriptan 100 mg.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

There was **no difference** between naratriptan 2.5 mg and sumatriptan 100 mg for **sustained pain relief up to 24h** in **adults with migraine**.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **naratriptan 2.5 mg** resulted in **less adverse events** compared to sumatriptan 100 mg.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

6.6.15 Naratriptan vs zolmitriptan

Naratriptan 2.5 mg versus zolmitriptan 2.5 mg for acute treatment of migraine attack in adults			
Bibliography: SR Ashcroft 2004(73) Including Schoenen 1999(78)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 4 h	154 (1 study)	Naratriptan: 20/79 Zolmitriptan: 18/75 RR (95% CI): 1.05 (0.61 to 1.83) NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: na Directness: ok Imprecision: -1
Headache relief at 4 h	154 (1 study)	Naratriptan: 46/79 Zolmitriptan: 43/75 RR (95% CI) : 1.02 (0.78 to 1.33) NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: na Directness: ok Imprecision: -1
Sustained pain relief up to 24h	154 (1 study)	Naratriptan: 32/79 Zolmitriptan: 29/75 RR (95% CI) : 1.05 (0.71 to 1.55) NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: na Directness: ok Imprecision: -1
Adverse events	154 (1 study)	Naratriptan: 18/79 Zolmitriptan: 34/75	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: na Directness: ok

		RR (95% CI) : 0.50 (0.31 to 0.81) **SS in favour of naratriptan (less adverse events with naratriptan)**	Imprecision: -1

Table 44

This systematic review by Ashcroft 2004 searched for RCTs of naratriptan for the acute treatment of migraine attacks in adults.

One RCT comparing naratriptan to zolmitriptan was found.
Given that migraine trials often include patients who are randomised to treatment but who do not have a migraine attack during the study period, the denominator was the number of patients randomised who had a migraine attack of moderate or severe intensity.

The study was judged to have a low risk of bias. However this trial was stopped early due to difficulties in obtaining supplies of one of the trial drugs, it is important that these results are interpreted with caution, particularly as these are based on a single study.

Note that Bird 2014 identified a non-published trial (311CIL/0099 2000) for the same comparison. The MA Bird 2014 has not analysed data for this comparison. No other results are presented for this comparison in the present report.

There was **no difference** between naratriptan 2.5 mg and zolmitriptan 2.5 mg for **pain freedom at 4h** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between naratriptan 2.5 mg and zolmitriptan 2.5 mg for **headache relief at 4h** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate

There was **no difference** between naratriptan 2.5 mg and zolmitriptan 2.5 mg for **sustained pain relief up to 24h** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate

In **adults with migraine**, **naratriptan** 2.5 mg resulted in **fewer adverse events** compared to zolmitriptan 2.5 mg.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate

6.6.16 Rizatriptan vs zolmitriptan

Rizatriptan versus zolmitriptan for acute treatment of migraine attack in adults (			
Bibliography: SR Xu 2016(41) Including Pascual 2000(54)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 1h	727 (1 study)	OR (95% CI): 1.22 (0.73 to 2.02) NS	⊕⊕⊖⊖ **LOW** Study quality: -2; single study with unclear allocation concealment, randomization and blinding Consistency: na Directness: ok Imprecision: ok
Pain relief at 1h	727 (1 study)	OR (95% CI): 1.20 (0.88 to 1.63) NS	⊕⊕⊖⊖ **LOW** Study quality: -2; single study with unclear allocation concealment, randomization and blinding Consistency: na Directness: ok Imprecision: ok
Pain free at 2 h	727 (1 study)	OR (95% CI): 1.22 (0.90 to 1.66) NS	⊕⊕⊖⊖ **LOW** Study quality: -2; single study with unclear allocation concealment, randomization and blinding Consistency: na Directness: ok Imprecision: ok
Pain relief at 2h	727 (1 study)	OR (95% CI): 1.05 (0.81 to 1.35) NS	⊕⊕⊖⊖ **LOW** Study quality: -2; single study with unclear allocation concealment, randomization and blinding Consistency: na Directness: ok Imprecision: ok
Nausea absence at 2h	727 (1 study)	OR (95% CI): 1.12 (0.87 to 1.44) NS	⊕⊕⊖⊖ **LOW** Study quality: -2; single study with unclear allocation concealment, randomization and blinding Consistency: na Directness: ok Imprecision: ok
Migraine recurrence	727 (1 study)	OR (95% CI): 0.96 (0.68 to 1.36) NS	⊕⊕⊖⊖ **LOW** Study quality: -2; single study with unclear allocation concealment, randomization and blinding Consistency: na Directness: ok Imprecision: ok

Adverse events	727 (1 study)	OR (95% CI): 0.89 (0.63 to 1.27) NS	⨁⨁⊖⊖ **LOW** Study quality: -2; single study with unclear allocation concealment, randomization and blinding Consistency: na Directness: ok Imprecision: ok

Table 45

In this NMA, authors performed a systematic review for double-blind RCTs that compared NSAIDs and triptans. They initially carried out a conventional pair-wise meta-analysis which directly compares each pair of treatments then the NMA was performed for each endpoint. In this document we have only reported data from direct comparisons.

One RCT comparing naratriptan to rizatriptan was found. Zolmitriptan 2.5 mg and rizatriptan 10 mg were used. Medication administered when migraine headache pain was of moderate or severe intensity

There are some methodological problems that limit our confidence in the estimate of the results: it is a single study with unclear risk of bias pertaining to randomization, allocation concealment and blinding.

There was **no difference** between rizatriptan and zolmitriptan for **pain freedom at 1h** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between rizatriptan and zolmitriptan for **pain relief at 1h** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between rizatriptan and zolmitriptan for **pain freedom at 2h** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between rizatriptan and zolmitriptan for **pain relief at 2h** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between rizatriptan and zolmitriptan for **nausea absence at 2h** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between rizatriptan and zolmitriptan for **migraine recurrence** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between rizatriptan and zolmitriptan for **adverse events** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

6.6.17 Sumatriptan vs almotriptan

Oral sumatriptan 50 mg versus almotriptan 12.5 mg for acute treatment of migraine attack of moderate to severe basal pain intensity in adults			
Bibliography: SR Derry 2012(87) Including Spierings 2001(180)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2 h	1173 (1 study)	Sumatriptan: 143/582 (25%) Almotriptan: 106/591 (18%) (*P* = 0.005, **SS in favour of sumatriptan** as reported in the original study)	⨁⨁⨁⊖ **MODERATE** Study quality: -1; single study with unclear allocation concealment and randomization Consistency: na Directness: ok Imprecision: ok
Pain relief at 2 h (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	1173 (1 study)	Sumatriptan: 333/582 (57%) Almotriptan: 343/591 (58%) Insufficient data for analysis	Insufficient data
Use of rescue medication up to 24 h	1173 (1 study)	Sumatriptan: 193/582 (33%) Almotriptan: 217/591 (37%) Insufficient data for analysis	Insufficient data
Adverse events over 24 h	1173 (1 study)	Sumatriptan: 113/582 (19%) Almotriptan: 90/591 (15%) (P = 0.06, NS as reported in the original study)	⨁⨁⨁⊖ **MODERATE** Study quality: -1; single study with unclear allocation concealment and randomization Consistency: na Directness: ok Imprecision: na
Palpitations	1173 (1 study)	Sumatriptan: 0/582 (1.3%) Almotriptan: 2/591 (1.0%)	Insufficient data

		Insufficient data for analysis	
Vasodilation	1173 (1 study)	Sumatriptan: 8/582 (1.3%) Almotriptan: 6/591 (1.0%) Insufficient data for analysis	Insufficient data

Table 46

Oral sumatriptan 100 mg versus almotriptan 12.5 mg for acute treatment of migraine attack of moderate to severe baseline pain intensity in adults			
Bibliography: SR Derry 2012(87) Including Dodick 2002(109), Dowson 2002(56)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2h	754 (2 studies)	Sumatriptan: 129/387 Almotriptan: 102/367 RR (95% CI): 1.2 (0.97 to 1.49) NS I^2: 0%	⊕⊕⊖⊖ **LOW** Study quality: -2; unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok
Sustained pain-free over 24 h (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	754 (2 studies)	Sumatriptan: 111/387 Almotriptan: 110/367 RR (95% CI): 0.96 (0.77 to 1.19) NS I^2: 0%	⊕⊕⊖⊖ **LOW** Study quality: -2; unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok
Adverse events over 24 h	378 (1 study)	Sumatritpan: 43/194 (22%) Almotritptan: 16/184 (8.6%) Insufficient data for analysis	Insufficient data

Table 47

This systematic review by Derry 2012 searched for double-blind RCTs comparing oral sumatriptan to placebo or an active control to treat an acute migraine headache episode in adults.

Three RCTs comparing sumatriptan to almotriptan were found. One RCT used sumatriptan 50 mg, while two RCTs used sumatriptan 100 mg. The two dosages were analyzed separately.
Authors analysed studies using a single dose of sumatriptan in established pain of at least moderate intensity separately from studies in which medication was taken before pain became well established or in which a second dose of medication was permitted.

All the studies included for this comparison were performed in patients with basal pain of least moderate intensity.

There are some methodological problems that limit our confidence in the estimate of the results: all three RCTs had an unclear risk of bias pertaining to randomization and allocation concealment, and two RCTs had an unclear risk of bias pertaining to blinding.

Sumatriptan 50 mg vs almotriptan 12.5 mg

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan 50 mg** resulted in **more pain freedom at 2h** compared to almotriptan 12.5 mg.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

We have **insufficient data** to compare pain relief at 2h in sumatriptan 50 mg versus almotriptan 12.5 mg.

We have **insufficient data** to compare use of rescue medication up to 24h in sumatriptan 50 mg versus almotriptan 12.5 mg.

There was **no difference** between sumatriptan 50 mg and almotriptan 12.5 mg for **adverse events** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

We have **insufficient data** to compare palpitations in sumatriptan 50 mg versus almotriptan 12.5 mg.

We have **insufficient data** to compare vasodilatation in sumatriptan 50 mg versus almotriptan 12.5 mg.

Sumatriptan 100 mg vs almotriptan 12.5 mg

There was **no difference** between sumatriptan 100 mg and almotriptan 12.5 mg for **pain freedom at 2h** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between sumatriptan 100 mg and almotriptan 12.5 mg for **sustained pain freedom over 24h** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

We have **insufficient data** to compare adverse events over 24h in sumatriptan 100 mg versus almotriptan 12.5 mg.

6.6.18 Sumatriptan vs eletriptan

Oral sumatriptan 50 mg versus eletriptan 40 mg for acute treatment of migraine attack of moderate to severe baseline pain intensity in adults			
Bibliography: SR Derry 2012(87) Including 160-104(88), Sandrini 2002(65)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2 h (PO)	721 (2 studies)	Sumatriptan: 18% (64/362) Eletriptan: 24% (86/359) **RR (95% CI): 0.74 (0.55 to 0.98)** NNT (95% CI): 16 (8.2 to 270) **SS in favour of eletriptan** I^2: 48%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear randomization and allocation concealment in one study Consistency: ok Directness: ok Imprecision: ok
Pain relief at 2 h (PO) **(**Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	721 (2 studies)	Sumatriptan: 51% (186/362) Eletriptan: 60% (217/359) **RR (95% CI): 0.85 (0.75 to 0.97)** NNT (95% CI): 11 (6.1 to 54) **SS in favour of eletriptan** I^2: 19%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear randomization and allocation concealment in one study Consistency: ok Directness: ok Imprecision: ok
Pain relief at 1 h (PO) **(**Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	721 (2 studies)	Sumatriptan: 25% (90/362) Eletriptan: 25% (90/359) RR (95% CI): 0.99 (0.77 to 1.3) NS I^2:73%	⊕⊕⊖⊖ **LOW** Study quality: -1; unclear randomization and allocation concealment in one study Consistency: -1 Directness: ok Imprecision: ok
Relief of nausea	374 (2 studies)	Sumatriptan: 71/188 Eletriptan: 93/186 **RR (95% CI): 0.76 (0.6 to 0.95)** NNT: 8.2	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear randomization and allocation concealment in one study Consistency: ok Directness: ok Imprecision: ok

		SS in favour of eletriptan I^2:46%	
Relief of photophobia	528 (2 studies)	Sumatriptan: 107/261 Eletriptan: 132/267 RR (95% CI): 0.83 (0.69 to 1.00) NS I^2: 60%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear randomization and allocation concealment in one study Consistency: ok Directness: ok Imprecision: ok
Relief of phonophobia	513 (2 studies)	Sumatriptan: 120/257 Eletriptan: 139/260 RR (95% CI): 0.87 (0.73 to 1.04) NS I^2: 66%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear randomization and allocation concealment in one study Consistency: ok Directness: ok Imprecision: ok
Relief of functional disability at 2h	590 (2 studies)	Sumatriptan: 51% (153/298 Eletriptan: 62% (180/292 **RR (95% CI): 0.83 (0.72 to 0.96)** NNT (95% CI): 9.7 (5.5 to 43) **SS in favour of eletriptan** I^2: 73%	⊕⊕⊖⊖ **LOW** Study quality: -1; unclear randomization and allocation concealment in one study Consistency: -1 Directness: ok Imprecision: ok

Table 48

Oral sumatriptan 100 mg versus eletriptan 40 mg for acute treatment of migraine attack of moderate to severe baseline pain intensity in adults			
Bibliography: SR Derry 2012(87) Including Goadsby 2000(62), Mathew 2003(113), Sandrini 2002(65)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2h	2263 (3 studies)	Sumatriptan: 24% (271/1130) Eletritpan: 32% (366/1133)	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear randomization and allocation concealment in 2 studies Consistency: ok

		RR (95% CI): 0**.74 (0.65 to 0.85)** NNT (95% CI): 12 (8.3 to 22) **SS in favour of eletriptan** I^2: 0%	Directness: ok Imprecision: ok
Pain relief at 2 h (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	2263 (3 studies)	Sumatriptan: 55% (622/1130) Eletritpan: 62% (706/1133) **RR (95% CI): 0.88 (0.82 to 0.95)** NNT (95% CI): 14 (8.9 to 31) **SS in favour of eletriptan** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear randomization and allocation concealment in 2 studies Consistency: ok Directness: ok Imprecision: ok
Pain free at 1 h	2263 (3 studies)	Sumatriptan: 5% (59/1130) Eletritpan: 7% (75/1133) RR (95% CI): 0.79 (0.57 to 1.1) NS I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear randomization and allocation concealment in 2 studies Consistency: ok Directness: ok Imprecision: ok
Pain relief at 1 h (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	2263 (3 studies)	Sumatriptan: 25% (282/1130) Eletritpan: 32% (368/1133) **RR (95% CI): 0.77 (0.67 to 0.88)** NNT (95% CI): 13 (8.9 to 26) **SS in favour of eletriptan** I^2: 32%	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear randomization and allocation concealment in 2 studies Consistency: ok Directness: ok Imprecision:
Sustained pain-relief over 24 h (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.)	1998 (2 studies)	Sumatriptan: 34% (340/1001) Eletritpan: 43% (430/997) **RR (95% CI): 0.79 (0.70 to 0.88)** NNT (95% CI): 11 (7.5 to 20) **SS in favour of eletriptan** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear randomization and allocation concealment in 2 studies Consistency: ok Directness: ok Imprecision: ok
Relief of nausea	1478 (3 studies)	Sumatriptan: 352/719 Eletritpan: 420/759	⊕⊕⊖⊖ **LOW** Study quality: -1 unclear randomization and allocation concealment in 2 studies

		RR (95% CI): 0.87 (0.79 to 0.96) NNT 16 **SS in favour of eletriptan** I^2: 87%	Consistency: -1 Directness: ok Imprecision: ok
Relief of photophobia	1692 (3 studies)	Sumatriptan: 438/855 Eletritpan: 500/837 **RR (95% CI): 0.85 (0.78 to 0.93)** NNT 12 **SS in favour of eletriptan** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear randomization and allocation concealment in 2 studies Consistency: ok Directness: ok Imprecision: ok
Relief of phonophobia	1361 (3 studies)	Sumatriptan: 352/691 Eletritpan: 405/670 **RR (95% CI): 0.84 (0.76 to 0.92)** NNT 11 **SS in favour of eletriptan** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear randomization and allocation concealment in 2 studies Consistency: ok Directness: ok Imprecision: ok
Relief of functional disability at 2h	2263 (3 studies)	Sumatriptan: 59% (553/936) Eletritpan: 68% (645/944) **RR (95% CI): 0.86 (0.81 to 0.92)** NNT (95% CI): 11 (7.4 to 20) **SS in favour of eletriptan** I^2: 36%	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear randomization and allocation concealment in 2 studies Consistency: ok Directness: ok Imprecision: ok
Use of rescue medication	1998 (2 studies)	Sumatriptan: 27% (261/960) Eletritpan: 21% (203/958) **RR (95% CI): 1.3 (1.1 to 1.5)** NNT (95% CI): 17 (10 to 46) **SS in favour of eletriptan (more use of rescue medication with sumatriptan)**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 unclear randomization and allocation concealment in 2 studies Consistency: ok Directness: ok Imprecision: ok

	I^2: 50%

Table 49

This systematic review by Derry 2012 searched for double-blind RCTs comparing oral sumatriptan to placebo or an active control to treat an acute migraine headache episode in adults.

Four RCTs comparing sumatriptan to eletriptan were found. Two RCT used sumatriptan 50 mg, while three RCTs used sumatriptan 100 mg. The two dosages were analyzed separately.

Authors analysed studies using a single dose of sumatriptan in established pain of at least moderate intensity separately from studies in which medication was taken before pain became well established or in which a second dose of medication was permitted.
All the studies included for this comparison were performed in patients with basal pain of least moderate intensity.

There are some methodological problems that limit our confidence in the estimate of the results: three RCTs had an unclear risk of bias pertaining to randomization and allocation concealment.

Sumatriptan 50 mg vs eletriptan 40 mg

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan 50 mg** resulted in **less pain freedom at 2h** compared to eletriptan 40 mg.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan 50 mg** resulted in **less pain relief at 2h** compared to eletriptan 40 mg.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between sumatriptan 50 mg and eletriptan 40 mg for **pain relief at 1h** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan 50 mg** resulted in **less relief of nausea** compared to eletriptan 40 mg.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between sumatriptan 50 mg and eletriptan 40 mg for **relief of photophobia** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between sumatriptan 50 mg and eletriptan 40 mg for **relief of phonophobia** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan 50 mg** resulted in **less relief of functional disability** compared to eletriptan 40 mg.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

Sumatriptan 100 mg vs eletriptan 40 mg

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan 100 mg** resulted in **less pain freedom at 2h** compared to eletriptan 40 mg.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan 100 mg** resulted in **less pain relief at 2h** compared to eletriptan 40 mg.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between sumatriptan 100 mg and eletriptan 40 mg for **pain freedom at 1h** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan 100 mg** resulted in **less pain relief at 1h** compared to eletriptan 40 mg.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan 100 mg** resulted in **less sustained pain relief over 24h** compared to eletriptan 40 mg.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan 100 mg** resulted in **less relief of nausea** compared to eletriptan 40 mg.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan 100 mg** resulted in **less relief of photophobia** compared to eletriptan 40 mg.
GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan 100 mg** resulted in **less relief of phonophobia** compared to eletriptan 40 mg.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan 100 mg** resulted in **less relief of functional disability at 2h** compared to eletriptan 40 mg.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan 100 mg** resulted in **more use of rescue medication** compared to eletriptan 40 mg.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

6.6.19 Sumatriptan vs rizatriptan

Oral sumatriptan 50 mg versus rizatriptan 10 mg for acute treatment of migraine attack of moderate to severe baseline pain intensity in adults			
Bibliography: SR Derry 2012(87) Including Goldstein 1998(85), Kolodny 2004(96)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2 h	2230 (2 studies)	Sumatriptan: 35% (394/1116) Rizatriptan: 39% (440/1114) RR (95% CI): 0.89 (0.80 to 1.0) NS I^2: 0%	⨁⨁⨁⊖ **MODERATE** Study quality: -1; unclear allocation concealment in two RCTs, unclear randomization in one RCT Consistency: ok Directness: ok Imprecision: ok
Pain relief at 2 h (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	2230 (2 studies)	Sumatriptan: 64% (710/1116) Rizatriptan: 70% (780/1114) **RR (95% CI): 0.91 (0.86 to 0.97)** NNT (95% CI): 16 (9.9 to 43) **SS in favour of rizatriptan** I^2: 72%	⨁⨁⊖⊖ **LOW** Study quality: -1; unclear allocation concealment in two RCTs, unclear randomization in one RCT Consistency: -1 Directness: ok Imprecision: ok

Pain relief at 1 h (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	2230 (2 studies)	Sumatriptan: 37% (409/1116) Rizatriptan: 41% (456/1114) **RR (95% CI): 0.90 (0.81 to 0.99)** **SS in favour of rizatriptan** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in two RCTs, unclear randomization in one RCT Consistency: ok Directness: ok Imprecision: ok
Presence of nausea at 2 h	2230 (2 studies)	RR (95% CI): 1.2 (1.0 to 1.4) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in two RCTs, unclear randomization in one RCT Consistency: nd Directness: ok Imprecision: ok
Presence of photophobia	2230 (2 studies)	RR (95% CI): 1.1 (0.96 to 1.2) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in two RCTs, unclear randomization in one RCT Consistency: nd Directness: ok Imprecision: ok
Presence of phonophobia	2230 (2 studies)	RR (95% CI): 1.1 (0.96 to 1.2) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in two RCTs, unclear randomization in one RCT Consistency: nd Directness: ok Imprecision: ok
Use of rescue medication up to 4h	1714 (2 studies)	Sumatriptan: 20% (167/851) Rizatriptan: 20% (175/863) RR (95% CI): 0.97 (0.80 to 1.2) NS I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in two RCTs, unclear randomization in one RCT Consistency: ok Directness: ok Imprecision: ok
Adverse events within 24h	1177 (2 studies)	Sumatriptan: 48% (276/578) Rizatriptan: 46% (276/599 RR (95% CI): 1.0 (0.92 to 1.2) NS I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in two RCTs, unclear randomization in one RCT Consistency: ok Directness: ok Imprecision: ok

Table 50

Oral sumatriptan 100 mg versus rizatriptan 10 mg for acute treatment of migraine attack of moderate to severe baseline pain intensity in adults
Bibliography: SR Derry 2012(87) Including Tfelt-Hansen 1998(83); Visser 1996(119)

Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Pain free at 2h	936 (2 studies)	Sumatriptan: 31% (143/460) Rizatriptan: 37% (178/476) **RR (95% CI): 0.82 (0.69 to 0.98)** NNT (95% CI): 16 (8.1 to 41) **SS in favour of rizatriptan** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in two RCTs, unclear randomization in one RCT Consistency: ok Directness: ok Imprecision: ok
Pain relief at 1 h (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	936 (2 studies)	Sumatriptan: 26% (120/460) Rizatriptan: 34% (163/476) **RR (95% CI): 0.76 (0.62 to 0.92)** NNT (95% CI): 12 (7.1 to 43) **SS in favour of rizatriptan** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in two RCTs, unclear randomization in one RCT Consistency: ok Directness: ok Imprecision: ok
Adverse events within 24 h	856 (2 studies)	Sumatriptan: 52% (217/421) Rizatriptan: 47% (203/435) RR (95% CI): 1.1 (0.96 to 1.3) NS I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment in two RCTs, unclear randomization in one RCT Consistency: ok Directness: ok Imprecision: ok

Table 51

This systematic review by Derry 2012 searched for double-blind RCTs comparing oral sumatriptan to placebo or an active control to treat an acute migraine headache episode in adults.

Four RCTs comparing sumatriptan to rizatriptan were found. Two RCT used sumatriptan 50 mg, and two RCTs used sumatriptan 100 mg. The two dosages were analyzed separately.

Authors analysed studies using a single dose of sumatriptan in established pain of at least moderate intensity separately from studies in which medication was taken before pain became well established or in which a second dose of medication was permitted.
All the studies included for this comparison were performed in patients with basal pain of least moderate intensity.

There are some methodological problems that limit our confidence in the estimate of the results: all RCTs had an unclear risk of bias pertaining allocation concealment and two had an unclear risk of bias pertaining to randomization.

Sumatriptan 50 mg vs rizatriptan 10 mg

There was **no difference** between sumatriptan 50 mg and rizatriptan 10 mg for **pain freedom at 2h** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan 50 mg** resulted in **less pain relief at 2h** compared to rizatriptan 10 mg.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan 50 mg** resulted in **less pain relief at 1h** compared to rizatriptan 10 mg.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between sumatriptan 50 mg and rizatriptan 10 mg for **use of rescue medication up to 4h** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between sumatriptan 50 mg and rizatriptan 10 mg for **the presence of nausea at 2h** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between sumatriptan 50 mg and rizatriptan 10 mg for **the presence of photophobia** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between sumatriptan 50 mg and rizatriptan 10 mg for **the presence of phonophobia** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between sumatriptan 50 mg and rizatriptan 10 mg for **adverse events within 24h** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

Sumatriptan 100 mg vs rizatriptan 10 mg

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan 100 mg** resulted in **less pain freedom at 2h** compared to rizatriptan 10 mg.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan 100 mg** resulted in **less pain relief at 1h** compared to rizatriptan 10 mg.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between sumatriptan 100 mg and rizatriptan 10 mg for **adverse events within 24h** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

6.6.20 Zolmitriptan vs frovatriptan

Zolmitriptan 2.5 mg versus frovatriptan 2.5 mg for acute treatment of migraine attack in adults			
Bibliography: SR Bird 2014(158) Including Tullo 2010(181)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2h	493 (1 study)	Zolmitriptan: 94/303 Frovatriptan: 80/308 NS	⊕⊕⊖⊖ **LOW** Study quality: -2; single study with unclear randomization, allocation concealment, blinding and unclear risk of incomplete outcome data Consistency: na Directness: ok Imprecision: na
Pain relief at 2h (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	493 (1 study)	Zolmitriptan: 142/245 Frovatriptan: 141/247 NS	⊕⊕⊖⊖ **LOW** Study quality: -2; single study with unclear randomization, allocation concealment, blinding and unclear risk of incomplete outcome data Consistency: na Directness: ok Imprecision: na
Adverse events	121 (1 study)	Zolmitriptan: 5/121 Frovatriptan: 2/121 No statistical analysis reported	*Insufficient data*
Angina-like symptoms	121 (1 study)	Zolmitriptan: 4/121 Frovatriptan: 0/121	*Insufficient data*

(tachycardia, thoracic constriction, or pain)		No statistical analysis reported

Table 52

This systematic review by Bird 2014 searched for double-blind RCTs comparing zolmitriptan to placebo or an active control to treat an acute migraine headache episode in adults.

One RCT comparing zolmitriptan versus frovatriptan was found.

The migraine episodes in this study were treated 'as soon as possible', and had different baseline pain intensities.

There are some methodological problems that limit our confidence in the estimate of the results: it is a single small study with unclear risk of bias pertaining to randomization, allocation concealment, blinding and incomplete outcome data.

There was **no difference** between zolmitriptan and frovatriptan for **pain freedom at 2h** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between zolmitriptan and frovatriptan for **pain relief at 2h** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

We have **insufficient data** to compare the risk of adverse events in zolmitriptan versus frovatriptan.

We have **insufficient data** to compare the risk of angina-like symptoms in zolmitriptan versus frovatriptan.

6.6.21 Zolmitriptan vs sumatriptan

Zolmitriptan 2.5 mg versus sumatriptan 50 mg for acute treatment of migraine attack of moderate or severe baseline pain intensity in adults			
Bibliography: SR Bird 2014(158) Including Gruffyd-Jones 2001(182), Gallagher 2000(183)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2h	1008 (1 study)	Zolmitriptan: 160/500 Sumatriptan: 187/508 No statistical analysis	Insufficient data

Pain relief at 2h (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	1609 (2 studies)	Zolmitriptan: 66% (521/795) Sumatriptan: 68% (554/814) RR (95% CI): 0.96 (0.90 to 1.03) NS I^2: 73%	⊕⊖⊖⊖ **VERY LOW** Study quality: -2; unclear allocation concealment and incomplete outcome data in two RCTs, unclear randomization and blinding in one RCT Consistency: -1 Directness: ok Imprecision: ok
Sustained pain-free over 24h (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	1008 (1 study)	Zolmitriptan: 126/500 Sumatriptan: 138/508 OR 0.90 (0.73 to 1.12) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1; single study with unclear allocation concealment and incomplete outcome data Consistency: na Directness: ok Imprecision: ok
Sustained pain relief over 24 h (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.)	3474 (1 study)	Zolmitriptan: 705/1680 Sumatriptan: 780/1794 OR 0.94 (0.78 to 1.14) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1; single study with unclear allocation concealment and incomplete outcome data Consistency: na Directness: ok Imprecision: ok
Use of rescue medication	2964 (1 study)	Zolmitriptan: 631/1271 Sumatriptan: 620/1693 No statistical analysis	Insufficient data
Adverse events	1777 (2 studies)	Zolmitriptan: 32% (283/878) Sumatriptan: 28% (251/893) RR (95% CI): 1.1 (0.99 to 1.3) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1; single study with unclear allocation concealment and incomplete outcome data Consistency: na Directness: ok Imprecision: ok

Table 53

Zolmitriptan 5 mg versus sumatriptan 50 mg for acute treatment of migraine attack of moderate or severe baseline pain intensity in adults			
Bibliography: SR Bird 2014(158) Including Gruffyd-Jones 2001(182), Gallagher 2000(183)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**

Pain free at 2h	1022 (1 study)	Zolmitriptan: 190/514 Sumatriptan: 187/508 No statistical analysis	Insufficient data
Pain relief at 2h (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	1633 (1 study)	Zolmitriptan: 67% (545/819) Sumatriptan: 68% (554/814) RR (95% CI): 0.98 (0.92 to 1.1) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1; single study with unclear allocation concealment and incomplete outcome data Consistency: na Directness: ok Imprecision: ok
Sustained pain-free over 24h (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	1022 (1 study)	Zolmitriptan: 125/514 Sumatriptan: 138/508 OR 1.09 (0.88 to 1.36) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1; single study with unclear allocation concealment and incomplete outcome data Consistency: na Directness: ok Imprecision: ok
Sustained pain relief over 24 h (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.)	3597 (1 study)	Zolmitriptan: 803/1803 Sumatriptan: 780/1794 OR 1.07 (0.89 to 1.29) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1; single study with unclear allocation concealment and incomplete outcome data Consistency: na Directness: ok Imprecision: ok
Use of rescue medication	3437 (1 study)	Zolmitriptan: 608/2744 Sumatriptan: 620/2693 No statistical analysis	Insufficient data
Adverse events	1789 (2 studies)	Zolmitriptan: 31% (280/896) Sumatriptan: 28% (251/893) RR (95% CI): 1.1 (0.96 to 1.3) NS	⊕⊕⊖⊖ **LOW** Study quality: -2; unclear allocation concealment and incomplete outcome data in two RCTs, unclear randomization and blinding in one RCT Consistency: Directness: ok Imprecision: ok

Table 54

Zolmitriptan 5 mg versus sumatriptan 100 mg for acute treatment of migraine attack of moderate or severe baseline pain intensity in adults			
Bibliography: SR Bird 2014(158) Including Geraud 2000(111)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**

Pain free at 2h (PO)	1002 (1 study)	Zolmitriptan: 144/491 Sumatriptan: 150/499 P<0.05 **SS in favour of sumatriptan 100 mg**	⊕⊕⊕⊖ **MODERATE** Study quality: -1; single study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: ok
Pain relief at 2h (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	1002 (1 study)	Zolmitriptan: 288/491 Sumatriptan: 304/498 P<0.05 **SS in favour of sumatriptan 100 mg**	⊕⊕⊕⊖ **MODERATE** Study quality: -1; single study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: ok
Sustained pain relief over 24 h (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.)	1002 (1 study)	Zolmitriptan: 180/498 Sumatriptan: 195/504 No statistical analysis	Insufficient data
Use of rescue medication	1002 (1 study)	Zolmitriptan: 189/498 Sumatriptan: 192/504 No statistical analysis	Insufficient data
Adverse events	983 (1 study)	Zolmitriptan: 287/491 Sumatriptan: 279/492 No statistical analysis	Insufficient data

Table 55

This systematic review by Bird 2014 searched for double-blind RCTs comparing zolmitriptan to placebo or an active control to treat an acute migraine headache episode in adults.

Three RCTs comparing zolmitriptan versus sumatriptan were found. Different dosages (zolmitriptan 2.5 mg and 5 mg; sumatriptan 50 mg and 100 mg) were analyzed separately.

Authors analysed studies using a single dose of zolmitriptan in established pain of at least moderate intensity separately from studies in which the medication was taken before pain became well established, or in which a second dose of medication was required.

There are some methodological problems that limit our confidence in the estimate of the results: all studies had an unclear risk of bias pertaining to allocation concealment, two studies had unclear risk of bias pertaining to randomization, one RCT had unclear risk of bias pertaining to blinding, and two RCTs had an unclear risk of bias pertaining to incomplete outcome data.

Zolmitriptan 2.5 mg versus sumatriptan 50 mg

We have **insufficient data** to compare pain freedom at 2h in zolmitriptan 2.5 mg versus sumatriptan 50 mg.

There was **no difference** between zolmitriptan 2.5 mg and sumatriptan 50 mg for **pain relief at 2h** in **adults with migraine of moderate or severe baseline pain intensity**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between zolmitriptan 2.5 mg and sumatriptan 50 mg for **sustained pain freedom over 24h** in **adults with migraine of moderate or severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between zolmitriptan 2.5 mg and sumatriptan 50 mg for **sustained pain relief over 24h** in **adults with migraine of moderate or severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

We have **insufficient data** to compare use of rescue medication in zolmitriptan 2.5 mg versus sumatriptan 50 mg **of moderate or severe baseline pain intensity**.

There was **no difference** between zolmitriptan 2.5 mg and sumatriptan 50 mg for **adverse events** in **adults with migraine of moderate or severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

Zolmitriptan 5 mg versus sumatriptan 50 mg

We have **insufficient data** to compare pain freedom at 2h in zolmitriptan 5 mg versus sumatriptan 50 mg.

There was **no difference** between zolmitriptan 5 mg and sumatriptan 50 mg for **pain relief at 2h** in **adults with migraine of moderate or severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between zolmitriptan 5 mg and sumatriptan 50 mg for **sustained pain freedom over 24h** in **adults with migraine of moderate or severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between zolmitriptan 5 mg and sumatriptan 50 mg for **sustained pain relief over 24h** in **adults with migraine of moderate or severe baseline pain intensity**.

GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

We have **insufficient data** to compare use of rescue medication in zolmitriptan 5 mg versus sumatriptan 50 mg.

There was **no difference** between zolmitriptan 5 mg and sumatriptan 50 mg for **adverse events** in **adults with migraine of moderate or severe baseline pain intensity**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

Zolmitriptan 5 mg versus sumatriptan 100 mg

In **adults with migraine of moderate or severe baseline pain intensity**, **zolmitriptan 5 mg** resulted in **less pain freedom at 2h** compared to sumatriptan 100 mg.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate or severe baseline pain intensity**, **zolmitriptan 5 mg** resulted in **less pain relief at 2h** compared to sumatriptan 100 mg.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

We have **insufficient data** to compare sustained pain relief over 24h in zolmitriptan 5 mg versus sumatriptan 100 mg.

We have **insufficient data** to compare use of rescue medication in zolmitriptan 5 mg versus sumatriptan 100 mg.

We have **insufficient data** to compare adverse events in zolmitriptan 5 mg versus sumatriptan 100 mg.

6.7 Combinations with triptans

6.7.1 Sumatriptan + naproxen vs placebo

Sumatriptan + naproxen versus placebo for the acute treatment of a migraine attack of moderate to severe intensity in adults			
Bibliography: SR Law 2016(184) Including Brandes 2007 (study 1 and 2)(38), TRX109011/13(185), Smith 2005(39)			
Outcomes	**N° of participants (studies)**	**Results**	**Quality of the evidence (GRADE)**

	Follow up		
Pain free at 2 h	2596 (4 studies)	Sumatriptan + naproxen: 28% (362/1293) Placebo: 7.7% (100/1303) **RR (95% CI): 3.7 (3.0 to 4.5)** NNT (95% CI): 4.9 (4.3 to 5.7) **SS in favour of sumatriptan plus naproxen** I^2: 38%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization, blinding Consistency: ok Directness: ok Imprecision: ok
Pain relief at 2 h (Pain reduced from moderate or severe to none or mild without the use of rescue medication.)	2596 (4 studies)	Sumatriptan + naproxen: 58% (755/1293) Placebo: 27% (352/1303) **RR (95% CI): 2..2 (2.0 to 2.4)** NNT (95% CI): 3.2 (2.9 to 3.6) **SS in favour of sumatriptan plus naproxen** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization, blinding Consistency: ok Directness: ok Imprecision: ok
Sustained pain-free over 24 h (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	2596 (4 studies)	Sumatriptan + naproxen: 20% (262/1293) Placebo: 5.9% (77/1303) **RR (95% CI): 3.4 (2.7 to 4.4)** NNT (95% CI): 7.0 (5.9 to 8.7) **SS in favour of sumatriptan plus naproxen** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization, blinding Consistency: ok Directness: ok Imprecision: ok
Sustained pain relief over 24 h (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.)	2596 (4 studies)	Sumatriptan + naproxen: 43% (554/1293) Placebo: 16% (214/1303) **RR (95% CI): 2.6 (2.3 to 3.0)** NNT (95% CI): 3.8 (3.4 to 4.3) **SS in favour of sumatriptan plus naproxen** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization, blinding Consistency: ok Directness: ok Imprecision: ok
Relief of functional disability at 2 h	1984 (3 studies)	Sumatriptan + naproxen: 245/994 Placebo: 72/990 **RR (95% CI): 3.36 (2.63 to 4.29)**	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization, blinding Consistency: ok Directness: ok Imprecision: ok

		SS in favour of sumatriptan + naproxen I^2: 0%	
Adverse events over 24 h	2793 (4 studies)	Sumatriptan + naproxen: 21% (291/1394) Placebo: 11% (148/1399) **RR (95% CI): 2.0 (1.6 to 2.4)** NNH (95% CI): 9.7 (7.7 to 13) **SS in favour of placebo** I^2: 61%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; majority of studies with unclear allocation concealment, randomization, blinding Consistency: ok Directness: ok Imprecision: ok
Use of rescue medication	2169 (4 studies)	Sumatriptan + naproxen: 304/1083 Placebo: 643/1086 **RR (95% CI): 0.47 (0.42 to 0.53)** **SS in favour of sumatriptan + naproxen (less with sumatriptan + naproxen)** I^2: 81%	⊕⊕⊖⊖ **LOW** Study quality: -1; majority of studies with unclear allocation concealment, randomization, blinding Consistency: -1 Directness: ok Imprecision: ok

Table 56

Sumatriptan + naproxen versus placebo for the acute treatment of a migraine attack of mild intensity in adults			
Bibliography: SR Law 2016(184) Including Lipton 2009 (study 1 and 2)(186), Mannix 2009 (study 1 and 2)(187), Mathew 2009 (study 1 and 2)(188), Silberstein 2008 (study 1 and 2)(189)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2 h	3395 attacks (8 studies)	Sumatriptan + naproxen: 50% (1008/2025) Placebo: 18% (244/1370) **RR (95% CI): 2.8 (2.4 to 3.1)** NNT (95% CI): 3.1 (2.9 to 3.5) **SS in favour of sumatriptan + naproxen** I^2: 37%	⊕⊕⊖⊖ **LOW** Study quality: -1; majority of studies with unclear allocation concealment, randomization, blinding Consistency: ok Directness: -1 (+/- 650 participants for menstrual migraine) Imprecision: ok

Sustained pain-free over 24 h (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	3396 attacks (8 studies)	Sumatriptan + naproxen: 37% (741/2026) Placebo: 12% (166/1370) **RR (95% CI): 3.0 (2.6 to 3.6)** NNT (95% CI): 4.1 (3.7 to 4.6) **SS in favour of sumatriptan + naproxen** I^2: 41%	⊕⊕⊖⊖ **LOW** Study quality: -1; majority of studies with unclear allocation concealment, randomization, blinding Consistency: ok Directness: -1 (+/- 650 participants for menstrual migraine) Imprecision: ok
Relief of functional disability at 2 h	981 (2 studies)	Sumatriptan + naproxen: 208/496 Placebo: 71/485 **RR (95% CI): 2.91 (2.29 to 3.72)** **SS in favour of sumatriptan + naproxen** I^2: 94%	⊕⊕⊖⊖ **LOW** Study quality: -1; majority of studies with unclear allocation concealment, randomization, blinding Consistency: -1 Directness: ok Imprecision: ok
Relief of nausea at 2h	1705 (8 studies)	Sumatriptan + naproxen: 326/900 Placebo: 83/805 **RR (95% CI): 3.47 (2.79 to 4.32)** **SS in favour of sumatriptan + naproxen** I^2: 87%	⊕⊖⊖⊖ **VERY LOW** Study quality: -1; majority of studies with unclear allocation concealment, randomization, blinding Consistency: -1 Directness: -1 (included patients with moderate to severe basal pain intensity) Imprecision: ok
Relief of photophobia at 2h	3127 (8 studies)	Sumatriptan + naproxen: 949/1792 Placebo: 249/1335 **RR (95% CI): 2.77 (2.44 to 3.13)** **SS in favour of sumatriptan + naproxen** I^2: 33%	⊕⊕⊖⊖ **LOW** Study quality: -1; majority of studies with unclear allocation concealment, randomization, blinding Consistency: ok Directness: -1 (included patients with moderate to severe basal pain intensity) Imprecision: ok
Relief of phonophobia at 2h	3127 (8 studies)	Sumatriptan + naproxen: 878/1614 Placebo: 246/1242	⊕⊕⊖⊖ **LOW** Study quality: -1; majority of studies with unclear allocation

		RR (95% CI): 2.63 (2.33 to 2.97) **SS in favour of sumatriptan + naproxen** I^2: 51%	concealment, randomization, blinding Consistency: ok Directness: -1 (included patients with moderate to severe basal pain intensity) Imprecision: ok
Adverse events over 24 h	2823 (8 studies)	Sumatriptan + naproxen: 14% (241/1749) Placebo: 8.2% (88/1074) **RR (95% CI): 1.5 (1.2 to 1.9)** NNH (95% CI): 18 (13 to 30) **SS in favour of placebo** I^2: 0%	⨁⨁⊖⊖ **LOW** Study quality: -1; majority of studies with unclear allocation concealment, randomization, blinding Consistency: ok Directness: -1 (+/- 650 participants for menstrual migraine) Imprecision: ok
Use of rescue medication	3396 (8 studies)	Sumatriptan + naproxen: 375/2026 Placebo: 698/1370 **RR (95% CI): 0.42 (0.38 to 0.47)** **SS in favour of sumatriptan + naproxen (less with sumatriptan + naproxen)** I^2: 73%	⨁⊖⊖⊖ **VERY LOW** Study quality: -1; majority of studies with unclear allocation concealment, randomization, blinding Consistency: -1 Directness: -1 (+/- 650 participants for menstrual migraine) Imprecision: ok

Table 57

This systematic review by Law 2016 searched for double-blind RCTs comparing oral sumatriptan plus naproxen to placebo or an active control to treat a migraine headache episode in adults.

12 RCTs were found that compared sumatriptan + naproxen to placebo.
Authors analysed studies using a single dose of sumatriptan plus naproxen in established pain of at least moderate intensity **separately f**rom studies in which medication was taken before pain became well established, or in which a second dose of medication. Four studies were performed in moderate to severe migraine attacks; 8 studies were performed in mild migraine attacks. Law 2016 pooled the results of these two groups separately.

Most studies gave sumatriptan 85 mg plus naproxen 500 mg formulated as a combination tablet, while 2 studies gave sumatriptan 50 mg plus naproxen 500 mg as separate tablets taken together.

There are some methodological problems that limit our confidence in the estimate of the results: the majority of studies had an unclear risk of bias pertaining to allocation concealment, randomization and blinding. Some outcomes were downgraded for directness as 2 studies only included participants with menstrual migraine and for the outcomes concerning relief of associated symptom, data for both patients having mild intensity and moderate to severe migraine attacks were pooled.

migraine attack of moderate to severe intensity

In **adults with a migraine attack of moderate to severe intensity**, **sumatriptan + naproxen** resulted in **more pain freedom at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate to severe intensity**, **sumatriptan + naproxen** resulted in **more pain relief at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate to severe intensity**, **sumatriptan + naproxen** resulted in **more sustained pain freedom at 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate to severe intensity**, **sumatriptan + naproxen** resulted in **more sustained pain relief at 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate to severe intensity**, **sumatriptan + naproxen** resulted in **more relief of functional disability at 2h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate to severe intensity**, **sumatriptan + naproxen** resulted in **more adverse events over 24h** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with a migraine attack of moderate to severe intensity**, **sumatriptan + naproxen** resulted in **less use of rescue medication** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

migraine attack of mild intensity

In **adults with a migraine attack of mild intensity**, **sumatriptan + naproxen** resulted in **more pain freedom at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with a migraine attack of mild intensity**, **sumatriptan + naproxen** resulted in **more sustained pain freedom at 24h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with a migraine attack of mild intensity**, **sumatriptan + naproxen** resulted in **more relief of functional disability at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with a migraine attack of mild intensity**, **sumatriptan + naproxen** resulted in **more relief of nausea at 2h** compared to placebo.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

In **adults with a migraine attack of mild intensity**, **sumatriptan + naproxen** resulted in **more relief of photophobia at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with a migraine attack of mild intensity**, **sumatriptan + naproxen** resulted in **more relief of phonophobia at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with a migraine attack of mild intensity**, **sumatriptan + naproxen** resulted in **more adverse events over 24h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with a migraine attack of mild intensity**, **sumatriptan + naproxen** resulted in **less use of rescue medication** compared to placebo.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

6.7.2 Sumatriptan + naproxen vs sumatriptan

Sumatriptan + naproxen versus sumatriptan for acute treatment of migraine attack of moderate to severe baseline pain intensity in adults			
Bibliography: SR Law 2016(184) Including Brandes 2007 (study 1 and 2)(38), Smith 2005(39)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free at 2 h	1925 (3 studies)	Sumatriptan plus naproxen: 32% (317/976) Sumatriptan: 23% (217/949) **RR (95% CI): 1.4 (1.2 to 1.7)** NNT (95% CI): 10 (7.4 to 18) **SS in favour of sumatriptan + naproxen** I^2: 0%	⨁⨁⨁⊖ **MODERATE** Study quality: -1; unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok
Pain relief at 2 h (Pain reduced from moderate or severe to none or mild without the use of rescue medication.)	1925 (3 studies)	Sumatriptan + naproxen: 62% (607/976) Sumatriptan: 52% (493/949) **RR (95% CI): 1.2 (1.1 to 1.3)** NNT (95% CI): 9.8 (6.8 to 17) **SS in favour of sumatriptan + naproxen** I^2: 10%	⨁⨁⨁⊖ **MODERATE** Study quality: -1; unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok
Sustained pain-free over 24 h (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	1925 (3 studies)	Sumatriptan + naproxen: 24% (236/976) Sumatriptan: 14% (135/949) **RR (95% CI): 1.7 (1.4 to 2.1)** NNT (95% CI): 10 (7.4 to 15) **SS in favour of sumatriptan + naproxen** I^2: 19%	⨁⨁⨁⊖ **MODERATE** Study quality: -1; unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok
Sustained pain relief over 24 h (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a	1925 (3 studies)	Sumatriptan + naproxen: 46% (447/976) Sumatriptan: 33% (314/949) **RR (95% CI): 1.39 (1.24 to 1.55)** **NNT (95% CI): 7.9 (5.9 to 12)**	⨁⨁⨁⊖ **MODERATE** Study quality: -1; unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok

second dose of study medication.)		**SS in favour of sumatriptan + naproxen** I^2: 0%	
Relief of nausea at 2 h	718 (2 studies)	Sumatriptan + naproxen: 148/377 Sumatriptan: 89/381 **RR (95% CI): 1.51 (1.21 to 1.87)** **SS in favour of sumatriptan + naproxen** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok
Relief of photophobia at 2 h	1186 (2 studies)	Sumatriptan + naproxen: 253/588 Sumatriptan: 214/598 **RR (95% CI): 1.20 (1.04 to 1.39)** **SS in favour of sumatriptan + naproxen** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok
Relief of phonophobia at 2 h	1186 (2 studies)	Sumatriptan + naproxen: 275/574 Sumatriptan: 217/572 **RR (95% CI): 1.26 (1.10 to 1.45)** **SS in favour of sumatriptan + naproxen** I^2: 7%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok
Relief of functional disability at 2 h	1353 (2 studies)	Sumatriptan + naproxen: 220/685 Sumatriptan: 152/669 **RR (95% CI): 1.41 (1.18 to 1.69)** **SS in favour of sumatriptan + naproxen** I^2: 24%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok
Adverse events over 24 h	1952 (3 studies)	Sumatriptan + naproxen: 26% (255/988)	⊕⊕⊕⊖ **MODERATE**

		Sumatriptan: 26% (249/964) RR (95% CI): 1.0 (0.9 to 1.2) NS I^2: 0%	Study quality: -1; unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok
Use of rescue medication	1952 (3 studies)	Sumatriptan + naproxen: 252/976 Sumatriptan: 367/949 **RR (95% CI): 0.66 (0.58 to 0.76)** **SS in favour of sumatriptan + naproxen (less with sumatriptan + naproxen)** I^2: 0%	⨁⨁⨁⊖ **MODERATE** Study quality: -1; unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok

Table 58

This systematic review by Law 2016 searched for double-blind RCTs comparing oral sumatriptan plus naproxen to placebo or an active control to treat a migraine headache episode in adults.

3 RCTs were found that compared sumatriptan + naproxen to sumatriptan.
Authors analysed studies using a single dose of sumatriptan plus naproxen in established pain of at least moderate intensity separately from studies in which medication was taken before pain became well established, or in which a second dose of medication. All studies were performed in migraine attacks of moderate to severe pain intensity.
Two studies gave sumatriptan 85 mg plus naproxen 500 mg formulated as a combination tablet, while 1 study gave sumatriptan 50 mg plus naproxen 500 mg as separate tablets taken together.

There are some methodological problems that limit our confidence in the estimate of the results: all studies had an unclear risk of bias pertaining to allocation concealment, 3 to randomization and 2 to blinding.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan + naproxen** resulted in **more pain freedom at 2h** compared to sumatriptan.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan + naproxen** resulted in **more pain relief at 2h** compared to sumatriptan.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan + naproxen** resulted in **more sustained pain freedom over 24h** compared to sumatriptan.
GRADE: MODERATE quality of evidence

Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan + naproxen** resulted in **more sustained pain relief over 24h** compared to sumatriptan.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan + naproxen** resulted in **more relief of nausea at 2h** compared to sumatriptan.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan + naproxen** resulted in **more relief of photophobia at 2h** compared to sumatriptan.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan + naproxen** resulted in **more relief of phonophobia at 2h** compared to sumatriptan.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan + naproxen** resulted in **more relief of functional disability at 2h** compared to sumatriptan.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between sumatriptan + naproxen and sumatriptan for **adverse events** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan + naproxen** resulted in **less use of rescue medication** compared to sumatriptan.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

6.7.3 Sumatriptan + naproxen vs naproxen

Sumatriptan + naproxen versus naproxen for acute treatment of migraine attack of moderate to severe baseline pain intensity in adults
Bibliography: SR Law 2016(184)

Including Brandes 2007 (study 1 and 2)(38), Smith 2005(39)

Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Pain free at 2 h	1944 (3 studies)	Sumatriptan + naproxen: 32% (317/976) Naproxen: 16% (155/968) **RR (95% CI): 2.0 (1.7 to 2.4)** NNT (95% CI): 6.1 (5.0 to 7.9) **SS in favour of sumatriptan + naproxen** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok
Pain relief at 2 h (Pain reduced from moderate or severe to none or mild without the use of rescue medication.)	1944 (3 studies)	Sumatriptan + naproxen: 62% (607/976) Naproxen: 44% (426/968) **RR (95% CI): 1.4 (1.2 to 1.5)** NNT (95% CI): 5.5 (4.4 to 7.2) **SS in favour of sumatriptan + naproxen** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok
Sustained pain-free over 24 h (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	1944 (3 studies)	Sumatriptan + naproxen: 24% (236/976) Naproxen: 11% (104/968) **RR (95% CI): 2.3 (1.8 to 2.8)** NNT (95% CI): 7.4 (6.0 to 9.9) **SS in favour of sumatriptan + naproxen** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok
Sustained pain relief over 24 h (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.)	1944 (3 studies)	Sumatriptan + naproxen: 46% (447/976) Naproxen: 28% (271/968) **RR (95% CI): 1.6 (1.5 to 1.9)** NNT (95% CI): 5.6 (4.5 to 7.4) **SS in favour of sumatriptan + naproxen** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok
Relief of nausea at 2 h	726 (2 studies)	Sumatriptan + naproxen: 148/377	⊕⊕⊕⊖ **MODERATE**

		Naproxen: 126/349 RR (95% CI): 1.09 (0.90 to 1.32) NS I^2: 0%	Study quality: -1; unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok
Relief of photophobia at 2 h	1176 (2 studies)	Sumatriptan + naproxen:253/588 Naproxen: 182/588 **RR (95% CI): 1.39 (1.19 , 1.62)** **SS in favour of sumatriptan + naproxen** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok
Relief of phonophobia at 2 h	1135 (2 studies)	Sumatriptan + naproxen: 275/574 Naproxen: 181/561 **RR (95% CI): 1.48 (1.28 to 1.72)** **SS in favour of sumatriptan + naproxen** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok
Relief of functional disability at 2 h	1352 (2 studies)	Sumatriptan + naproxen: 220/685 Naproxen: 131/667 **RR (95% CI): 1.63 (1.35 to 1.97)** **SS in favour of sumatriptan + naproxen** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok
Adverse events over 24 h	1990 (3 studies)	Sumatriptan + naproxen: 255/988 Naproxen: 143/9982 **RR (95% CI): 1.77 (1.47 to 2.13)** **SS in favour of naproxen** I^2: 39 %	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok

Use of rescue medication	1944 (3 studies)	Sumatriptan + naproxen: 252/976 Naproxen: 407/968 **RR (95% CI): 0.61 (0.54 to 0.70)** **SS in favour of sumatriptan + naproxen (less with sumatriptan + naproxen)** I^2: 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear allocation concealment, randomization and blinding Consistency: ok Directness: ok Imprecision: ok

Table 59

This systematic review by Law 2016 searched for double-blind RCTs comparing oral sumatriptan plus naproxen to placebo or an active control to treat a migraine headache episode in adults.

3 RCTs were found that compared sumatriptan + naproxen to naproxen.
Authors analysed studies using a single dose of sumatriptan plus naproxen in established pain of at least moderate intensity separately from studies in which medication was taken before pain became well established, or in which a second dose of medication. All studies were performed in migraine attacks of moderate to severe pain intensity.
Two studies gave sumatriptan 85 mg plus naproxen 500 mg formulated as a combination tablet, while 1 study gave sumatriptan 50 mg plus naproxen 500 mg as separate tablets taken together.

There are some methodological problems that limit our confidence in the estimate of the results: all studies had an unclear risk of bias pertaining to allocation concealment, 3 to randomization and 2 to blinding.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan + naproxen** resulted in **more pain freedom at 2h** compared to naproxen.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan + naproxen** resulted in **more pain relief at 2h** compared to naproxen.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan + naproxen** resulted in **more sustained pain freedom over 24h** compared to naproxen.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan + naproxen** resulted in **more sustained pain relief over 24h** compared to naproxen.

GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between sumatriptan + naproxen and naproxen for **relief of nausea at 2h** in **adults with migraine of moderate to severe baseline pain intensity**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan + naproxen** resulted in **more relief of photophobia at 2h** compared to naproxen.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan + naproxen** resulted in **more relief of phonophobia at 2h** compared to naproxen.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan + naproxen** resulted in **more relief of functional disability at 2h** compared to naproxen.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan + naproxen** resulted in **more adverse events over 24h** compared to naproxen.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine of moderate to severe baseline pain intensity**, **sumatriptan + naproxen** resulted in **less use of rescue medication** compared to naproxen.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

6.7.4 Naratriptan + naproxen vs naratriptan

We found a systematic review (Ashcroft 2004(73)) that searched for RCTs that of naratriptan taken for acute treatment of migraine in adults.

It found one RCT that compared naratriptan 2.5 mg against naratriptan 2.5 mg plus naproxen 500 mg in 50 patients. This trial does not meet our inclusion criteria and is not reported in the present document.

6.8 Gepants

6.8.1 Rimegepant vs placebo

Rimegepant versus placebo for acute treatment of migraine in adults			
Bibliography: SR Gao(190) Including Marcus 2014(191), Croop 2019(192), Lipton 2019(193), Lipton 2018(194)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain free (2h)	3827 (4 studies)	Rimegepant: 20.6% Placebo: 12.5% **RR (95% CI): 1.70 (1.39 to 2.08)** **SS in favour of rimegepant** I^2: 43%	⨁⨁⨀⨀ **LOW** Study quality: -2; high risk of bias pertaining to randomization, selective outcome reporting and missing outcome data Consistency: ok Directness: ok Imprecision: ok
Pain relief (2h)	3827 (4 studies)	Rimegepant: 58.6% Placebo: 44.6% **RR (95% CI): 1.34 (1.25 to 1.44)** **SS in favour of rimegepant** I^2: 17.1 %	⨁⨁⨀⨀ **LOW** Study quality: -2; high risk of bias pertaining to randomization, selective outcome reporting and missing outcome data Consistency: ok Directness: ok Imprecision: ok
Freedom from most bothersome symptom at 2 h	3827 (4 studies)	Rimegepant: 36% Placebo: 25.1% **RR (95% CI): 1.44 (1.23 to 1.68)** **SS in favour of rimegepant** I^2: 54.5%	⨁⨁⨀⨀ **LOW** Study quality: -2; high risk of bias pertaining to randomization, selective outcome reporting and missing outcome data Consistency: ok Directness: ok Imprecision: ok
Freedom from nausea at 2 h	3827 (4 studies)	Rimegepant: 50.3% Placebo: 44.7% **RR (95% CI): 1.16 (1.07 to 1.26)**	⨁⨁⨀⨀ **LOW** Study quality: -2; high risk of bias pertaining to randomization, selective outcome reporting and missing outcome data Consistency: ok Directness: ok

		SS in favour of rimegepant I^2: 0%	Imprecision: ok
Freedom from photophobia at 2 h	3827 (4 studies)	Rimegepant: 35.5% Placebo: 23.9% **RR (95% CI): 1.49 (1.33 to 1.68)** **SS in favour of rimegepant** I^2: 14.3%	⊕⊕⊖⊖ **LOW** Study quality: -2; high risk of bias pertaining to randomization, selective outcome reporting and missing outcome data Consistency: ok Directness: ok Imprecision: ok
Freedom from phonophobia at 2 h	3827 (4 studies)	Rimegepant: 40.1% Placebo: 29.1% **RR (95% CI): 1.41 (1.23 to 1.62)** **SS in favour of rimegepant** I^2: 39.1%	⊕⊕⊖⊖ **LOW** Study quality: -2; high risk of bias pertaining to randomization, selective outcome reporting and missing outcome data Consistency: ok Directness: ok Imprecision: ok
Sustained pain free (24 h)	3827 (4 studies)	Rimegepant: 22.1% Placebo: 12.3% **RR (95% CI): 2.18 (1.38 to 3.44)** **SS in favour of rimegepant** I^2: 86%	⊕⊖⊖⊖ **VERY LOW** Study quality: -2; high risk of bias pertaining to randomization, selective outcome reporting and missing outcome data Consistency: -1 Directness: ok Imprecision: ok
Sustained pain free (48 h)	3827 (4 studies)	Rimegepant: 12.9% Placebo: 5.9% **RR (95% CI): 2.45 (1.56 to 3.84)** **SS in favour of rimegepant** I^2: 66.1%	⊕⊕⊖⊖ **LOW** Study quality: -2; high risk of bias pertaining to randomization, selective outcome reporting and missing outcome data Consistency: ok Directness: ok Imprecision: ok
Sustained pain relief (24 h)	3827 (4 studies)	Rimegepant: 47.1% Placebo: 29.4% **RR (95% CI): 1.69 (1.53 to 1.87)** **SS in favour of rimegepant**	⊕⊕⊖⊖ **LOW** Study quality: -2; high risk of bias pertaining to randomization, selective outcome reporting and missing outcome data Consistency: ok Directness: ok Imprecision: ok

		I^2: 0%	
Sustained pain relief (48 h)	3827 (4 studies)	Rimegepant: 39.6% Placebo: 24.1% **RR (95% CI): 1.64 (1.46 to 1.86)** **SS in favour of rimegepant** I^2: 0%	⨁⨁⊖⊖ **LOW** Study quality: -2; high risk of bias pertaining to randomization, selective outcome reporting and missing outcome data Consistency: ok Directness: ok Imprecision: ok
Total adverse events	3827 (4 studies)	Rimegepant: 4.4% Placebo: 3.7% RR (95% CI): 1.17 (0.88 to 1.55) NS I^2: 40.5%	⨁⨁⊖⊖ **LOW** Study quality: -2; high risk of bias pertaining to randomization, selective outcome reporting and missing outcome data Consistency: ok Directness: ok Imprecision: ok

Table 60

This systematic review by Gao 2019 searched for RCTs that compared rimegepant to placebo for the acute treatment of migraine in adults.

4 RCTs comparing rimegepant to placebo were found.
A dose a 75 mg was used in these different studies.

There are some methodological problems that limit our confidence in the estimate of the results: there was a high risk of bias pertaining to randomization in one RCT, a moderate to high risk of bias pertaining to selective reporting in 2 RCTs; a high risk of missing outcome data in one RCT.

In **adults with migraine**, **rimegepant** resulted in **more pain freedom at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **rimegepant** resulted in **more pain relief at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **rimegepant** resulted in **more freedom from most bothersome symptom at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **rimegepant** resulted in **more freedom from nausea at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **rimegepant** resulted in **more freedom from photophobia at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **rimegepant** resulted in **more freedom from phonophobia at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **rimegepant** resulted in **more sustained pain freedom (24h)** compared to placebo.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

In **adults with migraine**, **rimegepant** resulted in **more sustained pain freedom (48h)** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **rimegepant** resulted in **more sustained pain relief (24h)** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **rimegepant** resulted in **more sustained pain relief (48h)** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between rimegepant and placebo for **total adverse events** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

6.8.2 Ubrogepant vs placebo

Ubrogepant versus placebo for acute treatment of migraine in adults

Bibliography: SR VanderPluym 2021(1)

Including Dodick 2019(195), Lipton 2019(196), Voss 2016(197)

Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Pain free (2h)	4192 (3 studies)	Ubrogepant: 459/2931 Placebo: 129/1261 **RR (95% CI): 1.58 (1.31 to 1.90)** **SS in favour of ubrogepant** I^2=0.00%	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Pain relief (2h) (Improvement of pain from moderate to severe at baseline to mild or none or pain scale improved at least 50% from baseline at defined assessment time)	4192 (3 studies))	Ubrogepant: 1357/2931 Placebo: 494/1261 **RR (95% CI): 1.21 (1.12 to 1.31)** **SS in favour of ubrogepant** I^2=0.00%	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Pain relief (24h) (Improvement of pain from moderate to severe at baseline to mild or none or pain scale improved at least 50% from baseline at defined assessment time)	1686 (1 study)	Ubrogepant : 303/1123 Placebo : 93/563 **RR (95% CI): 1.63 (1.33 to 2.01)** **SS in favour of ubrogepant**	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: na Directness: ok Imprecision: ok
Sustained pain free (24h) (No pain at initial assessment and remains at follow-up assessment with no use of rescue medication or relapse)	4192 (3 studies	Ubrogepant: 310/2931 Placebo: 83/1261 **RR (95% CI): 1.63 (1.29 to 2.07)** **SS in favour of ubrogepant** I^2=0.00%	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Sustained pain free (1 week) (No pain at initial assessment and remains at follow-up assessment with no use of rescue medication or relapse)	834 (1 study)	Ubrogepant : 66/695 Placebo : 7/139 RR (95% CI): 1.89 (0.88 to 4.02) NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: na Directness: ok Imprecision: -1

Sustained pain relief (24h) (pain relief at defined assessment time that remains improved at follow-up assessment with no use of rescue medication or relapse)	2506 (2 studies)	Ubrogepant: 509/1808 Placebo: 125/698 **RR (95% CI): 1.55 (1.30 to 1.85)** **SS in favour of ubrogepant** I^2= 66.05%	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Sustained pain relief (1 week) (Pain relief at defined assessment time that remains improved at follow-up assessment with no use of rescue medication or relapse)	834 (1 study)	Ubrogepant: 181/695 Placebo: 28/139 RR (95% CI): 1.29 (0.91 to 1.84) NS	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: na Directness: ok Imprecision: ok
Restored function (2h) (No restriction to perform work or usual activities)	3358 (2 studies)	Ubrogepant : 737/2236 Placebo : 292/1122 **RR (95% CI): 1.27 (1.13 to 1.42)** **SS in favour of ubrogepant** I^2= 0.00%	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Restored function (24h) (No restriction to perform work or usual activities)	3358 (2 studies)	Ubrogepant: 1331/2236 Placebo: 573/1122 **RR (95% CI): 1.17 (1.09 to 1.25)** **SS in favour of ubrogepant** I^2= 0.00%	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Cardiovascular adverse events	834 (1 study)	Rate Ratio: 2.00 95% CI: 0.11 to 36.61 NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: na Directness: ok Imprecision: -1
Serious adverse events	3358 (2 studies)	Rate Ratio: 2.54 95% CI: 0.28 to 23.11 NS I^2=N/A	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: ok Directness: ok Imprecision: -1
Total adverse events	4192 (3 studies)	Rate Ratio: 1.11 95% CI: 0.96 to 1.28	⊕⊕⊕⊕ **HIGH** Study quality: ok

	NS I^2=0%	Consistency: ok Directness: ok Imprecision: ok

Table 61

This systematic review by VanderPluym 2021 searched for RCTs comparing abortive pharmacologic or noninvasive nonpharmacologic therapy with placebo, usual care, another pharmacologic therapy, noninvasive nonpharmacologic therapy, wait list, no treatment, or attention control in adults with migraine.

3 RCTs comparing ubrogepant to placebo were found.
2 different doses of ubrogepant were investigated in 2 RCTs, 5 different doses were compared in 1 RCT. Reported data are for ubogepant as a pooled group.

Overall, all three RCTs were judged to have a low risk of bias.

In **adults with migraine**, **ubrogepant** resulted in **more pain freedom at 2h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **ubrogepant** resulted in **more pain relief at 2h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **ubrogepant** resulted in **more pain relief over 24h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **ubrogepant** resulted in **more sustained pain freedom over 24h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **ubrogepant** resulted in **more sustained pain freedom over 1 week** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **ubrogepant** resulted in **more sustained pain relief over 24h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

There was **no difference** between ubrogepant and placebo for **sustained pain relief over 1 week** in **adults with migraine**.
GRADE: HIGH quality of evidence

Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **ubrogepant** resulted in **more restored function at 24h** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

There was **no difference** between ubrogepant and placebo for cardiovascular adverse events in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between ubrogepant and placebo for serious adverse events in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between ubrogepant and placebo for total adverse events in **adults with migraine**.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

7 Prophylaxis of migraine in adults: summary and conclusions from the literature review

7.1 Beta-blockers

7.1.1 Atenolol vs placebo

Atenolol vs placebo for the prevention of migraine			
Bibliography: SR Jackson 2019(198) Including Forssman 1983(199), Johannsson 1987(200)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Headache frequency (headache days per month) At week 12	96 (2 studies) 12-13 weeks	**WMD -1.7 (-3.0 to -0.32) SS in favour of atenolol**	⨁⨁⊖⊖ **LOW** Study quality:-2 (small sample size, unclear randomization, allocation concealment, selective reporting) Consistency: ok Directness: ok Imprecision: ok
50% improvement in headaches At week 12	96 (2 studies) 12-13 weeks	**RR 1.8 (1.0 to 3.2) SS in favour of atenolol**	⨁⨁⊖⊖ **LOW** Study quality:-2 (small sample size, unclear randomization, allocation concealment, selective reporting) Consistency: ok Directness: ok Imprecision: ok
Headache index At 12 weeks	96 (2 studies) 12-13 weeks	**SMD -0.65 (-1.3 to -0.01) SS in favour of atenolol**	⨁⨁⊖⊖ **LOW** Study quality:-2 (small sample size, unclear randomization, allocation concealment, selective reporting) Consistency: ok Directness: ok Imprecision: ok

Table 62

This systematic review by Jackson 2019 searched for all RCTs at least 4 weeks in duration comparing beta-blockers versus placebo or other pharmacological interventions in the prevention of migraine or tension-type headache.

It found 2 RCTs comparing atenolol to placebo.

There are some methodological problems that limit our confidence in the estimate of the results: both studies had a small to very small sample size, one study had an unclear risk of bias pertaining to randomization, allocation concealment, and selective reporting.

In **adults with migraine**, **atenolol** resulted in **fewer headache days per month** compared to placebo.
GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **atenolol** resulted in **more participants with ≥50% improvement in headaches** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **atenolol** resulted in **a lower headache index** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

7.1.2 Bisoprolol vs placebo

Bisoprolol vs placebo for the prevention of migraine			
Bibliography: SR Jackson 2019(198) including Van de Ven 1997(201)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Headache frequency **(headache days per month)** **At week 12**	226 (1 study) 12 weeks	Bisoprolol 5 mg **WMD -0.90 (-1.53 to -0.27)** **SS in favour of bisoprolol** Bisoprolol 10 mg **WMD -0.90 (-1.6 to -0.24)** **SS in favour of bisoprolol**	⨁⨁⨀⨀ **LOW** Study quality: -2 single study with unclear randomization, allocation concealment and blinding Consistency: ok Directness: ok Imprecision: ok
Headache duration (hours per month) **At week 12**	226 (1 study) 12 weeks	WMD -1.9 (-6.5 to 2.5) NS	⨁⨀⨀⨀ **VERY LOW** Study quality: -2 single study with unclear randomization, allocation concealment and blinding Consistency: ok Directness: ok Imprecision: -1

Table 63

This systematic review by Jackson 2019 searched for all RCTs at least 4 weeks in duration comparing beta-blockers versus placebo or other pharmacological interventions in the prevention of migraine or tension-type headache.

It found 1 RCT comparing bisoprolol to placebo.

There are some methodological problems that limit our confidence in the estimate of the results: there was only one single study with an unclear risk of bias pertaining to randomization, allocation concealment and blinding.

In **adults with migraine**, **bisoprolol** resulted in **fewer headache days per month** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between bisoprolol and placebo for **headache duration** in **adults with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

7.1.3 Metoprolol vs placebo

Metoprolol vs placebo for the prevention of migraine			
Bibliography: SR Jackson 2019(198) Including Li 2006(202), Siniatchkin 2007(203), Yang 2006(204)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Headache frequency **(headache days per month)** **At week 12**	140 (3 studies) 12 weeks	WMD -0.90 (-2.2 to 0.41) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (3 very small RCTs not meeting our inclusion criteria for sample size) Consistency: ok Directness: -1 different doses Imprecision: ok
50% improvement in headaches **At week 12**	140 (3 studies) 12 weeks	**RR 1.7 (1.0 to 2.9)** **SS in favour of metoprolol** **I^2 =66.1%**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (3 very small RCTs not meeting our inclusion criteria for sample size) Consistency: ok Directness: -1 different doses Imprecision: ok

Table 64

This systematic review by Jackson 2019 searched for all RCTs at least 4 weeks in duration comparing beta-blockers versus placebo or other pharmacological interventions in the prevention of migraine or tension-type headache.

It found 2 RCTs comparing metoprolol to placebo.

There are some methodological problems that limit our confidence in the estimate of the results: the three included studies were very small and did not meet our inclusion criteria for sample size individually. All three RCTs studied different doses of metoprolol (90, 125 and 200 mg).

There was **no difference** between metoprolol and placebo for **headache days per month** in **adults with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

In **adults with migraine**, **metoprolol** resulted in **more participants with ≥50% improvement in headaches** compared to placebo.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

7.1.4 Propranolol vs placebo

Propranolol vs placebo for the prevention of migraine			
Bibliography: SR Jackson 2019(198) Including Borgesen 1974(205), Diener 2004(206), Johnson 1986(207), Mikkelsen 1986(208), Pradalier 1989(209), Standnes 1982(210), Stovner 2014(211), Tfelt-Hansen 1984(212), Wideroe 1974(213)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Headache frequency **(headache days per month)** **At week 12**	811 (9 studies) 12 weeks	**WMD -1.2 (-1.8 to-0.60)** **SS in favour of propranolol** **I^2 = 77%**	⨁⨀⨀⨀ **VERY LOW** Study quality: -2 (6 very small studies, 2 with unclear randomization and allocation concealment, 1 with high risk of selective reporting) Consistency: -1 Directness: -1 different doses Imprecision: ok
Headache frequency (headache days per month) **At week 24**	575 (1 study) 12 weeks	**WMD -0.9 (-1.5 to -0.32)** **SS in favour of propranolol**	⨁⨁⨀⨀ **LOW** Study quality:-2 single study with unclear randomization, allocation concealment and high risk of other bias Consistency: na Directness: ok Imprecision: ok

50% improvement in headaches **At week 12**	811 (9 studies) 12 weeks	**RR 1.4 (1.1 to 1.8)** **SS in favour of propranolol** **I^2 = 59.5%**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (6 very small studies, 2 with unclear randomization and allocation concealment, 1 with high risk of selective reporting) Consistency: ok Directness: -1 different doses Imprecision: ok
Analgesic medication consumption (number of doses per month) **At week 12**	811 (9 studies) 12 weeks	**WMD -2.1 (-3.2 to -0.95)** **SS in favour of propranolol** **I^2 = 85.2%**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (6 very small studies, 2 with unclear randomization and allocation concealment, 1 with high risk of selective reporting) Consistency: -1 Directness: -1 different doses Imprecision: ok
Headache Index **At week 12**	811 (9 studies) 12 weeks	**SMD -0.41 (-0.65 to -0.17)** **SS in favour of propranolol** **I^2 =0%**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (6 very small studies, 2 with unclear randomization and allocation concealment, 1 with high risk of selective reporting) Consistency: ok Directness: -1 different doses Imprecision: ok
Headache severity **At week 12**	811 (9 studies) 12 weeks	SMD 0.18 (-0.30 to 0.01) NS I^2 = 46.0%	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (6 very small studies, 2 with unclear randomization and allocation concealment, 1 with high risk of selective reporting) Consistency: ok Directness: -1 different doses Imprecision: ok
Headache duration (hours per month) **At week 12**	811 (9 studies) 12 weeks	**WMD -1.6 (-3.0 to -0.11)** **SS in favour of propranolol** **I^2 = 0%**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (6 very small studies, 2 with unclear randomization and allocation concealment, 1 with high risk of selective reporting) Consistency: ok Directness: -1 different doses Imprecision: ok

Table 65

This systematic review by Jackson 2019 searched for all RCTs at least 4 weeks in duration comparing beta-blockers versus placebo or other pharmacological interventions in the prevention of migraine or tension-type headache.

It found 9 RCTs comparing propranolol to placebo.

There are some methodological problems that severely limit our confidence in the estimate of the results: 6 RCTs did not meet our inclusion criteria for sample size. Two remaining studies had an unclear risk of bias pertaining to randomization and allocation concealment; one study had a high risk of bias pertaining to selective reporting.

In **adults with migraine**, **propranolol** resulted in **fewer headache days per month** compared to placebo (at week 12).
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

In **adults with migraine**, **propranolol** resulted in **fewer headache days per month** compared to placebo (at week 24).
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **propranolol** resulted in **more participants with ≥50% improvement in headaches** compared to placebo.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

In **adults with migraine**, **propranolol** resulted in **less analgesic medication consumption** compared to placebo.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

In **adults with migraine**, **propranolol** resulted in **a lower headache index** compared to placebo.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between propranolol and placebo for **headache severity** in the **in adults with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

In **adults with migraine**, **propranolol** resulted in **a lower headache duration** compared to placebo.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

7.1.5 Timolol vs placebo

Timolol vs placebo for the prevention of migraine			
Bibliography: SR Jackson 2019(198) including Standnes 1982(210), Tfelt-Hansen 1984(212)			
Outcomes	**N° of participants (studies)** **Follow up**	**Results**	**Quality of the evidence (GRADE)**

Headache frequency **(headache days per month)** **At week 12**	121 (2 studies) 12 weeks	**WMD -1.53 (-2.5 to -0.78)** **SS in favour of timolol** **I² = 0%**	⨁⨁⊖⊖ **LOW** Study quality: -2; small sample sizes, 1 RCT with unclear randomization, allocation concealment and high risk of selective reporting Consistency: ok Directness: ok Imprecision: ok
50% improvement in headaches **At week 12**	121 (2 studies) 12 weeks	**RR 1.8 (1.4 to 2.3)** **SS in favour of timolol** **I² =0%**	⨁⨁⊖⊖ **LOW** Study quality: -2; small sample sizes, 1 RCT with unclear randomization, allocation concealment and high risk of selective reporting Consistency: ok Directness: ok Imprecision: ok

Table 66

This systematic review by Jackson 2019 searched for all RCTs at least 4 weeks in duration comparing beta-blockers versus placebo or other pharmacological interventions in the prevention of migraine or tension-type headache.

It found 2 RCTs comparing timolol to placebo.

There are some methodological problems that limit our confidence in the estimate of the results: the two RCTs are small to very small in size. The largest study had an unclear risk of bias pertaining to randomization, allocation concealment and a high risk of bias pertaining to selective reporting.

In **adults with migraine**, **timolol** resulted in **fewer headache days per month** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **timolol** resulted in **more participants with ≥50% improvement in headaches** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

7.1.6 Metoprolol vs bisoprolol

Metoprolol vs bisoprolol for the prevention of migraine
Bibliography: SR Jackson 2019(198) Including Worz 1992(214)

Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Headache frequency **(headache days per month)** **At week 12**	125 (1 study) 12 weeks	WMD -0.09 (-0.62 to 0.44) NS	⨁⨁⊖⊖ **LOW** Study quality: -2 single study with high risk pertaining to randomization, allocation concealment, incomplete outcome data Consistency: na Directness: ok Imprecision: ok
Medication use (doses/month)	125 (1 study) 12 weeks	WMD 0.01 (-0.30 to 0.32) NS	⨁⨁⊖⊖ **LOW** Study quality: -2 single study with high risk pertaining to randomization, allocation concealment, incomplete outcome data Consistency: na Directness: ok Imprecision: ok
Headache severity	125 (1 study) 12 weeks	WMD 0.19 (-0.13 to 0.3) NS	⨁⨁⊖⊖ **LOW** Study quality: -2 single study with high risk pertaining to randomization, allocation concealment, incomplete outcome data Consistency: na Directness: ok Imprecision: ok
Headache duration (hours per month)	125 (1 study) 12 weeks	WMD 0.30 (-4.2 to 4.8) NS	⨁⨁⊖⊖ **LOW** Study quality: -2 single study with high risk pertaining to randomization, allocation concealment, incomplete outcome data Consistency: na Directness: ok Imprecision: ok

Table 67

This systematic review by Jackson 2019 searched for all RCTs at least 4 weeks in duration comparing beta-blockers versus placebo or other pharmacological interventions in the prevention of migraine or tension-type headache.

It found 1 RCT comparing metoprolol to bisoprolol.

There are some methodological problems that limit our confidence in the estimate of the results: there is only a single study with a high risk of bias pertaining to randomization, allocation concealment and incomplete outcome data, and an unclear risk of bias pertaining to blinding.

There was **no difference** between metoprolol and bisoprolol for **number of migraine headache days per month** in the **in adults with migraine**.

GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between metoprolol and bisoprolol for **acute medication use** in the **in adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between metoprolol and bisoprolol for **headache severity** in the **in adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between metoprolol and bisoprolol for **headache duration** in the **in adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

7.1.7 Propranolol vs metoprolol

Jackson 2019 reported results for propranolol vs metoprolol for some outcomes at a time points of 16 weeks, 24 weeks and 28 weeks. However, we believe this to be an inaccuracy: it is unclear which studies these results are extracted from, as the only studies presented in Jackson 2019 that compare propranolol to metoprolol are short in duration (8 weeks or less). As these RCTs do not meet our inclusion criteria (for duration and sample size), we did not report this comparison.

7.1.8 Timolol vs propranolol

Timolol vs propranolol for the prevention of migraine			
Bibliography: SR Jackson 2019(198) including Standnes 1982(210), Tfelt-Hansen 1984(212)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Headache frequency **(headache days per month)**	121 (2 studies)	WMD 0.37 (-0.45 to 1.2) NS I^2 = 0%	⨁⨁⨀⨀ **LOW** Study quality: -2; 2 small studies, 1 RCT with unclear randomization and high risk of bias pertaining to selective reporting Consistency: ok Directness: ok Imprecision: ok

At week 12	

Table 68

This systematic review by Jackson 2019 searched for all RCTs at least 4 weeks in duration comparing beta-blockers versus placebo or other pharmacological interventions in the prevention of migraine or tension-type headache.

It found 2 RCTs comparing timolol to propranolol.

There are some methodological problems that limit our confidence in the estimate of the results: both studies had small to very small sample sizes. One RCT had an unclear risk of bias pertaining to randomization and a high risk of bias pertaining to selective reporting.

There was **no difference** between timolol and propranolol for **number of migraine headache days per month** in the **in adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

7.1.9 Propranolol vs topiramate

Propranolol vs topiramate for the prevention of migraine			
Bibliography: SR Jackson 2019(198) Including Diener 2004(206), Yuan 2005(215)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Headache frequency (headache days per month)	642 (2 studies) 12 weeks 575 (1 study) 26 weeks	At week 12 WMD 0.10 (-0.98 to 1.2) NS At week 24 WMD -0.75 (-1.6 to 0.13) NS	⨁⨁⊖⊖ **LOW** Study quality: -2; one very small study, larger study has unclear randomization and allocation bias and a high risk of other bias Consistency: ok Directness: ok Imprecision: ok
50% reduction in headache At week 12	575 (1 study) 26 weeks	RR 1.2 (0.98 to 1.4) NS I^2 = 0%	⨁⨁⊖⊖ **LOW** Study quality: -2; one very small study, larger study has unclear randomization and allocation bias and a high risk of other bias Consistency: ok Directness: ok Imprecision: ok

Table 69

This systematic review by Jackson 2019 searched for all RCTs at least 4 weeks in duration comparing beta-blockers versus placebo or other pharmacological interventions in the prevention of migraine or tension-type headache.

It found 2 RCTs comparing propranolol to topiramate.

There are some methodological problems that limit our confidence in the estimate of the results: one study had a very small sample size, while the larger study had an unclear risk of bias pertaining to randomization and allocation bias and a high risk of "other bias" (as assessed by Jackson 2019, no further details provided).

There was **no difference** between propranolol and topiramate for **number of migraine headache days per month** in the **in adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between propranolol and topiramate for **participants with 50% reduction in headache** in the **in adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

7.1.10 Propranolol vs riboflavin

propranolol vs riboflavin for the prevention of migraine			
Bibliography: SR Jackson 2019(198) Including Nambiar 2011(216)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Headache frequency **(headache days per month)** **At week 12**	100 (1 study) 24 weeks	WMD -0.04 (-0.59 to 0.51) NS	⨁⨁⊖⊖ **LOW** Study quality: -2; single study with high risk of bias pertaining to randomization, allocation concealment, blinding, selective reporting Consistency: na Directness: ok Imprecision: ok
Headache severity **12 weeks**	100 (1 study) 24 weeks	**WMD 0.42 (0.02 to 0.82)** **SS in favour of riboflavin** **Lower headache severity with riboflavin**	⨁⨁⊖⊖ **LOW** Study quality: -2; single study with high risk of bias pertaining to randomization, allocation concealment, blinding, selective reporting

			Consistency: na Directness: ok Imprecision: ok
Headache severity **24 weeks**	100 (1 study) 24 weeks	WMD 0.11 (-0.29 to 0.50) NS	⨁⨁⊖⊖ **LOW** Study quality: -2; single study with high risk of bias pertaining to randomization, allocation concealment, blinding, selective reporting Consistency: na Directness: ok Imprecision: ok
Headache duration (hours per month) **12 weeks**	100 (1 study) 24 weeks	WMD -0.10 (-0.39 to 0.19) NS	⨁⨁⊖⊖ **LOW** Study quality: -2; single study with high risk of bias pertaining to randomization, allocation concealment, blinding, selective reporting Consistency: na Directness: ok Imprecision: ok
Headache duration (hours per month) **24 weeks**	100 (1 study) 24 weeks	WMD 0.30 (-0.06 to 6.6) NS	⨁⨁⊖⊖ **LOW** Study quality: -2; single study with high risk of bias pertaining to randomization, allocation concealment, blinding, selective reporting Consistency: na Directness: ok Imprecision: ok

Table 70

This systematic review by Jackson 2019 searched for all RCTs at least 4 weeks in duration comparing beta-blockers versus placebo or other pharmacological interventions in the prevention of migraine or tension-type headache.

It found 1 RCT comparing propranolol to riboflavin.

There are some methodological problems that limit our confidence in the estimate of the results: there was only a single small study with high risk of bias pertaining to randomization, allocation concealment, blinding and selective reporting.

There was **no difference** between propranolol and riboflavin for **number of migraine headache days per month** in the **in adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **riboflavin** resulted in **a lower headache severity (at 12 weeks)** compared to propranolol.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between propranolol and riboflavin for **headache severity (at 24 weeks)** in **adults with migraine**.

GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between propranolol and riboflavin for **headache duration (at 12 weeks)** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between propranolol and riboflavin for **headache duration (at 24 weeks)** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

7.2 Sartans

7.2.1 Candesartan vs placebo

Candesartan vs placebo for the prevention of migraine in adults			
Bibliography: SR Jackson 2015(217) Including Stovner 2014(211), Tronvik 2003(218)			
Outcomes	**N° of participants (studies)** **Follow up**	**Results**	**Quality of the evidence (GRADE)**
Headache frequency (number of headaches per month) at 12 weeks	118 (2 studies) 12 weeks	MD -0.9 (-1.8 to 0.03) NS I^2 = 31.7%	⨁⨁⨁⊖ **MODERATE** Study quality: -1; small studies, one of which with unclear risk of incomplete outcome data and selective reporting Consistency: ok Directness: ok Imprecision: ok
>50% improvement at 12 weeks	57 (1 study) 12 weeks	**RR 18.0 (2.5 to 130.4)** **SS in favour of candesartan**	⨁⨁⊖⊖ **LOW** Study quality: -2 very small study; unclear risk of incomplete outcome data and selective reporting Consistency: na Directness: ok Imprecision: ok

Table 71

SR Jackson 2015(217) searched for RCTs comparing active treatments versus placebo or active controls for the preventive treatment of migraine.

Two studies comparing candesartan to placebo were found.

There are some methodological problems that limit our confidence in the estimate of the results: both are very small studies, one of which with unclear risk of incomplete outcome data and selective reporting.

There was **no difference** between candesartan and placebo for **headache frequency** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **candesartan** resulted in **more participants with at least 50% improvement** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

7.2.2 Telmisartan vs placebo

telmisartan vs placebo for the prevention of migraine in adults			
Bibliography: Bibliography: SR Jackson 2015(217) Including Diener 2009(219)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Headache frequency (number of headaches per month)	95 (1 study) 12 weeks	**MD -1.9 (-3.6 to -0.23) SS in favour of telmisartan**	⨁⨁⨀⨀ **LOW** Study quality: -2; one small study with unclear risk relating to randomization, allocation concealment, blinding, incomplete outcome data and selective reporting Consistency: na Directness: ok Imprecision: ok
>50% improvement	95 (1 study) 12 weeks	RR 1.6 (0.85 to 3.0) NS	⨁⨀⨀⨀ **VERY LOW** Study quality: -2; one small study with unclear risk relating to randomization, allocation concealment, blinding, incomplete outcome data and selective reporting Consistency: na Directness: ok Imprecision: -1

Table 72

SR Jackson 2015(217) searched for RCTs comparing active treatments versus placebo or active controls for the preventive treatment of migraine.

One RCT comparing telmisartan to placebo was found.

This single small study had an unclear risk of bias relating to randomization, allocation concealment, blinding, incomplete outcome data and selective reporting. This severely limits our confidence in the results.

In **adults with migraine**, **telmisartan** resulted in **a lower headache frequency** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between telmisartan and placebo for **participants with at least 50% improvement** in **adults with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

7.3 Calcium antagonists

7.3.1 Verapamil vs control

SR Jackson 2015(217) searched for RCTs comparing active treatments versus placebo or active controls for the preventive treatment of migraine. Two RCTs comparing verapamil to placebo were found. None met our inclusion criteria for sample size or duration. No RCTs comparing verapamil to an active control were found.

7.3.2 Flunarizine vs placebo

Flunarizine vs placebo for the prevention of migraine in adults			
Bibliography: Stubberud 2019(220) Including Diamond 1993(221), Frenken 1984(222), Louis 1981(223), Mentenopoulos 1985(224), Pini 1985(225), Sørensen 1986(226)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mean reduction in migraine frequency (after 3 months of treatment)	249 (5 studies) 12 weeks	**MD -0.44 (-0.61 to -0.26) SS in favour of flunarizine I^2 = 27%**	⨁⨁⨀⨀ **LOW** Study quality:-2; studies with very small sample size, 1 study with unclear randomization, allocation concealment, blinding and high risk of incomplete outcome data and selective reporting Consistency: ok Directness: ok Imprecision: ok
Proportion of responders	113 (3 studies)	Flunarazine: 36/55 Placebo: 11/58 **OR 8.86 (3.57 to 22.00)**	⨁⨁⨀⨀ **LOW** Study quality: -2; all studies with very small sample size Consistency: ok Directness: ok

(≥50% reduction in migraine frequency)		**SS in favour of flunarizine** **I^2 = 0%**	Imprecision: ok
Adverse events	113 (3 studies)	Flunarazine: 12/55 Placebo: 10/58 RD 0.04 (-0.08 to 0.17) NS I^2 = 0%	⨁⨁⨀⨀ **LOW** Study quality: -2; all studies with very small sample size Consistency: ok Directness: ok Imprecision: ok

Table 73

This systematic review by Stubberud 2019(220) searched for prospective, randomized or pseudo-RCTs comparing flunarizine to placebo or other pharmacological and nonpharmacological treatments for the prevention of migraine.

It found 6 RCTs comparing flunarizine to placebo.

There are some methodological problems that limit our confidence in the estimate of the results: all the studies had a small to very small sample size. The one RCT with adequate sample size had an unclear risk of bias pertaining to randomization, allocation concealment and blinding, and a high risk of bias pertaining to incomplete outcome data and selective reporting.

In **adults with migraine**, **flunarizine** resulted in **a greater mean reduction in migraine frequency** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **flunarizine** resulted in **a larger proportion of participants with ≥50% reduction in migraine frequency** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between flunarizine and placebo for **adverse events** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

7.3.3 Flunarizine vs metoprolol

Flunarizine vs metoprolol for the prevention of migraine in adults			
Bibliography: Stubberud 2019(220) Including Sørensen 1991(227)			
Outcomes	**N° of participants (studies)** **Follow up**	**Results**	**Quality of the evidence (GRADE)**

Mean reduction in migraine frequency (after 3 months of treatment)	127 (1 study) 5 months	MD -0.10 (-1.08 to 0.88) NS	⨁⨁⊖⊖ **LOW** Study quality: -2 single study with unclear randomization, allocation concealment, blinding Consistency: na Directness: ok Imprecision: ok

Table 74

This systematic review by Stubberud 2019(220) searched for prospective, randomized or pseudo-RCTs comparing flunarizine to placebo or other pharmacological and nonpharmacological treatments for the prevention of migraine.

It found 1 RCT comparing flunarizine to metoprolol.

There are some methodological problems that limit our confidence in the estimate of the results: here was only a single, small study with unclear risk of bias pertaining to randomization, allocation concealment and blinding of assessors.

There was **no difference** between flunarizine and metoprolol for **mean reduction in migraine frequency** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

7.3.4 Flunarizine vs propranolol

Flunarizine vs propranolol for the prevention of migraine in adults			
Bibliography: Stubberud 2019(220) Including Bordini 1997(228), Ludin 1989(229), Diener 2002(230), Gawel 1992(231), Shimell 1990(232), Soyka 1987a(233), Soyka 1987b(234)			
Outcomes	**N° of participants (studies)** **Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mean reduction in migraine frequency (after 4 months of treatment)	1151 (7 studies) 4 months	MD -0.08 (-0.34 to 0.18) NS I^2 = 0%	⨁⨁⊖⊖ **LOW** Study quality: -2; 3 studies with very small sample sizes, 3 studies with unclear randomization, allocation concealment, 4 studies with unclear blinding, 3 studies with high risk of incomplete outcome data and selective reporting Consistency: ok Directness: ok Imprecision: ok

Intensity of migraine headache (after 4 months of treatment)	135 (2 studies) 4 months	MD 0.22 (-0.12 to 0.57) NS	⨁⨁⊖⊖ **LOW** Study quality: -2; 1 study with very small sample size, 1 study with unclear randomization, allocation concealment, blinding and high risk of incomplete outcome data and selective reporting Consistency: ok Directness: ok Imprecision: ok
Duration of migraine headache (after 4 months of treatment)	1063 (5 studies) 4 months	MD 0.60 (-1.48 to 2.69) NS	⨁⨁⊖⊖ **LOW** Study quality: -2; 1 study with very small sample size, 3 studies with unclear randomization, allocation concealment, 4 studies with unclear blinding, 3 studies with high risk of incomplete outcome data and selective reporting Consistency: ok Directness: ok Imprecision: ok
Doses of acute medication	583 (2 studies) 4 months	SMD 0.07 (-0.09 to 0.23) NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1; 1 study with very small sample size, 1 larger study with unclear blinding Consistency: ok Directness: ok Imprecision: ok
Adverse events	1133 (6 studies) 4 months	RD -0.04 (-0.09 to 0.02) NS	⨁⨁⊖⊖ **LOW** Study quality: -2; 2 studies with very small sample sizes, 3 studies with unclear randomization, allocation concealment, 4 studies with unclear blinding, 3 studies with high risk of incomplete outcome data and selective Consistency: ok Directness: ok Imprecision: ok

Table 75

This systematic review by Stubberud 2019(220) searched for prospective, randomized or pseudo-RCTs comparing flunarizine to placebo or other pharmacological and nonpharmacological treatments for the prevention of migraine.

It found 7 RCTs comparing flunarizine to propranolol.

There are some methodological problems that limit our confidence in the estimate of the results: 3 studies had a very small sample size, 3 larger studies had an unclear risk of bias pertaining to randomization and allocation concealment, 4 studies had an unclear risk of bias pertaining to blinding, 3 studies had a high risk of bias pertaining to incomplete outcome data and selective reporting.

There was **no difference** between flunarizine and propranolol for **mean reduction in migraine frequency** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between flunarizine and propranolol for the **intensity of migraine headache** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between flunarizine and propranolol for the **duration of migraine headache** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between flunarizine and propranolol for **doses of acute medication** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between flunarizine and propranolol for **adverse events** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

7.3.5 Flunarizine vs topiramate

Flunarizine vs topiramate for the prevention of migraine in adults			
Bibliography: Stubberud 2019(220) Including Luo 2012(235)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mean reduction in migraine frequency (after 3 months of treatment)	83 (1 study) 12 months	MD -0.30 (-0.97 to 0.37) NS	⨁⨁⨀⨀ **LOW** Study quality: -2; single unblinded study with unclear randomization and allocation concealment and high risk of incomplete outcome data and selective reporting Consistency: na Directness: ok Imprecision: ok

Table 76

This systematic review by Stubberud 2019(220) searched for prospective, randomized or pseudo-RCTs comparing flunarizine to placebo or other pharmacological and nonpharmacological treatments for the prevention of migraine.

It found 1 RCT comparing flunarizine to topiramate.

There are some methodological problems that limit our confidence in the estimate of the results: it was a single unblinded study with a small sample size, unclear risk of bias pertaining to randomization and allocation concealment and a high risk of bias pertaining to incomplete outcome data and selective reporting.

There was **no difference** between flunarizine and topiramate for **mean reduction in migraine frequency** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

7.4 Anticonvulsants

7.4.1 Topiramate vs placebo

Topiramate vs placebo for the prevention of migraine in adults			
Bibliography: Cochrane Linde 2013a(236) Including: Brandes 2004(237), de Tommaso 2007(238), Diener 2004(206), Diener 2007(239), Edwards 2000(240), Gupta 2007(241), Lipton 2011(242), Mei 2004(243), Silberstein 2004(244), Silberstein 2006(245), Storey 2001(246)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Headache frequency	1793 (9 studies) 4 weeks – 26 weeks	**MD -1.2 (1.59 to -0.8) SS in favour of topiramate** I^2 39%	⨁⨁⨀⨀ **LOW** Study quality: -2; 4 of the RCTs did not meet our inclusion criteria (for sample size or duration). Of the remaining RCTs some had an unclear risk of bias pertaining to randomization, allocation concealment and blinding. 1 RCT had a high risk of bias pertaining to selective reporting Consistency: ok Directness: ok Imprecision: ok
patients with ≥50% reduction in	1246 (9 studies)	Topiramate 310/660 Placebo 136/586	⨁⨁⨀⨀ **LOW** Study quality: -2; 5 of the RCTs did not meet our inclusion

headache frequency	4 weeks – 18 weeks	**OR 3.18 (2.1 to 4.82)** **SS In favour of topiramate** I^2 54% **RR 2.02 (1.57 to 2.6)** **SS in favour of topiramate** I^2 46%	criteria (for sample size or duration). Of the remaining RCTs some had an unclear risk of bias pertaining to randomization, allocation concealment and blinding. 1 RCT had a high risk of bias pertaining to selective reporting Consistency: ok Directness: ok Imprecision: ok

Table 77Table 78

Topiramate 50 mg vs placebo for the prevention of migraine in adults			
Bibliography: Cochrane Linde 2013a(236) Including: Brandes 2004(237), de Tommaso 2007(238), Diener 2004,(206) Diener 2007(239), Edwards 2000(240), Gupta 2007(241), Lipton 2011(242), Mei 2004(243), Silberstein 2004(244), Silberstein 2006(245), Storey 2001(246)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
MSQ role-function restrictive	463 (2 studies) 18 weeks	Topiramate 50 mg/day vs placebo **MD 5.83 (2.25 to 9.41)** **SS in favour of topiramate** I^2 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear blinding of assessor in 2 studies, unclear randomization method in 1 RCT Consistency: ok Directness: ok Imprecision: ok
MSQ role-function prevention	463 (2 studies) 18 weeks	Topiramate 50 mg/day vs placebo MD 2.84 (-0.24 to 5.92) NS I^2 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear blinding of assessor in 2 studies, unclear randomization method in 1 RCT Consistency: ok Directness: ok Imprecision: ok
MSQ- emotional function	463 (2 studies) 18 weeks	Topiramate 50 mg/day vs placebo **MD 4.58 (0.61 to 8.54)** **SS in favour of topiramate** I^2 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear blinding of assessor in 2 studies, unclear randomization method in 1 RCT Consistency: ok Directness: ok Imprecision: ok
SF-36 general health	463 (2 studies) 18 weeks	Topiramate 50 mg/day vs placebo MD 1.45 (-2.18 to 5.08) NS I^2= 5.3%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear blinding of assessor in 2 studies, unclear randomization method in 1 RCT Consistency: ok Directness: ok Imprecision: -1

Table 79

Topiramate 100 mg vs placebo for the prevention of migraine in adults
Bibliography: Cochrane Linde 2013a(236) Including: Brandes 2004(237), de Tommaso 2007(238), Diener 2004(206), Diener 2007(239), Edwards 2000(240), Gupta 2007(241), Lipton 2011(242), Mei 2004(243), Silberstein 2004(244), Silberstein 2006(245), Storey 2001(246)

Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
MSQ role-function restrictive	474 (2 studies) 18 weeks	Topiramate 100 mg/day vs placebo **MD 10.08 (6.55 to 13.6)** **SS in favour of topiramate** I^2 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear blinding of assessor in 2 studies, unclear randomization method in 1 RCT Consistency: ok Directness: ok Imprecision: ok
MSQ role-function prevention	474 (2 studies) 18 weeks	Topiramate 100 mg/day vs placebo **MD 6.39 (3.37 to 9.41)** **SS in favour of topiramate** I^2 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear blinding of assessor in 2 studies, unclear randomization method in 1 RCT Consistency: ok Directness: ok Imprecision: ok
MSQ- emotional function	474 (2 studies) 18 weeks	Topiramate 100 mg/day vs placebo **MD 10.22 (6.31 to 14.14)** **SS in favour of topiramate** I^2 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear blinding of assessor in 2 studies, unclear randomization method in 1 RCT Consistency: ok Directness: ok Imprecision: ok
SF-36 general health	474 (2 studies) 18 weeks	Topiramate 100 mg/day vs placebo MD 4.18 (-1.21 to 9.57) NS I^2 58.4%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear blinding of assessor in 2 studies, unclear randomization method in 1 RCT Consistency: ok Directness: ok Imprecision: -1
Any adverse event	883 (2 studies) 26 weeks	Topiramate 100 mg/day: 318/430 Placebo: 287/443 **RD 0.09 (0.03 to 0.15)** **SS in favour of placebo** I^2 0%	⊕⊕⊖⊖ **LOW** Study quality: -2; unclear blinding in 2 studies, high risk of selective reporting in 1 study Consistency: ok Directness: ok Imprecision: ok

Table 80

Topiramate 200 mg vs placebo for the prevention of migraine in adults
Bibliography: Cochrane Linde 2013a(236)

Including: Brandes 2004(237), de Tommaso 2007(238), Diener 2004(206), Diener 2007(239), Edwards 2000(240), Gupta 2007(241), Lipton 2011(242), Mei 2004(243), Silberstein 2004(244), Silberstein 2006(245), Storey 2001(246)

Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
MSQ role-function restrictive	458 (2 studies) 18 weeks	Topiramate 200 mg/day vs placebo **MD 10.36 (6.68 to 14.04)** **SS in favour of topiramate** I^2 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear blinding of assessor in 2 studies, unclear randomization method in 1 RCT Consistency: ok Directness: ok Imprecision: ok
MSQ role-function prevention	458 (2 studies) 18 weeks	Topiramate 200 mg/day vs placebo **MD 5.06 (1.87 to 8.25)** **SS in favour of topiramate** I^2 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear blinding of assessor in 2 studies, unclear randomization method in 1 RCT Consistency: ok Directness: ok Imprecision: ok
MSQ- emotional function	458 (2 studies) 18 weeks	Topiramate 200 mg/day vs placebo **MD 8.45 (4.38 to 12.52)** **SS in favour of topiramate** I^2 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear blinding of assessor in 2 studies, unclear randomization method in 1 RCT Consistency: ok Directness: ok Imprecision: ok
SF-36 general health	458 (2 studies) 18 weeks	Topiramate 200 mg/day vs placebo MD 2.58 (-1.6 to 1.5) NS I^2 0%	⊕⊕⊕⊖ **MODERATE** Study quality: -1; unclear blinding of assessor in 2 studies, unclear randomization method in 1 RCT Consistency: ok Directness: ok Imprecision: ok
Any adverse event	213 (1 study) 20 weeks	Topiramate 200 mg/day: 126/140 Placebo: 51/73 **RD 0.2 (0.08 to 0.32)** **SS in favour of placebo**	⊕⊕⊖⊖ **LOW** Study quality: -2; single study with unclear randomization, allocation concealment, blinding, high risk of selective reporting Consistency: na Directness: ok Imprecision: ok

Table 81

This systematic review by Linde 2013(236) searched for RCTs or pseudo-randomized trials comparing topiramate to placebo, no intervention, or active drug treatment in the prevention of migraine in adults (at least 16 years of age).

It found 11 RCTs comparing topiramate to placebo.

There are some methodological problems that limit our confidence in the estimate of the results: 5 of the RCTs did not meet our inclusion criteria (for sample size or duration). Of the remaining RCTs some had an unclear risk of bias pertaining to randomization, allocation concealment and blinding. Two RCTs had a high risk of bias pertaining to selective reporting.

In **adults with migraine**, **topiramate** resulted in **a lower headache frequency** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **topiramate** resulted in **more patients with ≥50% reduction in headache frequency** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

Topiramate 50 mg

In **adults with migraine**, **topiramate 50 mg** resulted in **a higher* MSQ role-function restrictive score** compared to placebo. *(* Higher scores mean better daily functioning)*
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between topiramate 50 mg and placebo for **MSQ role function prevention score** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **topiramate 50 mg** resulted in **a higher* MSQ emotional function score** compared to placebo. *(* Higher scores mean better daily functioning)*
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between topiramate 50 mg and placebo for **SF-36 general health score** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

Topiramate 100 mg

In **adults with migraine**, **topiramate 100 mg** resulted in **a higher* MSQ role-function restrictive score** compared to placebo. *(* Higher scores mean better daily functioning)*
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **topiramate 100 mg** resulted in **a higher* MSQ role-function prevention score** compared to placebo. *(* Higher scores mean better daily functioning)*
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **topiramate 100 mg** resulted in **a higher* MSQ emotional function score** compared to placebo. *(* Higher scores mean better daily functioning)*
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between topiramate 100 mg and placebo for **SF-36 general health score** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **topiramate 100 mg** resulted in **more adverse events** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

Topiramate 200 mg

In **adults with migraine**, **topiramate 200 mg** resulted in **a higher* MSQ role-function restrictive score** compared to placebo. *(* Higher scores mean better daily functioning)*
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **topiramate 200 mg** resulted in **a higher* MSQ role-function prevention score** compared to placebo. *(* Higher scores mean better daily functioning)*
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **topiramate 200 mg** resulted in **a higher* MSQ emotional function score** compared to placebo. *(* Higher scores mean better daily functioning)*
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between topiramate 200 mg and placebo for **SF-36 general health score** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **topiramate 200 mg** resulted in **more adverse events** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

7.4.2 Topiramate vs amitriptyline

Topiramate vs amitriptyline for the prevention of migraine in adults			
Bibliography: Cochrane Linde 2013a(236) Including Dodick 2019(195)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Responders **(patients with ≥50% reduction in headache frequency)**	330 (1 study)	Amitriptyline 50-100 mg 73/159 Topiramate 50-100 mg 95/171 OR 0.68 (95%CI 0.44 to 1.05) NS	⨁⨁⊖⊖ **LOW** Study quality: -2; single study with unclear randomization, incomplete outcome data, selective reporting Consistency: na Directness: ok Imprecision: ok
MIDAS score	295 (1 study)	Amitriptyline 50-100 mg Mean (SD) -14.2 (20.7) Topiramate 50-100 mg Mean (SD) -12.1 (23.4) MD 2.1 (-2.93 to 7.13) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2; single study with unclear randomization, incomplete outcome data, selective reporting Consistency: na Directness: ok Imprecision: -1

Table 82

This systematic review by Linde 2013(236) searched for RCTs or pseudo-randomized trials comparing topiramate to placebo, no intervention, or active drug treatment in the prevention of migraine in adults (at least 16 years of age).

It found 1 RCT comparing topiramate to amitriptyline.

There are some methodological problems that limit our confidence in the estimate of the results: there is only a single study with an unclear risk of bias pertaining to the blinding of the assessors, and to incomplete outcome data and selective reporting.

There was **no difference** between topiramate and amitiptyline for **patients with ≥50% reduction in headache frequency** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between topiramate and amitiptyline for **MIDAS score** in **adults with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

7.4.3 valproate vs placebo

Valproate vs placebo for the prevention of migraine in adults			
Bibliography: Cui 2020(247) Including Jensen 1994(248), Sarchielli 2014(249), Sadeghian 2015(250)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
≥ 50% reduction in headache frequency	278 (3 studies) 3-6 months	Valproate vs placebo **OR 5.07 (2.75 to 9.36) SS in favour of valproate** I^2 = 42%	⨁⊖⊖⊖ **VERY LOW** Study quality: -2; very small sample sizes; largest study is MOH Consistency: ok Directness: -1, includes population with medication overuse headache Imprecision: ok

Table 83

This systematic review by Cui 2020 searched for parallel group RCTs comparing valproate to placebo or other drugs in the prevention of migraine.

It found 3 RCTs comparing valproate to placebo.

There are some methodological problems that severely limit our confidence in the estimate of the results: two studies had very small sample sizes, and the largest study included participants with medication overuse headache (population excluded from our report).

In **adults with migraine**, **valproate** resulted in **more participants with ≥ 50% reduction in headache frequency** compared to placebo.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

7.4.4 Valproate vs topiramate

Valproate vs topiramate for the prevention of migraine in adults
Bibliography: Cui 2020(247)

Including Afshari 2012(251), Bartolini 2005(252), Krymchantowski 2011(253)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
≥ 50% reduction in headache frequency	278 (3 studies) 3-6 months	OR 0.74 (0.39 to 1.40) NS I^2 = 0%	⨁⊖⊖⊖ **VERY LOW** Study quality: -2; very small sample sizes Consistency: ok Directness: -1, includes population with chronic migraine, and one RCT with divalproex Imprecision: ok

Table 84

This systematic review by Cui 2020 searched for parallel group RCTs comparing valproate to placebo or other drugs in the prevention of migraine.

It found 3 RCTs comparing valproate to topiramate.

There are some methodological problems that severely limit our confidence in the estimate of the results: all studies had very small sample sizes, one study included participants with chronic migraine (population excluded from our report) and one study used divalproex (intervention excluded from our report).

There was **no difference** between valproate and placebo for **participants with ≥ 50% reduction in headache frequency** in **adults with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

7.4.5 valproate vs magnesium

Valproate vs magnesium for the prevention of migraine			
Bibliography: RCT Khani(254)			
Outcomes	**N° of participants (studies) Follow up**	**Results (95% CI)**	**Quality of the evidence (GRADE)**
Migraine frequency (PO) Month 3	222 (1 study) 12 weeks	valproate vs magnesium **MD -2.31 (-2.62 to -2.01)** **SS in favour of valproate**	⨁⨁⊖⊖ **LOW** Study quality: -2 single study with multiple methodological problems Consistency: na Directness: ok Imprecision: ok
Migraine severity Month 3	222 (1 study) 12 weeks	valproate vs magnesium **MD -0.70 (-1.00 to -0.39)** **SS in favour of valproate**	⨁⨁⊖⊖ **LOW** Study quality: -2 single study with multiple methodological problems Consistency: na

			Directness: ok Imprecision: ok
Duration of attacks (hours) Month 3	222 (1 study) 12 weeks	valproate vs magnesium **MD -1.09 (-1.90 to -0.29)** **SS in favour of valproate**	⨁⨁⨀⨀ **LOW** Study quality: -2 single study with multiple methodological problems Consistency: na Directness: ok Imprecision: ok
Number of painkillers used per month Month 3	222 (1 study) 12 weeks	valproate vs magnesium **MD -0.65 (-0.89 to -0.39)** **SS in favour of valproate**	⨁⨁⨀⨀ **LOW** Study quality: -2 single study with multiple methodological problems Consistency: na Directness: ok Imprecision: ok
MIDAS score (migraine-related disabilities)	222 (1 study) 12 weeks	valproate vs magnesium **p<0.001** **SS in favour of valproate**	⨁⨁⨀⨀ **LOW** Study quality: -2 single study with multiple methodological problems Consistency: na Directness: ok Imprecision: ok
HIT-6 score (36-78) (severity of headache impact on daily life)	222 (1 study) 12 weeks	valproate vs magnesium **p<0.001** **SS in favour of valproate**	⨁⨁⨀⨀ **LOW** Study quality: -2 single study with multiple methodological problems Consistency: na Directness: ok Imprecision: ok

Table 85

We found a single RCT comparing valproate to magnesium.

There are some methodological problems that limit our confidence in the estimate of the results: the study had unclear allocation concealment, high risk of attrition bias as drop-outs (38 patients) were excluded from analysis, and high risk of bias pertaining to selective reporting as the safety endpoints were not analyzed due to faulty reports.

In **adults with migraine**, **valproate** resulted in **a lower migraine frequency** compared to magnesium.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **valproate** resulted in **a lower migraine severity** compared to magnesium.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **valproate** resulted in **a lower duration of attacks** compared to magnesium.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **valproate** resulted in **a lower number of painkillers used per month** compared to magnesium.
GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **valproate** resulted in **fewer migraine-related disabilities (evaluated by the MIDAS score)** compared to magnesium.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **valproate** resulted in **a lower severity of headache impact on daily life (evaluated by the HIT-6 score)** compared to magnesium.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

7.4.6 valproate vs riboflavin

Valproate vs riboflavin for the prevention of migraine			
Bibliography: Rahimdel(255)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Frequency of headaches (Times/month)	90 (1 study) 12 weeks	riboflavin: decreased from 9.2 (SD 6.2) to 2.4 (SD 1.6) valproate: decreased from 6.5 (SD 3.1) to 2.1 (SD 1.0) between-group difference NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2; single small study with unclear randomization, allocation concealment, blinding, incomplete outcome data and selective reporting Consistency: na Directness: -1; definition of migraine not well described; population age 15-55y Imprecision: ok
Duration of headaches (hours)	90 (1 study) 12 weeks	riboflavin: decreased from 15.1 (SD 7.1) to 4.2 (SD 2.6) valproate: decreased from 16.2 (SD 10.6) to 8.2 (SD 4.7) between-group difference NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2; single small study with unclear randomization, allocation concealment, blinding, incomplete outcome data and selective reporting Consistency: na Directness: -1; definition of migraine not well described; population age 15-55y Imprecision: ok
Severity of headaches (% of patients with reduction of severity)	90 (1 study) 12 weeks	riboflavin: 71.8% valproate: 76.2% between-group difference NS p=0.9	⨁⊖⊖⊖ **VERY LOW** Study quality: -2; single small study with unclear randomization, allocation concealment, blinding, incomplete outcome data and selective reporting Consistency: na

			Directness: -1; definition of migraine not well described; population age 15-55y Imprecision: ok
Adverse events	90 (1 study) 12 weeks	9 patients in total developed adverse events (including weight gain, dizziness and gastrointestinal problems) **SS more adverse events in valproate group** **P=0.005**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2; single small study with unclear randomization, allocation concealment, blinding, incomplete outcome data and selective reporting Consistency: na Directness: -1; definition of migraine not well described; population age 15-55y Imprecision: ok

Table 86

We found a single RCT comparing valproate to riboflavin for the prevention of migraine.

There are some methodological problems that severely limit our confidence in the estimate of the results: the single study was small and the included population was nog very well described. There was an unclear risk of bias pertaining to randomization, allocation concealment, blinding, incomplete outcome data and selective reporting.

There was **no difference** between valproate and riboflavin for **headache frequency** in **adults with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between valproate and riboflavin for **headache duration** in **adults with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between valproate and riboflavin for **headache severity** in **adults with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

In **adults with migraine**, **valproate** resulted in **more adverse events** compared to riboflavin.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

7.4.7 Lamotrigine vs placebo

Lamotrigine vs placebo for the prevention of migraine in adults
Bibliography: Cochrane Linde 2013b(256)

Including: Gupta 2007(241), Steiner 1997(257)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Headache frequency	190 (2 studies) 4 weeks – 3 months	MD -0.49 (-1.83 to 0.85) NS I^2 = 72%	⨁⊖⊖⊖ **VERY LOW** Study quality: -2; two small to very small RCTs, one with insufficient duration Consistency: -1 Directness: ok Imprecision: ok

Table 87

This systematic review by Linde 2013b(256) searched for all randomized or pseudo-randomized trials comparing an antiepileptic drug other than gabapentin, pregabalin, topiramate, or valproate to placebo, no intervention or active drug treatment for the prevention of migraine in adults.

It found 2 RCTs comparing lamotrigine to placebo.

There are some methodological problems that severely limit our confidence in the estimate of the results: both studies had a very small sample size and one of the RCTs had a very short duration (4 weeks treatment).

There was **no difference** between lamotrigine and placebo for **headache frequency** in **migraine in adults**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

7.5 Antidepressants

7.5.1 Amitriptyline vs placebo

Amitriptyline vs placebo for the prevention of migraine in adults			
Bibliography: SR Xu 2017{Xu, 2017 #131; Including Couch 1976{Couch, 1976 #380}, Gomersall 1973(258), Mathew 1981(259), Ziegler 1987(260) Additional RCT: Gonçalves 2016(261)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Migraine frequency	238 (4 studies) 4-26 week	**Std. MD -0.86 (-1.23 to -0.48)** **SS in favour of amitriptyline** **I^2 = 48%**	⨁⨁⊖⊖ **LOW** Study quality: -2; 3 very small studies, unclear randomization, allocation, blinding in one study Consistency: ok Directness: ok

			Imprecision: ok
	118 (1 study) 12 weeks s	placebo: MD -1.1 amitriptyline: MD -2.2 **MD -1.1 (95%CI -1.5 to -0.7)** **SS in favour of amitriptyline**	
Migraine frequency **At 24 weeks**	100 (2 studies) 26 weeks	**Std. MD -0.77 (-1.34 to -0.20)** **SS in favour of amitriptyline** **I^2 = 47%**	⊕⊕⊖⊖ **LOW** Study quality:-2; very small studies, unclear randomization, allocation, blinding Consistency: ok Directness: ok Imprecision: ok
Mean headache intensity (0-10) weeks 9-12	118 (1 study) 12 weeks	placebo: MD-1.8 amitriptyline: MD-3.5 **MD -1.3 (95%CI -1.7 to -0.9)** **SS in favour of amitriptyline**	⊕⊕⊖⊖ **LOW** Study quality: -2; single study, not ITT, unclear reason for dropouts Consistency: na Directness: ok Imprecision: ok
Mean attack duration (hours) weeks 9-12	118 (1 study) 12 weeks	placebo: MD -2.5 amitriptyline: MD -6.9 **MD -4.4 (95%CI -5.1 to -3.9)** **SS in favour of amitriptyline**	⊕⊕⊖⊖ **LOW** Study quality: -2; single study, not ITT, unclear reason for dropouts Consistency: na Directness: ok Imprecision: ok
number of analgesics used weeks 9-12	118 (1 study) 12 weeks	placebo: MD -0.6 amitriptyline: MD -1.4 **MD -1.0 (95%CI -1.5 to -0.5)** **SS in favour of amitriptyline**	⊕⊕⊖⊖ **LOW** Study quality: -2; single study, not ITT, unclear reason for dropouts Consistency: na Directness: ok Imprecision: ok
percentages of patients with greater than 50% reductions in migraine headache days	118 (1 study) 12 weeks	placebo: 20.4% amitriptyline: 39.1% **SS in favour of amitriptyline** **P<0.01**	⊕⊕⊖⊖ **LOW** Study quality: -2; single study, not ITT, unclear reason for dropouts Consistency: na Directness: ok Imprecision: ok
Adverse events	118 (1 study) 12 weeks	Placebo: 17/59 Amitriptyline: 46/59 **SS in favour of placebo** **p<0.03**	⊕⊕⊖⊖ **LOW** Study quality: -2; single study, not ITT, unclear reason for dropouts Consistency: na Directness: ok Imprecision: ok

Table 88

This systematic review and meta-analysis by Xu 2017 searched for all RCTs comparing tricyclic antidepressants versus placebo, and comparing amitriptyline versus other antidepressants, for the prevention of migraine in adults.

An additional RCT was found that compared amitriptyline, melatonin and placebo. The comparisons amitriptyline versus melatonin and melatonin versus placebo will be reported elsewhere in this document.

There are some methodological problems that limit our confidence in the estimate of the results: the most important of which were the lack of larger studies and unclear randomization, allocation concealment and blinding.

In **adults with migraine**, **amitriptyline** resulted in a **lower migraine frequency** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

7.5.2 Amitriptyline vs melatonin

Amitriptyline vs melatonin for the prevention of migraine in adults			
Bibliography: Gonçalves 2016(261)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Number of migraine headache days per month weeks 9-12	119 (1 study) 12 weeks	NS (no quantitative analysis reported)	⨁⨁⨀⨀ **LOW** Study quality: -2; single study, not ITT, unclear reason for dropouts, no quantitative analysis Consistency: na Directness: ok Imprecision: na
percentages of patients with greater than 50% reductions in migraine headache days	119 (1 study) 12 weeks	**SS in favour of melatonin P<0.05**	⨁⨁⨀⨀ **LOW** Study quality: -2; single study, not ITT, unclear reason for dropouts, no quantitative information Consistency: na Directness: ok Imprecision: ok
Adverse events	119 (1 study) 12 weeks	**SS in favour of melatonin p<0.03** (more adverse events with amitriptyline)	⨁⨁⨀⨀ **LOW** Study quality: -2; single study, not ITT, unclear reason for dropouts, no quantitative information Consistency: na Directness: ok Imprecision: ok

Table 89

In this RCT, amitriptyline, melatonin and placebo were compared for the prevention of migraine in adults. The duration of treatment was 12 weeks.

There are some methodological problems that limit our confidence in the estimate of the results: modified ITT, unclear reason for dropouts, and missing quantitative information for some outcomes.

There was **no difference** between amitriptyline and melatonin for **number of migraine headache days per month** in the **in adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **melatonin** resulted in **more participants with ≥50% reduction in migraine days** compared to amitriptyline.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **amitriptyline** resulted in **more adverse events** compared to melatonin.
GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

7.5.3 Venlafaxine

SR Wang 2020(262) searched for all RCTs comparing SNRI to placebo or other active drugs for the prevention of migraine in patients 16 years of age or older.

No RCTs met our inclusion criteria.

7.6 Gepants

7.6.1 Rimegepant vs placebo

Rimegepant vs placebo for the prevention of migraine in adults			
Bibliography: Dos Santos 2022{Dos Santos, 2022 #39 Including Croop 2021{Croop, 2021 #29}			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Change in the mean number of migraine days per month (PO) ***(weeks 9–12)***	695 (1 study) 12 weeks	Rimegepant: -4.3 (-4.8 to -3.9) Placebo: -3.5 (-4.0 to -3.0) **LS MD -0.8 (-1.5 to -0.2)** **SS in favour of rimegepant**	⨁⨁⨁⨀ **MODERATE** Study quality: -1; modified ITT, high risk of attrition bias Consistency: na Directness: ok Imprecision: ok
achievement of at least a 50% reduction from the in the mean number of moderate or severe migraine days (moderate or severe headache pain intensity) **per month** **(weeks 9–12)**	695 (1 study) 12 weeks	Rimegepant: 49% (44 to 54) Placebo: 41% (36 to 47) **LS MD 8% (0 to 15)** **p-value 0.044** **SS in favour of rimegepant**	⨁⨁⨁⨀ **MODERATE** Study quality: -1; modified ITT, high risk of attrition bias Consistency: na Directness: ok Imprecision: ok
change from the 4-week observation period in the mean number of	695 (1 study) 12 weeks	Rimegepant: -3.6 (-4.0 to -3.2) Placebo: -2.7 (-3.1 to -2.3)	⨁⨁⨁⨀ **MODERATE** Study quality: -1; modified ITT, high risk of attrition bias Consistency: na Directness: ok

migraine days per month (weeks 1–12)		**LS MD -0.8 (-1.3 to -0.3)** **SS in favour of rimegepant**	Imprecision: ok
mean number of rescue medication days per month **(week 9–12)**	695 (1 study) 12 weeks	Rimegepant: 3.7 (3.3 to 4.2) Placebo: 4.0 (3.5 to 4.4) LS MD -0.2 (-0.8 to 0.3) NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1; modified ITT, high risk of attrition bias Consistency: na Directness: ok Imprecision: ok
change from baseline in MSQ role function (restrictive domain score) at week 12	695 (1 study) 12 weeks	Rimegepant: 18.0 (15.5 to 20.6) Placebo: 14.6 (12.1 to 17.1) **LS MD 3.5 (0.2 to 6.7)** **SS in favour of rimegepant**	⨁⨁⨁⊖ **MODERATE** Study quality: -1; modified ITT, high risk of attrition bias Consistency: na Directness: ok Imprecision: ok
Change from baseline in MIDAS total score at week 12	695 (1 study) 12 weeks	Rimegepant: -11.8 (-15.4 to -8.2) Placebo: -11.7 (-15.3 to -8.1) LS MD -0.1 (-4.7 to 4.5) NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1; modified ITT, high risk of attrition bias Consistency: na Directness: ok Imprecision: ok
frequency of unique participants with: adverse events	741 (1 study) 12 weeks	Rimegepant: 133/370 (36%) Placebo: 133/371 (36%) No statistical testing	⨁⨁⨁⊖ **MODERATE** Study quality:-1;no independent assessment of adverse events Consistency: na Directness: ok Imprecision: na
frequency of unique participants with: serious adverse events	741 (1 study) 12 weeks	Rimegepant: 3/370 (1%) Placebo: 4/371 (1%) No statistical testing	⨁⨁⨁⊖ **MODERATE** Study quality: -1;no independent assessment of adverse events Consistency: na Directness: ok Imprecision: na

Table 90

Dos Santos 2022(263) performed a systematic search for trials with rimegepant. One completed RCT (Croop 2021), comparing rimegepant to placebo, was found.

There *are some methodological problems that limit our confidence in the estimate of the results. A modified intention-to-treat was utilized for the efficacy analysis, which resulted in only 695 out of 747 randomized participants to be included in the efficacy analysis. Additionally, the adverse events were not independently assessed.*

In **adults with migraine**, **rimegepant** resulted in **fewer migraine days per month** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate

In **adults with migraine**, **rimegepant** resulted in **a greater percentage achieving at least a 50% reduction from the mean number of moderate or severe migraine days per month** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate

There was **no difference** between rimegepant and placebo for **mean number of rescue medication days per month** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate

In **adults with migraine**, **rimegepant** resulted in **a greater change in MSQ role function (restrictive domain score)** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate

There was **no difference** between rimegepant and placebo for **change in MIDAS total score** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate

There was **no difference** between rimegepant and placebo for **unique participants with adverse events** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate

There was **no difference** between rimegepant and placebo for **unique participants with serious adverse events** in **adults with migraine**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate

7.6.2 Atogepant 10 mg vs placebo

Atogepant vs placebo for the prevention of migraine in adults			
Bibliography: SR Tao 2022 (264) Including Allergan 2021(265), Aliani 2021(266); Goadsby 2020(267) Additional RCT: Lipton 2022(2)			
Outcomes	**N° of participants (studies)** **Follow up**	**Results**	**Quality of the evidence (GRADE)**

mean monthly migraine days (PO)	698 (2 studies) 12 weeks	**Std MD -0.41 (-0.56 to -0.25)** **SS in favour of atogepant** **I^2 = 0%**	⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
monthly headache days	698 (2 studies) 12 weeks	**Std MD -0.43 (-0.59 to -0.28)** **SS in favour of atogepant** **I^2 = 0%**	⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
acute medication use days per month	698 (2 studies) 12 weeks	**Std MD -0.45 (-0.61 to -0.30)** **SS in favour of atogepant** **I^2 = 0%**	⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
≥50% reduction in monthly migraine days	698 (2 studies) 12 weeks	Atogepant 10 mg: 172/306 Placebo: 134/392 **RR 1.66 (1.23 to 2.23)** **SS in favour of atogepant** **I^2 = 65%**	⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) **RFR-domain** *MID 3.2 points*	428 (1 study) 12 weeks	**LSMD= 9.90 (5.45 to 14.36)** **SS in favour of atogepant**	⨁⨁⨁⊖ **MODERATE** Study quality:-1 modified ITT, 11.5% dropout; unclear risk of attrition bias Consistency: na Directness: ok Imprecision:ok
Total adverse events	722 (2 studies) 12 weeks	Atogepant 10 mg: 178/314 Placebo: 218/408 RR 1.11 (0.78 to 1.56) NS I^2 = 85%	⨁⨁⊖⊖ **LOW** Study quality:-1 unclear blinding, unclear risk of selective reporting in one study Consistency: -1 Directness: ok Imprecision: ok

Table 91

This systematic review by Tao 2022 (264) searched for all RCTs comparing atogepant to placebo for the prevention of migraine in adults. Three RCTs that met our inclusion criteria were found. An additional RCT was found, which reported prespecified secondary efficacy outcomes of one of the three previously included RCTs.

Generally the RCTs were methodologically sound, though some outcomes (like adverse events) were less well reported than others. For these outcomes, our confidence in the results is lowered.

In **adults with migraine**, **atogepant 10 mg** resulted in **fewer monthly migraine days** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **atogepant 10 mg** resulted in **fewer monthly headache days** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **atogepant 10 mg** resulted in **fewer acute medication use days** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **atogepant 10 mg** resulted in **more participants with ≥50% reduction in monthly migraine days** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **atogepant 10 mg** resulted in **a higher score on the migraine-specific questionnaire (RFR-domain)** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between **atogepant 10 mg** and placebo for **total adverse events** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

7.6.3 Atogepant 30 mg vs placebo

Atogepant vs placebo for the prevention of migraine in adults			
Bibliography: SR Tao 2022 (264) Including Allergan 2021(265), Aliani 2021(266); Goadsby 2020(267)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
mean monthly migraine days (PO)	797 (2 studies) 12 weeks	**Std MD -0.41 (-0.55 to -0.27)** **SS in favour of atogepant** **I^2 = 0%**	⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
monthly headache days	797 (2 studies) 12 weeks	**Std MD -0.42 (-0.60 to -0.24)** **SS in favour of atogepant** **I^2 = 38%**	⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
acute medication use days per month	797 (2 studies) 12 weeks	**Std MD -0.49 (-0.63 to -0.35)** **SS in favour of atogepant** **I^2 = 0%**	⨁⨁⨁⨁ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok
≥50% reduction in monthly migraine days	797 (2 studies) 12 weeks	Atogepant 30 mg: 228/405 Placebo:134/392 **RR 1.63 (1.07 to 2.49)** **SS in favour of atogepant** **I^2 = 85%**	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency:-1 Directness: ok Imprecision: ok
Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) **RFR-domain MID 3.2 points**	437 (1 study) 12 weeks	**LSMD= 10.08 (5.71 to 14.46)** **SS in favour of atogepant**	⨁⨁⨁⊖ **MODERATE** Study quality:-1 modified ITT, 11.5% dropout; unclear risk of attrition bias Consistency: na Directness: ok Imprecision:ok
Total adverse events	819 (2 studies) 12 weeks	Atogepant 30 mg: 234/411 Placebo:218/408 RR 1.08 (0.79 to 1.48) NS I^2 = 85%	⨁⨁⊖⊖ **LOW** Study quality: -1 unclear blinding, unclear risk of selective reporting in one study Consistency: -1 Directness: ok Imprecision: ok

Table 92

This systematic review by Tao 2022 (264) searched for all RCTs comparing atogepant to placebo for the prevention of migraine in adults. Three RCTs that met our inclusion criteria were found. An additional RCT was found, which reported prespecified secondary efficacy outcomes of one of the three previously included RCTs.

Generally the RCTs were methodologically sound, though some outcomes (like adverse events) were less well reported than others. For these outcomes, our confidence in the results is lowered.

In **adults with migraine**, **atogepant 30 mg** resulted in **fewer monthly migraine days** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **atogepant 30 mg** resulted in **fewer monthly headachedays** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **atogepant 30 mg** resulted in **fewer acute medication use days** compared to placebo.
GRADE: HIGH quality of evidence
Our confidence that the results of the studies reflect the true effect is high.

In **adults with migraine**, **atogepant 30 mg** resulted in **more participants with ≥50% reduction in monthly migraine days** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **atogepant 30 mg** resulted in **a higher score on the migraine-specific questionnaire (RFR-domain)** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between **atogepant 30 mg** and placebo for **total adverse events** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

7.6.4 Atogepant 60 mg vs placebo

Atogepant vs placebo for the prevention of migraine in adults			
Bibliography: SR Tao 2022 (264) Including Allergan 2021(265), Aliani 2021(266); Goadsby 2020(267)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
mean monthly migraine days (PO)	791 (2 studies) 12 weeks	**Std MD -0.42 (-0.73 to -0.11)** **SS in favour of atogepant** **I^2 = 79%**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency:-1 Directness: ok Imprecision: ok
monthly headache days	791 (2 studies) 12 weeks	**Std MD -0.41 (-0.73 to -0.10)** **SS in favour of atogepant** **I^2 = 80%**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency:-1 Directness: ok Imprecision: ok
acute medication use days per month	791 (2 studies) 12 weeks	**Std MD -0.46 (-0.60 to -0.32)** **SS in favour of atogepant** **I^2 = 80%**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency:-1 Directness: ok Imprecision: ok
≥50% reduction in monthly migraine days	791 (2 studies) 12 weeks	Atogepant 60 mg: 227/399 Placebo: 134/392 **RR 1.64 (1.01 to 2.66)** **SS in favour of atogepant** **I^2 = 89%**	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency:-1 Directness: ok Imprecision: ok
Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) **RFR-domain** **MID 3.2 points**	436 (1 study) 12 weeks	**LSMD = 10.80 (6.42 to 15.18)** **SS in favour of atogepant**	⨁⨁⨁⨀ **MODERATE** Study quality:-1 modified ITT, 11.5% dropout; unclear risk of attrition bias Consistency: na Directness: ok Imprecision:ok
Total adverse events	1564 (3 studies) 12-52 weeks	Atogepant 60 mg: 454/960 Placebo: 316/604 RR 0.96 (0.79 to 1.17) NS I^2 = 73%	⨁⨁⨀⨀ **LOW** Study quality: -1 unclear blinding, unclear risk of selective reporting in one study Consistency:-1 Directness: ok Imprecision: ok

Table 93

This systematic review by Tao 2022 (264) searched for all RCTs comparing atogepant to placebo for the prevention of migraine in adults. Three RCTs that met our inclusion criteria were found. An

additional RCT was found, which reported prespecified secondary efficacy outcomes of one of the three previously included RCTs.

Generally the RCTs were methodologically sound, though some outcomes (like adverse events) were less well reported than others. For these outcomes, our confidence in the results is lowered.

In **adults with migraine**, **atogepant 60 mg** resulted in **fewer monthly migraine days** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **atogepant 60 mg** resulted in **fewer monthly headachedays** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **atogepant 60 mg** resulted in **fewer acute medication use days** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **atogepant 60 mg** resulted in **more participants with ≥50% reduction in monthly migraine days** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **adults with migraine**, **atogepant 60 mg** resulted in **a higher score on the migraine-specific questionnaire (RFR-domain)** compared to placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between **atogepant 60 mg** and placebo for **total adverse events** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

7.7 Supplements

7.7.1 Magnesium vs placebo

Magnesium vs placebo for the prevention of migraine in adults			
Bibliography: SR Okoli 2019(268) Including Tarighat Esfanjani 2012(269), Mahdavi 2009(270), Koseoglu 2008(271), Peikert 1996(272)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Migraine frequency	266 (4 studies) 12 weeks	**MD -2.57 (-4.2 to -0.94)** **SS in favour of magnesium** **I^2 = 88%**	⨁⨀⨀⨀ **VERY LOW** Study quality: -2 unclear to high risk of bias related to allocation concealment, blinding, incomplete outcome data in most studies Consistency: -1 Directness: ok Imprecision: ok
Migraine duration	81 (1 study) 12 weeks	MD -0.21 (-0.70 to 0.28) NS	⨁⨁⨀⨀ **LOW** Study quality: -2 single study with high risk of bias related to allocation concealment and blinding of assessors. Unclear blinding of participant and incomplete outcome data Consistency: na Directness: ok Imprecision: ok
Migraine severity	226 (3 studies) 12 weeks	RoM −0.17 (−0.36 to 0.02) NS I^2 = 48%	⨁⨁⨀⨀ **LOW** Study quality: : -2 unclear to high risk of bias related to allocation concealment, blinding, incomplete outcome Consistency: ok Directness: ok Imprecision: ok
Days with migraine	226 (3 studies) 12 weeks	**MD -3.00 (-5.02 to -0.98)** **SS in favour of magnesium** **I^2 = 87%**	⨁⨀⨀⨀ **VERY LOW** Study quality: : -2 unclear to high risk of bias related to allocation concealment, blinding, incomplete outcome Consistency: -1 Directness:ok Imprecision: ok

Table 94

This systematic review by SR Okoli 2019(268) searched for all parallel and crossover RCTs that compared vitamins and mineral supplements to placebo or no treatment, in the prevention of migraine in adult and pediatric patients.

It found 4 RCTs comparing magnesium to placebo in adults. All studies had a treatment duration of 12 weeks.

There are some methodological problems that limit our confidence in the estimate of the results: the most important of which were a number of studies with an unclear to high risk of bias related to allocation concealment, blinding, and incomplete outcome data. There was a high inconsistency for some of the outcomes.

In **adults with migraine**, **magnesium** resulted in **a lower migraine frequency** compared to placebo.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between magnesium and placebo for **migraine duration** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between magnesium and placebo for **migraine severity** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **magnesium** resulted in **fewer days with migraine** compared to placebo.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

7.7.2 Coenzyme Q10 vs placebo

Coenzyme Q10 vs placebo for the prevention of migraine in adults			
Bibliography: SR Okoli 2019(268) Including Khorvash 2016(273), Sandor 2005(274)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Migraine frequency	97 (2 studies) 8-12 weeks	MD −0.44 (95% CI −2.14 to 1.26) NS I^2 = 53%	⨁⊖⊖⊖ **VERY LOW** Study quality: -2; included studies did not meet our inclusion criteria for sample size, duration Consistency: ok Directness: ok Imprecision:-1
Migraine duration	97 (2 studies) 8-12 weeks	MD −1.97 (95% CI −4.82 to 0.87) NS I^2 =0%	⨁⊖⊖⊖ **VERY LOW** Study quality: -2; included studies did not meet our inclusion criteria for sample size, duration Consistency: ok Directness: ok Imprecision:-1
Migraine severity	97 (2 studies) 8-12 weeks	RoM −0.05 (95% CI −0.20 to 0.11 NS I^2 = 0%	⨁⨁⊖⊖ **LOW** Study quality: -2; included studies did not meet our inclusion criteria for sample size, duration Consistency: ok Directness: ok Imprecision: ok

Table 95

This systematic review by SR Okoli 2019(268) searched for all parallel and crossover RCTs that compared vitamins and mineral supplements to placebo or no treatment, in the prevention of migraine in adult and pediatric patients.

It found 2 RCTs comparing coenzyme Q10 to placebo in adults.

Both studies did not meet our inclusion criteria for sample size individually. One RCT did not meet our inclusion criteria for duration. This limits our confidence in the estimate of the results.

There was **no difference** between coenzyme Q10 and placebo for **migraine frequency** in **adults with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between coenzyme Q10 and placebo for **migraine duration** in **adults with migraine**.

GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between coenzyme Q10 and placebo for **migraine severity** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

7.7.3 Riboflavin vs placebo

SR Okoli 2019 found only one RCT in adults comparing riboflavin to placebo; however, it did not meet our inclusion criteria (sample size).

7.7.4 Folic acid (vitamin B9) vs placebo

SR Liampas 2020b(275) searched for observational and interventional studies evaluating vitamin B6, folic acid (vitamin B9) or vitamin B12 in migraine and other primary headache disorders. None of the found studies met our inclusion criteria.

7.7.5 Melatonin vs placebo

Melatonin vs placebo for the prevention of migraine in adults			
Bibliography: SR Liampas 2020a(276) RCT Gonçalves 2016(261)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Number of migraine days per month Weeks 9-12	119 (1 study) 12 weeks	placebo: MD -1.1 melatonin: MD -2.7 Melatonin vs placebo **MD -1.6 (95%CI -2.4 to -0.9)** **SS in favour of melatonin**	⨁⨁⊖⊖ **LOW** Study quality: -2; single study, not ITT, unclear reason for dropouts Consistency: na Directness: ok Imprecision: ok
Mean headache intensity (0-10) weeks 9-12	119 (1 study) 12 weeks	placebo: MD-1.8 melatonin: MD -3.5 Melatonin vs placebo **MD -1.2 (95%CI -1.6 to -0.8)** **SS in favour of melatonin**	⨁⨁⊖⊖ **LOW** Study quality: -1; single study, not ITT, unclear reason for dropouts Consistency: na Directness: ok Imprecision: ok
Mean attack duration (hours) weeks 9-12	119 (1 study) 12 weeks	placebo: MD -2.5 melatonin: MD -7.2 Melatonin vs placebo **MD -4.8 (95%CI -5.7 to -3.9)** **SS in favour of melatonin**	⨁⨁⊖⊖ **LOW** Study quality: -1; single study, not ITT, unclear reason for dropouts Consistency: na Directness: ok Imprecision: ok
number of analgesics used	119 (1 study)	placebo: MD -0.6 melatonin: MD -1.6	⨁⨁⊖⊖ **LOW**

weeks 9-12	12 weeks	Melatonin vs placebo **MD -1.0 (95%CI -1.4 to -0.6)** **SS in favour of melatonin**	Study quality: -1; single study, not ITT, unclear reason for dropouts Consistency: na Directness: ok Imprecision: ok
percentages of patients with greater than 50% reductions in migraine headache days	119 (1 study) 12 weeks	placebo: 20.4% melatonin: 54.4% Melatonin vs placebo **SS in favour of melatonin** **P<0.01**	⊕⊕⊖⊖ **LOW** Study quality: -1; single study, not ITT, unclear reason for dropouts Consistency: na Directness: ok Imprecision: ok
Adverse events	119 (1 study) 12 weeks	Placebo: 17/59 Melatonin: 16/60 Melatonin vs placebo NS	⊕⊕⊖⊖ **LOW** Study quality: -1; single study, not ITT, unclear reason for dropouts Consistency: na Directness: ok Imprecision: ok

Table 96

We found a systematic review (Liampas 2020a(276)) that searched for RCTs or non-randomized studies with at least 1 group of participants with migraine and receiving exogenous melatonin. None of the RCTs comparing melatonin versus placebo met our inclusion criteria, except for one RCT comparing amitriptyline, melatonin and placebo. We reported this RCT individually (Gonçalves 2016(261)).

In this RCT, amitriptyline, melatonin and placebo were compared for the prevention of migraine in adults. The duration of treatment was 12 weeks.

There are some methodological problems that limit our confidence in the estimate of the results: modified ITT, unclear reason for dropouts, single study with a limited number of participants.

In **adults with migraine**, **melatonin** resulted in **fewer migraine days per month** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **melatonin** resulted in **a lower mean headache intensity** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **melatonin** resulted in **a lower mean attack duration** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **melatonin** resulted in **a lower number of analgesic used** compared to placebo.

GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **adults with migraine**, **melatonin** resulted in **a greater percentage of patients with greater than 50% reductions in migraine headache days** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between melatonin and placebo for **adverse effects** in **adults with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

8 Acute treatment of migraine attacks in children and adolescents: summary and conclusions from the literature review

8.1 Paracetamol vs placebo in children

Paracetamol vs placebo for the acute treatment of migraine in children			
Bibliography: SR Richer 2016(277) Including Hämäläinen 1997(278)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain-free at 2h	88 (1 study)	RR 1.40, 95% CI 0.75 to 2.58 NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 single small study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: -1
Headache relief at 2h (defined as a decrease in headache intensity from severe or moderate to mild or none at two hours prior to the use of rescue medication.)	88 (1 study)	No quantitative data provided NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 single small study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: -1 unable to assess
Rescue medication (% of participants taking rescue medication at two hours or earlier to a maximum of six hours after the test drug.)	88 (1 study)	No quantitative data provided NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 single small study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: -1 unable to assess
Headache recurrence (participants who were initially pain-free or achieved the study PO of headache relief within 2 hours without the use of rescue medication but who experienced recurrence of any headache from 2 to 48 hours.)	88 (1 study)	No quantitative data provided NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 single small study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: -1 unable to assess

Adverse events (any)	88 (1 study)	No quantitative data provided NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 single small study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: -1 unable to assess

Table 97

This systematic review by Richer 2016 searched for all placebo-controlled RCTs of pharmacological interventions for the acute treatment of migraine in children and adolescents (17 years old or less) in the outpatient setting.

Only one RCT comparing paracetamol to placebo, and meeting our inclusion criteria was found. Authors defined children as under 12 years of age and adolescents as 12 to 17 years of age. In the single study participants were 4 to 15.8 years. Investigators did not report results for children and adolescents separately. However, the mean age of inclusion was 10.7 years, so authors of the MA deemed the study to be predominantly in children.

There are some methodological problems that severely limit our confidence in the estimate of the results: a small single study with unclear risk of bias pertaining to randomization and allocation concealment. In the study multiple deviations from the original protocol were described.

There was **no difference** between paracetamol and placebo for **pain freedom at 2h** in **children with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between paracetamol and placebo for **headache relief at 2h** in **children with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between paracetamol and placebo for **use of rescue medication** in **children with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between paracetamol and placebo for **headache recurrence** in **children with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between paracetamol and placebo for **adverse events** in **children with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

8.2 Ibuprofen vs placebo in children

Ibuprofen vs placebo for the acute treatment of migraine in children			
Bibliography: SR Richer 2016(277) Including Hämäläinen 1997(278), Lewis 2002(279)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain-free at 2h	125 (2 studies)	Ibuprofen: 32/65 Placebo: 16/60 **RR : 1.87, 95% CI 1.15 to 3.04** **p: 0.01** **SS in favour of ibuprofen** I^2: 0%	⨁⨁⊖⊖ **LOW** Study quality: -1 unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: -1 low n of events
Headache relief at 2h (defined as a decrease in headache intensity from severe or moderate to mild or none at two hours prior to the use of rescue medication.)	125 (2 studies)	Ibuprofen: 48/65 Placebo: 29/60 **RR : 1.49, 95% CI 1.11 to 2.00** **p: 0.008** **SS in favour of ibuprofen** I^2: 0%	⨁⨁⊖⊖ **LOW** Study quality: -1 unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: -1 low n of events
Rescue medication (% of participants taking rescue medication at two hours or earlier to a maximum of six hours after the test drug.)	164 (2 studies)	Ibuprofen: 5/85 Placebo: 24/79 RR : 0.19, 95% CI 0.02 to 1.56 p: 0.12 NS I^2: 72%	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 unclear randomization and allocation concealment Consistency: -1 Directness: ok Imprecision: -1
Adverse events (any)	80 (1 study)	Ibuprofen: 4/40 Placebo: 4/40 RD: 0.00, 95% CI -0.13 to 0.13 p: 1.00 NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 single study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: -1 low n of event

Table 98

This systematic review by Richer 2016 searched for all placebo-controlled RCTs of pharmacological interventions for the acute treatment of migraine in children and adolescents (17 years old or less) in the outpatient setting.

2 RCTs comparing ibuprofen to placebo, and meeting our inclusion criteria were found.

Authors defined children as under 12 years of age and adolescents as 12 to 17 years of age. In 1 RCT participants were 4 to 15.8 years. Investigators did not report results for children and adolescents separately. However, the mean age of inclusion was 10.7 years, so authors of the MA deemed the study to be predominantly in children. The other RCT included only 6 to 12 year-olds children with a mean age of 9 years.

There are some methodological problems that limit our confidence in the estimate of the results: two small studies with unclear risk of bias pertaining to randomization and allocation concealment. In one study, multiple deviations from the original protocol were described.

In **children with migraine**, **ibuprofen** resulted in **more pain freedom at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **children with migraine**, **ibuprofen** resulted in **more headache relief at 2h** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between ibuprofen and placebo for **use of rescue medication** in **children with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between ibuprofen and placebo for **adverse events** in **children with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

8.3 Ibuprofen vs placebo in adolescents

This systematic review by Richer 2016 searched for all placebo-controlled RCTs of pharmacological interventions for the acute treatment of migraine in children and adolescents (17 years old or less) in the outpatient setting.
One study was included in the MA, evaluating Zolmitriptan (2.5 mg, PO) vs ibuprofen vs placebo in 32 children and adolescents. No raw data were reported and the study did not meet our inclusion criteria (sample size < 40 per group). We therefore excluded it the present document.

8.4 Ibuprofen vs paracetamol in children and adolescents

Ibuprofen vs paracetamol for the acute treatment of migraine in children and adolescents			
Bibliography: SR Jeric 2018(280) Including Hämäläinen 1997(278)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain-free at 2h	81 (1 study)	Ibuprofen: 24/40 Paracetamol: 16/41 OR: 2.34, 95% CI 0.96 to 5.71 p: 0.06 NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 single small study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: -1
Headache relief at 2h (Reduction in severe or moderate headache (grades 3 on a scale of 1 to 6) by two grades)	81 (1 study)	Ibuprofen: 27/40 Paracetamol: 22/41 OR 1.79, 95% CI 0.73 to 4.42 p: 0.20 NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 single small study with unclear randomization and allocation concealment Consistency: na Directness: ok Imprecision: -1
Adverse events (any)	81 (1 study)	No events Not estimable	Insufficient data

Table 99

This systematic review by Jeric 2018 searched for all RCTs analyzing ibuprofen and/or paracetamol as a pharmacological intervention for the treatment of acute migraine attacks in children and adolescents <18 years.

Only one RCT, comparing ibuprofen to paracetamol, and meeting our inclusion criteria was found. In this RCT participants were 4 to 15.8 years. Investigators did not report results for children and adolescents separately. However, the mean age of inclusion was 10.7 years, so authors considered the study population to be of mixed age group.

There are some methodological problems that severely limit our confidence in the estimate of the results: a small single study with unclear risk of bias pertaining to randomization and allocation concealment. In the study multiple deviations from the original protocol were described.

There was **no difference** between ibuprofen and paracetamol for **pain freedom at 2h** in **children and adolescents with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between ibuprofen and paracetamol for **headache relief at 2h** in **children and adolescents with migraine**.

GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

We have **insufficient data** to compare the risk of **adverse events** in ibuprofen versus paracetamol in children with migraine.

9 Prophylaxis of migraine in children and adolescents: summary and conclusions from the literature review

9.1 Magnesium versus placebo in children and adolescents

Magnesium versus placebo for the prevention of migraine in children and adolescents			
Bibliography: SR Shamliyan 2013(281) Including Wang 2003(282)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Migraine frequency	118 (1 study) 16 weeks	No quantative data provided NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2; single small RCT with inadequate randomization Consistency: na Directness: ok Imprecision: -1 not possible to assess, n
Severity of migraine attack	118 (1 study) 16 weeks	No quantative data provided **SS in favour of magnesium**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2; single small RCT with inadequate randomization Consistency: na Directness: ok Imprecision: -1 not possible to assess, n
Treatment discontinuation due to adverse events	118 (1 study) 16 weeks	Magnesium: 3/58 Placebo: 1/60 RR 95% CI: 3.1 (0.3 to 29.0) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2; single small RCT with inadequate randomization Consistency: na Directness: ok Imprecision: -1

Table 100

This systematic review by Shamliyan searched for all studies that examined preventive pharmacologic treatments for migraine in community-dwelling children.

Only one RCT comparing magnesium to placebo was found. Eligible age between 3 and 17.

There are some methodological problems that limit our confidence in the estimate of the results: there was only a single small study with inadequate randomization.

There was **no difference** between magnesium and placebo for **migraine frequency** in **children with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

In **children with migraine**, **magnesium** resulted in **a lower severity of migraine attacks** compared to placebo.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between magnesium and placebo for **treatment discontinuation due to adverse events** in **children with migraine**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

9.2 Riboflavin versus placebo in children and adolescents

Riboflavin versus placebo for the prevention of migraine in children and adolescents			
Bibliography: SR Locher 2020(283) Including Bruin 2010(284), MacLennan 2008(285), Talebian 2018(286)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Efficacy	107 (3 studies) 12-16 weeks	SMD (95% CI): 0.19 (–0.39 to 0.78) NS	⨁⨁⨀⨀ **LOW** Study quality: -1; 3 very small RCTs (inidivually not meeting minimum sample size) Consistency: ok Directness: ok Imprecision: -1
Acceptability	107 (3 studies) 12-16 weeks	RR (95% CI): 0.49 (0.12 to 1.97) NS	⨁⨁⨀⨀ **LOW** Study quality: -1; 3 very small RCTs (inidivually not meeting minimum sample size) Consistency: ok Directness: ok Imprecision: -1

Table 101

This systematic review by Locher searched for all RCTs of prophylactic pharmacologic treatments for children and adolescents younger than 18 years.

Three RCTs were found comparing riboflavin to placebo.

There are some methodological problems that limit our confidence in the estimate of the results: the three included studies are very small in size and do not meet our inclusion criteria for sample size individually.

There was **no difference** between riboflavin and placebo for **efficacy in preventing migraine** in **children with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between riboflavin and placebo for **acceptability** in **children with migraine**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

10 Cardiovascular safety aspects in older migraine patients: summary and conclusions from the literature review

We searched for RCTs or large cohort studies evaluating cardiovascular adverse events of migraine medication (acute or preventive) in older people (>65 y) with migraine.
We found 2 retrospective cohort studies, McKinley 2021(287) and Li 2022(288), both using data from a US health insurance database.

McKinley 2021 evaluated the risk of ischemic stroke and of CHD events (myocardial infarction hospitalization or coronary revascularization) in older migraine patients taking various drugs for migraine treatment versus matched non-migraine patients (not taking these drugs).

Li 2022 evaluated the risk of acute myocardial infarction (AMI) in triptan-treated migraine patients versus prescription NSAID-treated migraine patients and versus untreated migraine patients. A subpopulation of patients >65 years was analyzed.

In both studies there is a high risk of selection bias: it is for example possible that triptans, being contraindicated in people with cardiovascular risk factors, are being prescribed in patients with a perceived lower risk of cardiovascular events. There is also a risk of misclassification, as over-the-counter NSAID are not recorded and it is possible that patients taking NSAID are analyzed as not taking NSAID. Moreover, many migraine medications included in the McKinley 2021(287) have indications for other diseases. It is possible that patients with a history of migraine were taking these medications to treat other conditions with a higher cardiovascular risk (for example, antihypertensive medication).

We rate these results to have a VERY LOW quality of evidence as it is observational data with a high risk of bias.

There were SS **fewer CHD events** among migraine patients **without CVD** and taking a **triptan**, versus patients without migraine.

There were SS **fewer CHD events** among migraine patients **with CVD** and taking a **triptan**, versus patients without migraine

There were SS **more ischemic strokes** among migraine patients **with CVD** and taking an **NSAID**, versus patients without migraine.

There were SS **more ischemic strokes** among migraine patients **with CVD** and taking a **migraine-preventive antiepileptic** agent, versus patients without migraine.

There were SS **more ischemic strokes** among migraine patients **without CVD** and taking a **migraine-preventive antihypertensive agent**, versus patients without migraine.

There were SS **more ischemic strokes** among migraine patients **with CVD** and taking a **migraine-preventive antihypertensive agent**, versus patients without migraine.

There were SS **more ischemic strokes** among migraine patients **with CVD** and taking a **migraine-preventive antidepressant**, versus patients without migraine.

There was **no difference** between triptans and untreated migraine; or between triptans and NSAID for AMI.

11 Additional safety information from other sources

11.1 Paracetamol

11.1.1 Contra-indications

- Severe renal failure. (289)
- Severe liver failure. (289)

11.1.2 Adverse events

- Adverse events of paracetamol are rare and usually mild. (290)
- Little or no irritation of the gastro-intestinal tract. (289)
- Because of the initially often asymptomatic course of an intoxication with paracetamol, any suspicion of overdose requires urgent hospitalization. In adults, problems are to be expected from an intake of 10 g. If risk factors exist, toxicity can already be seen from lower amounts, even with chronic use of the usual maximum daily dose (4 g) (see section “Special precautions”). In children, hepatotoxicity can occur from 150 mg / kg. If measurement of the paracetamol plasma concentration shows that there is a real risk of hepatotoxicity, intravenous acetylcysteine is given as soon as possible as a preventative measure. (289)
- There are no arguments for a causal link between the use of paracetamol at an early age and the risk of asthma and wheezing, in contrast to what was suggested in observational studies. (289)
    - A recently published randomized double-blind study now provides good evidence that paracetamol is as safe as ibuprofen in terms of asthma control, at least in children with mild persistent asthma who need analgesic due to pain or fever. Although the focus of this study was the development of asthma with paracetamol, this study further weakens the suggestion that paracetamol negatively affects wheezing or asthma in young.(291)
    - A systematic review of observational studies on the adverse events of paracetamol was published in 2015. The authors of the study report a dose-dependent increase in total mortality and serious cardiovascular, gastrointestinal and renal adverse events for paracetamol. However, a critical interpretation of the results does not allow to conclude that there may be a causal link between paracetamol and the various adverse events described. (292)
- Medication-induced headache: prolonged, too frequent, high-dose use of analgesics (e.g. paracetamol, acetylsalicylic acid, or combinations with caffeine) due to headache (migraine-like or otherwise) can lead to an increase in the frequency of headache complaints, almost to the point of daily complaints.(293) This is a frequent cause of chronic headache. (289) In patients with analgesic overuse headaches, attempts should be made to discontinue the responsible drug. (293)
- Rare:
    - Hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency. (289)
    - Haematological reactions and serious skin reactions have been reported. (290)
    - Hypersensitivity has also rarely been reported. (290)
- In case of overdose: hepatotoxicicy with jaundice and sometimes fatal necrosis, usually only after 24 to 48 hours after the ingestion of large doses. (289)
  Acute oral overdosage with paracetamol, whether accidental or deliberate, is relatively common and can be extremely serious because of the narrow margin between therapeutic and toxic doses. Paracetamol-induced hepatotoxicity is a major cause of acute liver failure in

western countries. Hepatotoxicity may occur after ingestion of more than 150 mg/kg, or rarely, as little as 75 mg/kg, of paracetamol within a 24-hour period. (290)
Early signs of overdosage (very commonly nausea and vomiting although they may also include lethargy and sweating) usually settle within 24 hours. Abdominal pain may be the first indication of liver damage, which is not usually apparent for 24 to 48 hours and sometimes may be delayed for up to 4 to 6 days after ingestion. Liver damage is generally at a maximum 72 to 96 hours after ingestion. Hepatic failure, encephalopathy, coma, and death may result. Complications of hepatic failure include acidosis, cerebral oedema, haemorrhage, hypoglycaemia, hypotension, infection, and renal failure. (290)
Acute renal failure with acute tubular necrosis may develop, even in the absence of severe liver damage. Other non-hepatic symptoms that have been reported following paracetamol overdosage include myocardial abnormalities and pancreatitis. (290)

11.1.3 Interactions

- The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes. (290)
- The absorption of paracetamol may be accelerated by drugs such as metoclopramide. (290)
- Excretion may be affected and plasma concentrations altered when given with probenecid. (290)

11.1.4 Special precautions

- The threshold for hepatic toxicity has been lowered in the following risk patients: children, very lean adults (<50 kg), elderly people and patients with alcohol dependence, chronically malnourished patients and patients with hepatic or renal insufficiency.(289)
- In the event of liver disease (liver failure, chronic alcohol consumption), the maximum daily dose should be limited to 3 g per day (up to 2 g in patients <50 kg). Paracetamol should be avoided in people with acute hepatic impairment. (289)
- In the event of severe renal insufficiency, the dose must be reduced and a longer dosing interval of 6 to 8 hours must be respected. (289)
- It is important to ask patients with pain about the amount of paracetamol already taken, also in over the counter (OTC) and in both mono and combination preparations. (289)
- Patients with toothache appear to be an important risk group for accidental paracetamol intoxication. (289)
- The sodium content in effervescent preparations (tablets, powders, granules) can cause problems for patients on a strict low-salt diet. (289)

In order to prevent the development of drug-induced headaches: it is important to limit the use of analgesics and antimigraine drugs to a maximum of 6 to 8 days per month or 2 days per week in patients with headaches, particularly migraine, but also other forms of headache, and to consider prophylactic treatment in good time. (293)

Analgesics, ergot derivatives and triptans can be stopped abruptly, but the temporary worsening of headaches and the appearance of withdrawal symptoms such as nausea, vomiting, hypotension, tachycardia, anxiety and nervousness must be taken into account. These are likely to be less long-lasting when a triptan is discontinued. Transitional treatment may be initiated for a short period: e.g. with antiemetics, NSAIDs or corticosteroids. Sometimes hospitalisation is necessary. (293)

Remarks concerning administration route:

- The absorption of paracetamol from suppositories varies; oral administration is preferable, also in infants. (289)
- Orodispersible tablets offer no advantage in terms of speed of action or effectiveness. (289)
- Absorption may be poor due to gastric stasis which is commonly present in migraine. For this reason dispersible and effervescent preparations and compound preparations containing drugs such as metoclopramide which relieve gastric stasis have been advocated. (290)

11.1.5 Specific populations

11.1.5.1 Pregnancy and lactation

- Paracetamol appears to be safe during pregnancy and while breastfeeding. (289)

11.1.5.2 Children and adolescents

- The risk of severe toxicity after acute paracetamol overdose appears to be less in children than in adults at comparable doses; however, chronic use of supratherapeutic doses in children has resulted in unintentional overdoses and severe hepatotoxicity. (290)

11.2 Acetylsalicylic acid

11.2.1 Contra-indications

- Active bleeding and increased risk of bleeding. (289)
- (History of) peptic ulcer disease. (289)
- Children under 12 years of age with viral infections (especially influenza and chicken pox). (289)
- Severe renal insufficiency, severe hepatic insufficiency (at high doses). (289)

11.2.2 Adverse events

- After oral administration, local irritation of the gastric mucosa, even at low doses, with occasional severe gastric bleeding; local irritation is less severe with soluble, buffered or gastro-resistant formulations. (289).
- High doses of acetylsalicylic acid in any form, including parenteral, may also cause gastrointestinal damage due to prostaglandin inhibition, as with NSAIDs. (289)
- Hypersensitivity reactions (e.g. bronchospasm), especially in asthmatic patients with nasal polyps; cross-hypersensitivity with NSAIDs exists. (289)
- Prolonged inhibition of platelet aggregation, hence its place in cardiovascular prevention, but also with bleeding problems, such as bleeding after tooth extraction, gastrointestinal or central bleeding, and sometimes even after a single dose. (289)
- Aspirin and other salicylates may cause hepatotoxicity, particularly in patients with juvenile idiopathic arthritis or other connective tissue disorders. (290)
- Possible risk of Reye's syndrome. (289)
- Rare: haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency. (289)
- At high doses:
    - Tinnitus. (289)
    - Increased respiratory frequency and amplitude. (289)
    - Medication-induced headache: prolonged, too frequent, high-dose use of analgesics (e.g. paracetamol, acetylsalicylic acid, or combinations with caffeine) due to headache (migraine-like or otherwise) can lead to an increase in the frequency of headache complaints, almost to the point of daily complaints. (293) This is a frequent cause of chronic headache. (289)
- In acute overdose (mostly with doses above 10 g in adults): convulsions, respiratory depression with metabolic acidosis, fever, confusion and coma. (289)

- Mild chronic salicylate intoxication, or salicylism, usually occurs only after repeated use of large doses. Symptoms include dizziness, tinnitus, deafness, sweating, nausea and vomiting, headache, and confusion, and may be controlled by reducing the dosage. (290)

11.2.3 Interactions

- Increased risk of bleeding (especially gastrointestinal) when used in combination with antithrombotic or anticoagulant drugs, NSAIDs, SSRIs, SNRIs, or vortioxetine, and in cases of chronic or excessive alcohol consumption. (289)
- Increased risk of gastrointestinal injury with concomitant NSAID use. (289)
- Drugs such as metoclopramide in patients with migraine headache result in earlier absorption of aspirin and higher peak plasma-salicylate concentrations. Metoprolol may also increase peak plasma-salicylate concentrations. (290)
- Acetylsalicylic acid + NSAIDs (indomethacin, ibuprofen, naproxen): suspected decreased cardioprotective effect of acetylsalicylic acid. With regard to ibuprofen, the cardioprotective effect of acetylsalicylic acid could be maintained by administering ibuprofen a few hours after acetylsalicylic acid. (289)
- Acetylsalicylic acid and methotrexate: increased risk of adverse effects from methotrexate, especially when methotrexate is used at high doses in oncology. In patients with normal renal function taking low doses of methotrexate, the risk of increased methotrexate toxicity is very low. (289)
- Severe acidosis and central toxicity with high-dose combinations of salicylates and acetazolamide. (289)
- Theoretical risk of Reye's syndrome when combined with varicella vaccine. (289)

11.2.4 Special precautions

- The sodium content in effervescent preparations (tablets, powders, granules) can cause problems in patients on strict low-sodium diets. (289)
- Aspirin should be used cautiously in dehydrated patients and in the presence of uncontrolled hypertension. (290)
- Aspirin and other salicylates can interfere with thyroid function tests. (290)

In order to prevent the development of drug-induced headaches: it is important to limit the use of analgesics and antimigraine drugs to a maximum of 6 to 8 days per month or 2 days per week in patients with headaches, particularly migraine, but also other forms of headache, and to consider prophylactic treatment in good time. (293)

Analgesics, ergot derivatives and triptans can be stopped abruptly, but the temporary worsening of headaches and the appearance of withdrawal symptoms such as nausea, vomiting, hypotension, tachycardia, anxiety and nervousness must be taken into account. These are likely to be less long-lasting when a triptan is discontinued. Transitional treatment may be initiated for a short period: e.g. with antiemetics, NSAIDs or corticosteroids. Sometimes hospitalisation is necessary. (293)

Remarks concerning administration route:

- Aspirin given rectally may cause local irritation; anorectal stenosis has been reported. (290)
- Absorption may be poor due to gastric stasis which is commonly present in migraine. For this reason dispersible and effervescent preparations and compound preparations containing drugs such as metoclopramide which relieve gastric stasis have been advocated. (290)

11.2.5 Specific populations

11.2.5.1 Pregnancy and lactation

- **Acetylsalicylic acid is best avoided during pregnancy. (289)**
    - **First trimester: suspected teratogenic and abortifacient effect when using high doses. (289)**
    - **Third trimester: with chronic use of high doses, prolonged pregnancy and labour, and early closure of the ductus arteriosus. (289)**
    - **Perinatal: risk of bleeding in mother, foetus and newborn. (289)**

- **Use of low-dose acetylsalicylic acid (<100 mg p.d.) from the end of the first trimester is useful in certain women at high risk of pre-eclampsia; it is recommended to stop acetylsalicylic acid intake 5-10 days before the planned delivery date. (289)**
- **Breastfeeding:**
    - **Use of high doses of acetylsalicylic acid is not recommended given the risk of intoxication in the newborn; there are no data with low doses. (289)**
    - Aspirin has been associated with metabolic acidosis in the infant. The BNF also recommends that aspirin should be avoided in breast-feeding mothers because of the possible risk of Reye's syndrome in nursing infants; they also advise that infants with neonatal vitamin K deficiency may be at risk of hypoprothrombinaemia after the regular use of high doses of aspirin in breast-feeding mothers. (290)

11.2.5.2 Children and adolescents

- In children the use of aspirin has been implicated in some cases of Reye's syndrome, leading to severe restrictions on the indications for aspirin therapy in children. (290) Although a causal relationship remains to be established, the use of aspirin and other acetylated salicylates as analgesics or antipyretics is generally considered contra-indicated in children under the age of 12 years. (290)
- Intoxication: In children drowsiness and metabolic acidosis commonly occur; hypoglycaemia may be severe. (290)

11.2.5.3 Elderly

- Continuous prolonged use of aspirin should be avoided in the elderly because of the risk of gastrointestinal bleeding. (290)

11.3 NSAIDs

11.3.1 Contra-indications

- Third pregnancy trimester. (289)
- Active gastroduodenal ulcer. (289)
- Gastrointestinal haemorrhage or perforation with previous use of NSAIDs. (289)
- Active ulcerative colitis or Crohn's disease. (289)
- Active bleeding or bleeding disorders, blood dyscrasias.(289)

- Antecedents of asthma or urticaria due to the intake of acetylsalicylic acid or an NSAID. (289)
- Severe dehydration. (289)
- Moderate to severe heart failure. (289)

- For most systemically used NSAIDs, renal impairment and hepatic impairment are listed as contraindications in the SPC. The website "geneesmiddelenbijlevercirrose.nl" rates NSAIDs as "unsafe" (to be avoided) in liver cirrhosis. (289)

Diclofenac and prolonged, high-dose ibuprofen (≥2400mg/jour): also coronary artery disease, history of cerebrovascular disease, peripheral arterial disease and moderate to severe heart failure. (289)

11.3.2 Adverse events

- Gastrointestinal (GI) discomfort is the most frequent (GI discomfort, nausea, diarrhea; usually mild and reversible). (290) However, in some patients lesions of the GI mucosae: ulceration, bleeding, perforation. (289)
    - All NSAIDs can result in serious GI adverse events, sometimes without prior symptoms. (289)
    - GI injuries can occur with administration of NSAIDs regardless of the route of administration, including parenterally and rectally. (289)
    - The extent to which NSAIDs differ in terms of GI risk remains the subject of discussion. Piroxicam and ketorolac have a higher risk of GI adverse events and ulcer complications such as bleeding and perforation. With ibuprofen, COX-2 selective NSAIDs and perhaps nabumetone, there may be a lower risk of ulcer and ulcer complications compared to the other NSAIDs. (289)
- Increased risk of myocardial infarction and cerebrovascular accidents. (289)
    - The risk is probably greatest for the COX-2 selective NSAIDs and for aceclofenac and diclofenac, probably the lowest for naproxen. For ibuprofen, the data are not clear: there are only indications of an increased risk with long-term use of high doses. Very little data is available for the other NSAIDs, but it is believed that this cardiovascular risk cannot be excluded for any NSAID. (289)
    - The risk is likely to increase with the dose and the duration of treatment. (289)
- Fluid retention with worsening heart failure: all NSAIDs increase the risk of acute heart failure. (289)
- Blood pressure increase. (289)
  A meta-analysis shows an average blood pressure increase of 5 mmHg. The effect is greatest in patients taking antihypertensive therapy. (290)
- Acute and chronic renal failure. (289)
    - Acute renal failure, especially with volume depletion from diuretics or salt restriction, pre-existing heart failure, chronic renal failure, cirrhosis of the liver, ascites, nephrotic syndrome or peripheral vascular disease, or with concomitant use of ACE inhibitors or sartans. (289)
    - Approximately 1 in 200 patients older than 65 years develop an acute kidney problem within 45 days after the start of NSAID treatment.
    - A cohort study suggests a limited increased risk of kidney disease with the use of high-dose NSAIDs in young healthy adults. There could be a link with intense physical exertion and insufficient fluid intake. In this study, the most commonly made prescriptions involved ibuprofen and naproxen. (294)
    - In children, acute renal failure has been observed with dehydration (in case of fever or diarrhoea) or with high doses. (294)

    - Rare: interstitial nephritis, nephrotic syndrome. (289)
    - Long-term use or abuse of analgesics, including NSAIDs, is associated with nephropathy. (290)
- Bleeding, hematologic abnormalities. (289)
- Hypersensitivity (eg bronchospasm, angioneurotic edema), sometimes with cross-sensitivity with acetylsalicylic acid and between the NSAIDs. (289)
- Hyperkalaemia, especially in patients with renal insufficiency and patients taking potassium supplements, potassium-sparing diuretics, ACE inhibitors or sartans or using heparins. (289)
- Suspicion of reversible reduction in female fertility with long-term use. (289)
- Headache, vertigo and confusion, especially with arylacetic derivatives (including diclofenac) and indole derivatives. (289)
- NSAIDs can also cause drug-induced headache. In patients with analgesic headache, attempts should be made to discontinue the offending drug. (293)
- Hearing loss and tinnitus are also associated with use of NSAID. (290)
- Hepatotoxicity: reversible elevation of transaminases is common; rarely potentially fatal acute liver failure. Diclofenac is most often associated with hepatotoxicity. (289)
- Deterioration and provoking of all sorts of skin disorders ranging to Lyell syndrome and Stevens-Johnson syndrome with all NSAIDs (especially with piroxicam). (289)
- Increased incidence of serious skin complications (abscess, necrosis) in patients with varicella or zona treated with an NSAID. (289)
- May mask symptoms of infection (fever, pain), which may delay initiation of appropriate treatment and worsen the prognosis of the infection (this risk has been observed especially in the context of community-acquired bacterial pneumonia and bacterial complications of chickenpox) 4. (289)
- Photodermatosis has been described (probably mainly piroxicam and topical use (probably mainly ketoprofen gel). (295)
- NSAIDs (including ibuprofen) have also been associated with hyponatremia. The incidence is probably low. (296)
- Optical neuropathy has been described with NSAIDs. (297)

11.3.3 Interactions

- Increased risk of gastrointestinal lesions due to NSAIDs with concomitant use of corticosteroids, acetylsalicylic acid (even in low doses) and with chronic or excessive alcohol consumption. (289)
- Increased risk of bleeding from NSAIDs with concomitant use of antithrombotics, acetylsalicylic acid (even in low doses), SSRIs and selective serotonin and noradrenaline reuptake inhibitors (SRNIs). (289)
- Some NSAIDs are thought to reduce the cardioprotective effect of acetylsalicylic acid (especially investigated for ibuprofen). The cardioprotective effect of acetylsalicylic acid could be preserved by administering the NSAID a few hours after the acetylsalicylic acid preparation. (289)
- Increased risk of nephrotoxicity of cyclosporin. (289)

- Increased risk of adverse events with methotrexate, especially when methotrexate is used in high doses as an anti-tumor agent. In patients with normal renal function on low doses of methotrexate (such as for example in rheumatoid arthritis) the risk of increased methotrexate toxicity is very low. (289)
- Increased risk of lactic acidosis triggered by metformin. (289)
- Reduced effect of diuretics and most antihypertensive drugs. (289)
- More pronounced increase in kalemia when associated with potassium-sparing diuretics, potassium supplements, ACE inhibitors, sartans and heparins. (289)
- Deterioration of renal function (with a further increase in the risk of acute renal failure) when associated with diuretics, ACE inhibitors or sartans, especially with stenosis of the renal arteries or volume depletion, and certainly with concomitant treatment of an NSAID and a diuretic together with a ACE inhibitor or sartan. (289)
- Increased risk of heart failure when associated with pioglitazone. (289)
- Increase in the plasma concentration of lithium due to reduced renal excretion. (289)

Diclofenac, ibuprofen and naproxen: are substrates of CYP2C9. (289)

Ibuprofen: is a CYP2C8 substrate. (289)

11.3.4 Special precautions

- Because of their adverse events, the NSAIDs should only be used if the risk-benefit ratio appears to be positive: in many cases, a product with less toxicity may suffice (eg paracetamol in osteoarthritis or in fever). (289)
- Association with a proton pump inhibitor (PPI), or misoprostol allows to reduce the gastrointestinal toxicity of the NSAIDs with a protective effect on ulcer complications such as perforation or bleeding. This association is recommended for at-risk patients: persons> 65 years of age, and persons with significant comorbidity, with antecedents of peptic ulcer (certainly if bleeding or perforation complications), and with concomitant administration of corticosteroids, acetylsalicylic acid or another antiaggregant or an anticoagulant . (289)
- NSAIDs should be used with caution in patients with inflammatory bowel disease as they may aggravate the condition. (289)
- Some NSAIDs can interfere with thyroid function tests by lowering serum-thyroid hormone concentrations. (290)
- In the event of acute episodes of dehydration (diarrhoea, vomiting, fever, etc.) lasting more than 24 hours, consideration should be given to dose reduction or temporary discontinuation of the NSAID to avoid acute renal injury, particularly in vulnerable patients and those taking a diuretic, ACE inhibitor or sartan. (289)
- In the case of renal insufficiency (if not contraindicated; see also under Contraindications): avoid NSAID or give the lowest effective dose for the shortest possible time. Monitor kidney function, sodium and water retention. (290)
- The sodium content in effervescent preparations (tablets, powders, granules) can cause problems for patients on a strict low-salt diet. (289)

In order to prevent the development of drug-induced headaches: it is important to limit the use of analgesics and antimigraine drugs to a maximum of 6 to 8 days per month or 2 days per week in patients with headaches, particularly migraine, but also other forms of headache, and to consider prophylactic treatment in good time. (293)

Analgesics, ergot derivatives and triptans can be stopped abruptly, but the temporary worsening of headaches and the appearance of withdrawal symptoms such as nausea, vomiting, hypotension, tachycardia, anxiety and nervousness must be taken into account. These are likely to be less long-lasting when a triptan is discontinued. Transitional treatment may be initiated for a short period: e.g. with antiemetics, NSAIDs or corticosteroids. Sometimes hospitalisation is necessary. (293)

Naproxen can be used to manage the aggravation of symptoms associated with the withdrawal of analgesics in medication-overuse headache. An oral dose of 250 mg three times daily or 500 mg twice daily should be taken regularly; some suggest a single course of 3 to 4 weeks, others a 6-week course with the dose of naproxen being reduced gradually. (290)

Diclofenac and high doses of ibuprofen: given cardiovascular adverse events, one should be cautious in patients with cardiovascular disease (see section "Contraindications"), with hypertension and with high cardiovascular risk. (289)

11.3.5 Specific populations

11.3.5.1 Pregnancy and lactation

Published data can be conflicting, making an informed decision difficult. The inhibition of prostaglandin synthesis may expose the fetus to cardiopulmonary toxicity, such as premature closure of the ductus arteriosus and pulmonary hypertension, and renal dysfunction which can progress to renal failure with oligohydramnios. (290)

- An NSAID such as ibuprofen can be used up to 28 weeks of pregnancy if used occasionally. (298)
- First trimester of pregnancy:
    - Use in the first trimester is associated with a limited risk of spontaneous abortion and teratogenicity. (289)
    - With short-term use and usual doses, the risk appears to be very low. According to Lareb, diclofenac, ibuprofen and naproxen, which have a long history of use, are the first choice among NSAIDs. (289)
- Second (and third) trimester of pregnancy:
    - Prolonged, high-dose use in the second half of pregnancy has been associated with decreased fetal urine output, which can lead to oligohydramnios and irreversible neonatal oliguria or anuria. (289)
    - Repeated or prolonged use is not recommended (289).
- Third trimester of pregnancy:
    - NSAIDs are contraindicated. (289)
    - Repeated use: risk of prolonged pregnancy and delivery, maternal, fetal or neonatal bleeding, fetal oliguria, premature closure of ductus arteriosus, and pulmonary hypertension. (289)
    - If treated for a short time: possible renal failure and heart failure in the fetus or newborn (289)
- Breastfeeding:
    - No adverse effects have been reported in children with ibuprofen and diclofenac to date, although both compounds have a long history of use. (289)
    - Naproxen and piroxicam pass into breast milk and may accumulate in children with prolonged use. (289)

- Other NSAIDs are not or are less well documented. (289)

11.3.5.2 Children and adolescents

- Acute renal failure especially in cases of dehydration (fever or diarrhoea) or with high doses. In children with dehydration (eg with diarrhea) anti-inflammatory drugs such as ibuprofen should not be administered due to the risk of acute renal failure. On the other hand, when using ibuprofen in a child with fever or pain, extra attention must always be paid to good hydration. (289)
- An analysis of the outcome of treatment of 83 915 children found that the risk of hospitalisation for gastrointestinal bleeding, renal failure, or anaphylaxis was no greater in children given ibuprofen than in those given paracetamol. (290)

11.3.5.3 Elderly

- The adverse events of the NSAIDs are seen more often in the elderly and often also have a worse outcome in this age group. The indication should be very strict, and the dose and duration of treatment should be limited as much as possible. In the elderly, NSAIDs with a short half-life (eg ibuprofen) are preferable. (289)
- Caution in the elderly due to fluid retention with worsening heart failure. (290)

11.4 Associations of paracetamol and or acid acetylsalicylique with caffeine

Caffeine has been widely used in analgesic preparations to enhance the effects of both non-opioid and opioid analgesics but is of debatable benefit. (290)

See also contraindications, adverse events, interactions and special precautions related to paracetamol or acetylsalicylic acid.

11.4.1 Adverse events

- In the UK it is generally recommended that caffeine-containing analgesic preparations should not be used not only because of doubts about caffeine enhancing the analgesic effect but because it can add to gastrointestinal adverse effects and in large doses can itself cause headache. (290)

- As for theophylline: (290)
  - The commonest adverse effects of theophylline and xanthine derivatives, irrespective of the route, are gastrointestinal irritation and stimulation of the CNS.
  - Theophylline may cause nausea, vomiting, abdominal pain, diarrhoea, and other gastrointestinal disturbances, insomnia, headache, anxiety, irritability, restlessness, tremor, and palpitations. Overdosage may also lead to agitation, diuresis and repeated vomiting (sometimes haematemesis) and consequent dehydration, cardiac arrhythmias including tachycardia, hypotension, electrolyte disturbances including profound hypokalaemia, hyperglycaemia, hypomagnesaemia, metabolic acidosis, rhabdomyolysis, convulsions, and death.

- An increased caffeine intake has been associated with an increase in daytime blood pressure.[1] The study, in 82 healthy, normotensive adolescents, suggested that caffeine use may be a factor contributing to essential hypertension in young people. (290)
- Tolerance occurs rapidly to the stimulating effects of caffeine; physical signs of withdrawal including irritability, restlessness, lethargy, and headache may occur if intake is stopped abruptly. (290)
- Headache is a recognised symptom of caffeine withdrawal and even subjects who drink moderate amounts of coffee can develop headaches lasting 1 to 6 days when switched to a decaffeinated brand. (290)
- In a case-control study, investigating the possible association of dietary and medicinal caffeine use with chronic daily headache (CDH), caffeine was found to be a modest risk factor for CDH onset, regardless of headache type. (290)
- Medication-induced headache: Prolonged, too frequent, high-dose use of analgesics (e.g. paracetamol, acetylsalicylic acid, or combinations with caffeine) due to headache (migraine-like or otherwise) can lead to an increase in the frequency of headache complaints, almost to the point of daily complaints. (293) This is a frequent cause of chronic headache. (289)

11.4.2 Interactions

- Caffeine is a substrate and inhibitor of CYP1A2. (289)

11.4.3 Special precautions

In order to prevent the development of drug-induced headaches:

- It is important to limit the use of analgesics and antimigraine drugs to a maximum of 6 to 8 days per month or 2 days per week in patients with headaches, particularly migraine, but also other forms of headache, and to consider prophylactic treatment in good time. (293)
- Combinations should be avoided. (289)
- Analgesics (including caffeine preparations), ergot derivatives and triptans can be discontinued abruptly, but the temporary worsening of headache and the appearance of withdrawal symptoms such as nausea, vomiting, hypotension, tachycardia, anxiety and nervousness must be taken into account. These are likely to be less long-lasting when a triptan is discontinued. Transitional treatment may be initiated for a short period: e.g. with antiemetics, NSAIDs or corticosteroids. Sometimes hospitalisation is necessary. (293)

11.4.4 Specific populations

11.4.4.1 Pregnancy and lactation

- Studies of maternal caffeine intake on pregnancy outcomes have had mixed results. Although some prospective studies have found that maternal caffeine intake was associated with reduced fetal growth,[1,2] another study did not support this conclusion,[3] and a moderate reduction in caffeine intake in the second half of pregnancy was reported to have no effect on birth-weight or length of gestation.[4] Similarly, conflicting results have been reported for the effect of caffeine on miscarriage[5-8] and the risk of sudden infant death syndrome. (290)
- Breast feeding: caffeine is excreted slowly by the infant and may be associated with irritability and poor sleeping pattern when ingested by breast-feeding mothers. However, no

effects occur with moderate intake of caffeinated beverages (2 or 3 cups daily) and caffeine is usually compatible with breast feeding. (290)

11.5 Gastroprokinetics

11.5.1 Contra-indications

Alizapride and metoclopramide:

- History of tardive dyskinesia following treatment with antipsychotics. (289)
- Pheochromocytoma. (289)

Domperidone:

- Prolactinoma. (289)
- Risk factors for QT interval prolongation. (289)
- Concomitant use of other QT-prolonging drugs and CYP3A4 inhibitors. (289)
- Hepatic impairment. On the geneesmiddelenbijlevercirrose.nl website, domperidone is considered "to be avoided" in hepatic cirrhosis. (289)

11.5.2 Adverse events

- Hyperprolactinemia, in rare cases responsible for galactorrhea or impotence. (289)
- Gynecomastia. (299)
- Central effects: (289)
    - Drowsiness.
    - Extrapyramidal disorders, especially in children and adolescents.
    - Tardive dyskinesias with prolonged use, especially in the elderly, less common with domperidone.
    - Resting tremor due to extrapyramidal disorders, especially metoclopramide and alizapride, less frequent with domperidone. (300)
- Rare: abdominal cramps or diarrhoea. (289)

Domperidone:

- Commonly: dry mouth. (290)
- Domperidone does not readily cross the blood-brain barrier and the incidence of central effects such as extrapyramidal reactions or drowsiness may be lower than with metoclopramide; however, there have been reports of dystonic reactions and convulsions. (290)
- QT interval prolongation at high doses (>30 mg daily) and in people over 60 years of age. There is limited evidence of a risk of torsades de pointes and sudden death. (289)

Metoclopramide:

- Very rarely: neuroleptic malignant syndrome. (290)
- Intravenous: also risk of severe bradycardia. (289)

11.5.3 Interactions

- Acceleration of gastric emptying, with slowing of the rate of absorption of some drugs (e.g. digoxin) and accelerated absorption of others (e.g. acetylsalicylic acid, cyclosporine, paracetamol). (289)

- Decreased effect of gastroprokinetics when combined with drugs with anticholinergic properties (289) or opioid analgesics (290).
- Enhanced adverse effects of antipsychotics. (289)
-

Alizapride

- Excessive sedation in combination with other drugs with a sedative effect or with alcohol. (289)

Domperidone:

- Increased risk of torsades de pointes when combined with other drugs that increase the risk of QT interval prolongation. (289)
- Domperidone is a CYP3A4 and P-gp substrate. (289)
- Concomitant use with other QT-prolonging drugs and CYP3A4 inhibitors is contraindicated (289).

Metoclopramide

- Decreases the effect of levodopa and dopamine agonists. (289)
- Exessive sedation in combination with other drugs with sedative effect or alcohol (289)
- Metoclopramide is a CYP2D6 substrate (289)

11.5.4 Special precautions

Alizapride:

- Caution in patients with Parkinson's disease. (289)

Domperidone:

- Due to the risk of QT prolongation, caution should be exercised in patients with electrolyte disorders or underlying cardiac disease. (289)
- Should be used with great caution if given intravenously, because of the risk of arrhythmias, especially in patients predisposed to cardiac arrhythmias or hypokalaemia. (290)
- Should also be avoided in those with moderate or severe hepatic impairment. (290)

Metoclopramide:

- Caution in patients with Parkinson's disease. (289)

- The adult dose (by any route) should not exceed 10 mg 3 times daily, and the duration of treatment should not exceed 5 days. (289)
- Children, young adults, and the elderly should be treated with care as they are at increased risk of extrapyramidal reactions. (290)
- Care should also be taken when metoclopramide is given to patients with renal or hepatic impairment, or a history of depression, atopy (including asthma), or porphyria. (290)
- Intravenous metoclopramide should be given with caution to patients at increased risk of cardiovascular reactions, including those with cardiac conduction abnormalities such as sick sinus syndrome. (290)

11.5.5 Specific population

11.5.5.1 Pregnancy and lactation

For none of the antiemetics, the absence of teratogenicity has been clearly demonstrated. (289)

Alizapride: (301)

- Not recommended during pregnancy.
- There is insufficient data to assess the risk to the foetus.

Domperidone: (301)

- Can only be used in cases of severe vomiting.
- According to Lareb, there is not enough data in humans to determine the risk to the fetus.
- Domperidone increases the risk of QT interval prolongation in the mother. This risk is further increased in cases of severe vomiting with the potential for electrolyte disturbances, a known risk factor for QT interval prolongation. No data are available on the risk of QT interval prolongation in the fetus.
- According to CRAT, the data on domperidone in pregnancy are extensive and reassuring.

Metoclopramide: (301)

- Can be used.
- Data on the use of metoclopramide in the first trimester of pregnancy do not show a risk of congenital malformations.
- The risk of extrapyramidal disorders in the mother should be taken into account and short treatment periods (max. 5 days) should be preferred.
- There is a possible risk of adverse effects on the foetus in the event of exposure in the 2nd and 3rd trimesters of pregnancy (cardiac and extrapyramidal disorders) and at the end of pregnancy (drowsiness, disturbances in thermal regulation).
- The long-term effects of in utero exposure are not known.

Breast feeding:

Domperidone :

- No adverse effects have been seen in breast-fed infants whose mothers were given domperidone. (290)
- The last available guidance from the American Academy of Pediatrics considered domperidone to be usually compatible with breast feeding. (290)

Metoclopramide:

- Is excreted into breast milk. (290)
- The American Academy of Pediatrics considers that the use of metoclopramide by mothers during breast feeding may be of concern, owing to its dopamine-receptor blocking activity. (290)
- UK licensed product information states that problems in humans have not been reported. (290)

11.5.5.2 Children and adolescents

- Risk of extrapyramidal disorders (especially in children and adolescents). (289)

Domperidone:

- Contraindicated in children under 12 years and adolescents weighing less than 35 kg. (289)

Metoclopramide:

- Contraindicated in children under 1 year of age and not recommended for children and adolescents. (289)
- Should not be used in children and adolescents because of the increased risk of extrapyramidal disorders in these age groups. (289)
- In the EU the use of metoclopramide in children and young adults is restricted to a second-line option for prevention of delayed chemotherapy-induced nausea and vomiting and treatment of established postoperative nausea and vomiting. (290)

11.5.5.3 Elderly

- Tardive dyskinesia with prolonged use (especially in the elderly), less common with domperidone. (289)

Domperidone:

- QT interval prolongation at high doses (>30 mg daily) and in people over 60 years of age. Given the risk of QT interval prolongation, caution should be exercised in the elderly. (289)

11.6 Triptans

11.6.1 Contra-indications

- Coronary artery disease, history of cerebrovascular disease, peripheral arterial disease and uncontrolled hypertension. (289)
- Migraine with prolonged aura, migraine with brainstem aura, hemiplegic migraine and recurrent painful ophthalmoplegic neuropathy (formerly known as ophthalmoplegic migraine). (289)
- Triptans cannot be given if ergot derivatives are already being used. (289)

Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan and sumatriptan:

- Severe liver failure. (289)

Eleptritan and rizatriptan:

- Severe renal failure. (289)

Zolmitriptan:

Heart rhythm disorders. (289)

Wolff-Parkinson-White syndrome. (289)

11.6.2 Adverse events

- Nausea, vomiting, drowsiness and dizziness. (289)
- Feeling of heaviness and tightness in the chest; in rare cases this may be coronary spasm, but this risk is low in the absence of coronary artery disease or uncontrolled high blood pressure; palpitations. (289)
- Pain or sensations of heaviness, heat or cold, pressure, or tightness have also been commonly reported, can affect any part of the body including the throat and chest, and may be intense. These symptoms may be due to vasospasm, which on rare occasions has resulted in severe cardiovascular events including cardiac arrhythmias, myocardial ischaemia, or myocardial infarction. (290)
- Transient increases in blood pressure may occur soon after treatment. Rarely, significant increases in blood pressure, including hypertensive crisis with acute impairment of organ systems, have occurred even in patients without a history of hypertension. (290)
- Hypotension, bradycardia or tachycardia, palpitations, peripheral vascular disorders such as Raynaud's syndrome, and ischaemic colitis have been reported. (290)
- Visual disturbances have also occurred. (290)
- Induction of drug-induced headache with chronic overuse (289)
  Prolonged and too frequent use of too high doses of antimigraine drugs (triptans, ergot derivatives) or analgesics (e.g. paracetamol, acetylsalicylic acid, or combinations with caffeine) can increase the frequency of headaches and induce medication-induced headache. This is a common cause of chronic headache. Medication-induced headache develops more rapidly with triptans and ergot derivatives than with analgesics. Abrupt discontinuation of overdosed drugs is possible but may lead to temporary worsening of headache and withdrawal symptoms such as nausea, vomiting, hypotension, tachycardia, anxiety and agitation. (289)

<u>Sumatriptan:</u>

- There have been isolated reports of associated cerebrovascular events in patients receiving sumatriptan. (290)
- Whether misuse of sumatriptan is due to addiction or rebound headache, as seen with ergotamine, is unknown. A postmarketing study in 952 patients receiving sumatriptan found that 36 of the patients (4%) used sumatriptan daily or more than 10 times each week. This overuse was related to poor efficacy and not to rebound headache.One study and an anecdotal report suggest that, rather than producing euphoria or other effects associated with drugs of abuse such as morphine, sumatriptan is more likely to be associated with dysphoria and apathetic sedation. (290)

<u>Remarks concerning administration route:</u>

- Transient pain at the injection site is common after subcutaneous injections. (290)
- Stinging, burning, erythema, bruising, and bleeding have also been reported. (290)
- Irritation of the nasal mucosa and throat and epistaxis have been reported after intranasal use. (290)

11.6.3 Interaction

- Increased risk of coronary spasm with concomitant use of triptans and ergot derivatives; an interval of at least 24 hours between the two drugs should be observed after taking an ergot derivative, and at least 6 hours after taking a triptan. (289)
- A risk of serotonin syndrome has been suggested in combination with other drugs with serotonergic effects, but the evidence is weak. (289)

Almotriptan and eletriptan:

- Are substrates of CYP3A4. (289)
- Almotriptan is also a substrate of CYP2D6. (289)
- Eletriptan is also a P-gp substrate. (289)

Rizatriptan, sumatriptan and zolmitriptan:

- Are MAO-A substrates. When combined with an MAO inhibitor, plasma concentrations of these triptans may increase, resulting in an increased risk of adverse effects (including coronary spasm). (302)
- Moclobemide inhibits their metabolism (to a lesser extent for zolmitriptan), resulting in an increased risk of adverse effects. (289)
- Rizatriptan: risk of a sharp increase in plasma concentrations when given concomitantly with propranolol. (289)
- Oral sumatriptan appeared to delay gastric emptying and might affect the absorption of other drugs, as judged by its delaying effect on paracetamol absorption in migraine patients. (290)
- Zolmitriptan is a CYP1A2 substrate. (289)

Frovatriptan:

- Is a substrate of CYP1A2. (289)

11.6.4 Special precautions

- Triptans should only be used where there is a clear diagnosis of migraine or cluster headache and care should be taken to exclude other potentially serious neurological conditions. They should not be used for prophylaxis and should not be given to patients with basilar, hemiplegic, or ophthalmoplegic migraine. (290)
- Triptans cannot be used repeatedly (no more than 10 days per month). (289)

In order to prevent the development of drug-induced headaches: it is important to limit the use of analgesics and antimigraine drugs to a maximum of 6 to 8 days per month or 2 days per week in patients with headaches, particularly migraine, but also other forms of headache, and to consider prophylactic treatment in good time (293) .

Analgesics, ergot derivatives and triptans can be stopped abruptly, but the temporary worsening of headaches and the appearance of withdrawal symptoms such as nausea, vomiting, hypotension, tachycardia, anxiety and nervousness must be taken into account. These are likely to be less long-lasting when a triptan is discontinued. Transitional treatment may be initiated for a short period: e.g. with antiemetics, NSAIDs or corticosteroids. Sometimes hospitalisation is necessary (293) .

Specific populations

11.6.4.1 Pregnancy and lactation

- Pregnancy:
  - Sumatriptan has the longest history of use, with reassuring data for occasional use, particularly in the first trimester of pregnancy. The use of sumatriptan in the second and third trimester is less well documented. (289)
  - With some triptans, embryotoxic effects have been observed in animals. (289)
- Breastfeeding:
  - Sumatriptan and eletriptan are probably safe during lactation. (289)

11.7 CGRP receptor antagonists

11.7.1 Adverse events

- Nausea. (289)
- Hypersensitivity reactions, including dyspnoea and severe rash. (289)

11.7.2 Interactions

- Rimegant is a substrate for CYP3A4 and P-gp. According to the SPC, concomitant administration with strong CYP3A4 inhibitors or with strong or moderate CYP3A4 inducers is not recommended. A further dose of rimegepant should be avoided within 48 hours of concomitant use with moderate CYP3A4 inhibitors or strong P-gp inhibitors. (289)

11.7.3 Special precautions

- Patients with certain severe cardiovascular diseases were excluded from the clinical studies. No safety data are available in these patients. (289)
- Rimegepant is not recommended in patients with severe hepatic impairment (289).

11.7.4 Specific populations

11.7.4.1 Pregnancy and lactation:

- It is not possible to comment on the safety of rimegepant in pregnancy (insufficient data). (289)

11.8 Beta-blockers

11.8.1 Contra-indications

- Sinus node disease. (289)
- Second or third degree atrioventricular block. (289)
- Asthma (especially non-cardioselective β-blockers-i.e.propranolol); COPD is a relative contraindication for non-cardioselective β-blockers. (289)
- Acute or inadequately controlled heart failure. (289)
- Combination with intravenous verapamil. (289)
- On the website https://www.geneesmiddelenbijlevercirrose.nl, metoprolol is considered "to be avoided" in cases of hepatic cirrhosis (289)

11.8.2 Adverse events

- Beta-blockers are generally well tolerated and most adverse effects are mild and transient. (290) The most frequent and serious adverse effects are related to their beta-adrenergic blocking activity. (290)
- Fatigue and decreased exercise capacity. (289)
- Sinus bradycardia (less marked with β-blockers with intrinsic sympathomimetic activity), atrioventricular block, development or worsening of heart failure. (289)
- Asthma attack in patients with a history of bronchospasm; lower risk when using cardioselective β-blockers. (289)
- Cold extremities, worsening of vascular spasm (Raynaud's), probably less so with β-blockers with vasodilator effect. (289)
- Erectile dysfunction. (289)
- Central effects (including sleep disturbances, nightmares, depression), especially with lipophilic β-blockers. (289)
- Aggravation of an anaphylactic reaction, and decreased effect of adrenaline in its management. (289)
- Exacerbation of psoriasis (289)
- Severe angina and myocardial infarction if discontinued in patients with coronary artery disease. (289)
- Increased insulin resistance, with elevated blood glucose and hypertriglyceridaemia. The long-term clinical relevance is unclear, as despite these effects, β-blockers eventually lead to a reduction in cardiovascular mortality and morbidity, even in patients with diabetes. (289)
- Dry eyes. (303)
- Allopecia has been described, probably with a low incidence. (304)

11.8.3 Interactions

For all antihypertensives, excessive fall in blood pressure, especially orthostatic, when several antihypertensives are combined, when nitrates, molsidomine, phosphodiesterase type 5 inhibitors, levodopa or alcohol are combined, and when hypovolaemia occurs. (289)

- Increased risk of adverse effects of β-blockers (bradycardia, atrioventricular block and decreased myocardial contractility) when combined with verapamil, to a lesser extent when combined with diltiazem, or when used concomitantly with antiarrhythmics. (289)
- The use of intravenous verapamil is contraindicated in patients on β-blockers because of the risk of heart failure, complete AV block and shock. For the same reason, intravenous β-blockers are contraindicated in chronic verapamil use. (289).
- Increased risk of bradycardia when combined with ivabradine. (289).
- Increased risk of vascular spasm when combined with ergot derivatives. (289)
- Worsening of hypoglycaemic episodes in patients on antidiabetic drugs, and symptoms of hypoglycaemia may be masked (less so with cardioselective β-blockers). (289)
- Decreased effect of β2-mimetics in asthma and COPD: especially by non-selective β-blockers. (289)
- Decreased response to adrenaline in the treatment of anaphylaxis. (289)

- Increased plasma levels of drugs such as lidocaine whose clearance decreases with decreased cardiac output (289)

Metoprolol and propranolol:

- are substrates of CYP2D6. (289)

11.8.4 Special precautions

- Be careful to orthostatic hypotension, especially in hypovolemia and at initiation of therapy (first dose), especially with α-blockers, ACEIs, sartans, and vasodilators. Increase the dose gradually, especially in the elderly. (289)
- Abrupt withdrawal of beta blockers has sometimes resulted in angina, myocardial infarction, ventricular arrhythmias, and death. (290) Discontinuation of β-blockers should be done by gradual reduction of the daily dose, especially in coronary patients. (289)
- Cardioselective β-blockers can be used in patients with COPD and possibly in patients with mild to moderately severe asthma if there is a clear indication; however, attention should be paid to the development of bronchospasm with the first dose. (289)
- Beta blockers may mask the symptoms of hyperthyroidism and of hypoglycaemia. (290)
- They may unmask myasthenia gravis. (290)
- Beta blockers increase sensitivity to allergens and also the severity of anaphylactoid reactions; patients with a history of anaphylaxis to an antigen may be more reactive to repeated challenge with the antigen while taking beta blockers. (290)

Propranolol:

- The dose should be reduced in cases of hepatic impairment (289)

11.8.5 Specific populations

11.8.5.1 Pregnancy and lactation

- Pregnancy :
    - β-blockers can have harmful effects on the fetus and the newborn when used in the latter part of the third trimester.(298)
    - Maternal use of β -blockers can cause hypoglycaemia, hypotension, bradycardia, sedation and respiratory problems in the newborn. (298)
    - If the mother uses β-blockers until the end of pregnancy, it is advisable to increase the monitoring of the child's heart rate during the peripartum period. (298)

      Atenolol: in prolonged use: may cause fetal growth retardation. (289)

Metoprolol and propranolol: have also been associated with growth retardation, but the link is less clear with these beta-blockers. (289)

Other beta-blockers: there is almost no experience in pregnancy. (289)

- Breastfeeding:

Metoprolol and propranolol: safe to use. (289)

Atenolol: reaches high concentrations in breast milk and is not recommended during breastfeeding. (289)

11.8.5.2 Elderly

- Increase the dose gradually. (289)

11.9 Sartans

11.9.1 Contra-indications

- Pregnancy. (289)
- Bilateral renal artery stenosis or single kidney stenosis. (289)
- Hyperkalaemia. (289)
- Severe hepatic impairment is listed as a contraindication in the SPC for most sartans. (289)
- On the website https://www.geneesmiddelenbijlevercirrose.nl, all sartans are listed as "to be avoided" in cases of hepatic cirrhosis. (289)

11.9.2 Edverse events

- Those of ACE inhibitors, with the exception of cough which is rarer. (289)
- Adverse effects of ACE inhibitors:

    - Hypotension after the first dose of an ACE inhibitor or after an increase in dose, especially if there is prior stimulation of the renin-angiotensin system (hypovolaemia due to diuretics, heart failure, renal artery stenosis), particularly in the context of treatment of heart failure. (289)
    - Deterioration of renal function (and sometimes acute renal failure), especially in patients with pre-existing renal disease, in patients with heart failure, and in patients with severe hypovolaemia or dehydration. (289)
    - Hyperkalemia, rarely hyponatremia. (289)
    - Rash, taste disorders: especially with captopril. (289)
    - Gastrointestinal disorders (including diarrhoea). (289)

- Angioedema, sometimes occurring only after months or years of treatment, and more frequent in patients of African origin and in patients with a history of angioedema. (289)

11.9.3 Interactions

With all antihypertensive drugs, excessive fall in blood pressure, especially orthostatic, when several antihypertensive drugs are combined, when nitrates, molsidomine, phosphodiesterase type 5 inhibitors, levodopa or alcohol are combined, and when hypovolemia occurs.

- Increased risk of hyperkalaemia when combined with other potassium-sparing drugs (e.g. potassium supplements (including dietary salts), potassium-sparing diuretics, sartans, trimethoprim (co-trimoxazole), heparins and NSAIDs); this risk is particularly high in renal failure. (289)
- Further deterioration of renal function (with risk of acute renal failure) when combined with NSAIDs or diuretics, especially in cases of renal artery stenosis or hypovolaemia, and particularly in cases of concomitant treatment with sartans + NSAIDs + diuretics (289)
- Increased lithaemia. (289)

<u>Candesartan:</u>

- Is a CYP2C9 substrate (289)

11.9.4 Special precautions

- Be careful to orthostatic hypotension, especially in hypovolemia and at initiation of therapy (first dose), especially with α-blockers, ACE inhibitors, sartans, and vasodilators.
  - Start at low doses and increase them gradually, especially in the elderly and in the presence of cardiac or renal insufficiency. (289)
  - In hypovolemic patients, e.g., when treated with high-dose (loop) diuretics, start with a very low dose (e.g., ¼ of the usual dose) of sartan and increase it gradually, given the risk of hypotension with the first dose and with increasing dose. (289)
- In peripheral arterial disease or generalized atherosclerosis: sartans should be initiated cautiously, as the risk of renal artery stenosis is high in these patients. (289)
- Check renal function and blood potassium levels before initiating therapy or increasing the dose, and again about two weeks later. (289)
- For acute episodes of dehydration (diarrhea, vomiting, fever, etc.) lasting more than 24 hours, consider dose reduction or temporary discontinuation of sartan to avoid acute renal injury, especially in elderly or vulnerable patients. (289)

<u>Candesartan and telmisartan:</u>

- The dose should be reduced in patients with hepatic impairment. (289)

11.9.5 Specific populations

11.9.5.1 Pregnancy and lactation

Sartans, by analogy with ACE inhibitors, are contraindicated throughout pregnancy (risk of renal failure, anuria, hypotension, oligohydramnios, pulmonary hypoplasia and other fetal malformations). (289)

11.10 Verapamil

11.10.1 Contra-indications

- Second or third degree atrioventricular block. (289)
- Sinus node disease. (289)
- Concomitant use of ivabradine. (289)
- Heart failure. (289)
- Intravenous verapamil is contraindicated in patients on β-blockers, in the reciprocal tachycardia of Wolff-Parkinson-White syndrome and in ventricular tachycardia due to the risk of heart failure and shock. (289)
- On the website https://www.geneesmiddelenbijlevercirrose.nl, verapamil is listed as "to be avoided" in liver cirrhosis. (289)

11.10.2 Adverse events

- Treatment with verapamil is generally well tolerated, but adverse effects connected with its pharmacological effects on cardiac conduction can arise and may be particularly severe in patients with previous myocardial damage or hypertrophic cardiomyopathies. Adverse effects on the heart include bradycardia, AV block, worsening heart failure, and transient asystole. These effects are more common with parenteral than with oral therapy. (290)
- Hypotension. (289)
- Decreased cardiac contractility and excessive drop in heart rate (289)
- Constipation. (289)
- Nausea (290)
- Other adverse effects include dizziness, flushing, headaches, fatigue, dyspnoea, and peripheral oedema. There have been reports of skin reactions and some cases of abnormal liver function and hepatotoxicity. (290)
- Gingival hyperplasia. (289)
- Alopecia has been described, probably with a low incidence.(304)
- Very rarely: gynaecomastia. (299)

11.10.3 Interactions

With all antihypertensives, excessive fall in blood pressure, especially orthostatic, when several antihypertensives are combined, when nitrates, molsidomine, phosphodiesterase type 5 inhibitors, levodopa or alcohol are combined, and when hypovolaemia occurs. (289)

- Increased risk of adverse effects of β-blockers (bradycardia, atrioventricular block and decreased myocardial contractility) when combined with verapamil. (289)
- The use of intravenous verapamil is contraindicated in patients on β-blockers because of the risk of cardiac depression and shock. Conversely, this also applies to the intravenous administration of β-blockers in chronic verapamil use. (289)
- Verapamil slows down the metabolism of alcohol. (289)
- Verapamil is a substrate of CYP3A4. (289)

After oral administration, some calcium antagonists (e.g. verapamil) show high hepatic extraction on first pass. Their bioavailability is increased when combined with CYP3A4 inhibitors, and is decreased when combined with CYP3A4 inducers. (289)

- Verapamil is also a CYP3A4 inhibitor and a P-gp substrate and inhibitor. (289)

11.10.4 Specific populations

11.10.4.1 Children and adolescents

- Special care is required in using verapamil as an antiarrhythmic in infants as they may be more susceptible to verapamil-induced arrhythmias. (290)

11.10.4.2 Elderly

- Studies comparing the pharmacokinetics and pharmacodynamics of verapamil in elderly (61 years and older) and young subjects have found that clearance and elimination half-life are increased in older subjects, and increased plasma concentrations have also been reported. However, there may also be changes in the response to verapamil in older subjects that are not directly related to the plasma concentration. (290)

11.11 Flunarizine

11.11.1 Contra-indications

- History of depression. (289)

11.11.2 Adverse events

- Sedation. (289)
- Depression. (289)
- Weight gain. (289)
- Extrapyramidal symptoms (sometimes associated with depression (290)), parkinsonian syndrome, late abnormal movements. (305)
- Rare: galactorrhea (290)

11.11.3 Interactions

- Increased sedation when combined with other drugs with sedative effects or alcohol. (289)

11.11.4 Specific populations

11.11.4.1 Pregnancy and lactation

The available data on the safety of flunarizine use in human pregnancy are almost non-existent. (298)

11.12 Antidepressants : TCA (amitriptyline) and SNRI (venlafaxine)

11.12.1 Contra-indications of TCA (amitriptyline)

- Association with MAO inhibitors. (289)
- Recent myocardial infarction. (289)
- Cardiac arrhythmias (especially AV block). (289)
- Anticholinergic adverse events for products with an anticholinergic effect (especially amitriptyline). (289)

Amitriptyline:

- Severe liver insufficiency. (289)

11.12.2 Contra-indications of SNRI (venlafaxine)

- Association with MAO inhibitors. (289)

Venlafaxine:

  - Uncontrolled hypertension. (290)
  - Increased risk of ventricular arrhythmia. (290)
  - On the website "geneesmiddelenbijlevercirrose.nl", venlafaxine is considered "to be avoided" in cases of liver cirrhosis (289).

11.12.3 Adverse events : antidepressants in general

- Frequent: sexual disorders (ejaculation and erectile dysfunction, problems with libido and orgasm). (289)
- Excessive sweating. (289)
- Trembling, TCAs and venlafaxine can aggravate a physiological tremor. (306)
- Withdrawal symptoms with, for example, flu-like symptoms, gastrointestinal disorders, balance disorders, extrapyramidal disorders, psychological symptoms and sleep disorders, especially in the event of sudden discontinuation or rapid reduction of antidepressants. About half of the people who taper off antidepressants experience withdrawal symptoms. These are often severe and can last for several months. (289)
- Lowering the convulsion threshold, especially with TCAs, SSRIs and bupropion. (289)
- Initiating a manic phase in patients with bipolar disorder, with a higher risk for TCAs and venlafaxine than for SSRIs. (289)
- Hyponatraemia with risk of agitation and confusion, especially in the elderly (more frequently with the SSRIs and the serotonin and noradrenaline reuptake inhibitors. (289)
- Increased risk of aggressive behavior and suicidal thoughts, especially at the start of treatment: not excluding any antidepressant, but most commonly described with the SSRIs. (289)

11.12.4 Adverse events: TCA (amitriptyline)

- Weight gain. (289)
- Orthostatic hypotension and cardiac conduction disorders (quinidine-like effect), especially in the elderly, with pre-existing cardiovascular pathology and at high doses; in overdose: arrhythmias (eg torsades de pointes), with possibly fatal course. (289)
- Anticholinergic effects (especially amitriptyline). (289)
- Sedation, especially with amitriptyline. This sedative effect may be desirable in depression with anxiety or sleep disorders; the highest dose of the single daily dose is preferably taken in the evening. Other antidepressants are low or non-sedative, or even slightly activating ; they sometimes cause anxiety, agitation and insomnia, and are preferably not taken in the evening. (289)
- Gastrointestinal complaints include sour or metallic taste, stomatitis, and gastric irritation with nausea and vomiting. (290)
- Neurological symptoms such as peripheral neuropathy, tremor, ataxia, rarely extrapyramidal symptoms. Confusion, hallucinations, especially in the elderly. (290)
- Endocrine effects, including testicular enlargement, gynaecomastia and breast enlargement, and galactorrhoea. (290)
- Sexual dysfunction (290)
- Seizures have been reported after therapeutic doses of tricyclic antidepressants as well as after overdosage, although the mechanism by which the seizures are induced is unclear. (290)
- Rare: hypersensitivity reactions, photosensitization, blood abnormalities. (290)
- In the event of overdose (suicide attempt): the TCAs present a higher risk of fatal outcome than the other antidepressants. (289)

11.12.5 1.1.1 Adverse events SNRI (venlafaxine)

- Haemorrhages, especially in the skin and mucous membranes, e.g. gastrointestinal system. (289)
- Hyponatremia, especially in the elderly or when taking diuretics. (289)
- Withdrawal symptoms, which occur more frequently with SSRIs and SNRIs than with other antidepressants. (289)
- Persistent sexual dysfunction, even after stopping SSRIs and SNRIs. (289) (301)

<u>Venlafaxine:</u>

- Adverse effects that have been reported most frequently include nausea, headache, insomnia, somnolence, dry mouth, dizziness, constipation, sexual dysfunction, asthenia, sweating, and nervousness. (290)
- Other common adverse effects have included anorexia, diarrhoea, dyspepsia, abdominal pain, anxiety, urinary frequency, visual disturbances, mydriasis, vasodilatation, vomiting, tremor, paraesthesia, hypertonia, chills or fever, palpitations, weight gain or loss, increased serum-cholesterol, agitation, abnormal dreams, confusion, arthralgia, myalgia, tinnitus, pruritus, dyspnoea, yawning, and rashes. (290)
- Aggressive behaviour has developed with venlafaxine treatment particularly at the start and when stopping therapy. (290)
- Increased blood pressure (regular checks are advised). (289)
- Abuse, especially in patients with a history of addiction. (289)

- Alopecia has been described, probably with a low incidence.(304) (
- At very high doses (in reported cases, 5 to more than 10 times the maximum daily dose of 375 mg): amphetamine-like stimulant effect, which causes dependence in some people. (307)
- At high doses or in case of overdose: potentially very serious side effects: chest pain, hypertension, QT interval prolongation, tachycardia and agitation, but also bradycardia, hypotension, muscle weakness increasing the risk of falls, drowsiness, dizziness, convulsions, coma and even death. (307)

11.12.6 Interactions: antidepressants in general

- Increased risk of convulsions when associated with other agents that may provoke convulsions.(289)
- Increased risk of serotonin syndrome when associated with other agents with serotoninergic activity: amitriptyline, venlafaxine, duloxetine. (289)
- Exaggerated sedation when associating antidepressants with sedative effect (amitriptyline) with other drugs with sedative effect or with alcohol. (289)
- Increased risk of hyponatraemia when associating with agents that also have such an effect, such as thiazides and loop diuretics, NSAIDs, carbamazepine. (289)
- Serious adverse events (hypertensive and hyperpyretic crises that can be fatal) when associating MAO inhibitors (especially the non-selective ones) with other antidepressants. Other antidepressants should therefore not be administered within 2 weeks after stopping an MAO inhibitor. MAO inhibitors must also not be administered within 2 weeks after stopping another antidepressant. (289)

11.12.7 Interactions: TCA (amitriptyline)

- Reduced effect of antihypertensive drugs with central action by most TCAs and related antidepressants. (289)
- Enhanced effect of sympathomimetics, eg used as decongestants, by most TCAs and related antidepressants. (289)
- Increased risk of anticholinergic adverse events when associated with other agents with an anticholinergic effect. (289)
- Drugs that prolong the QT interval, including antiarrhythmics such as amiodarone or quinidine, the antihistamines astemizole and terfenadine, some antipsychotics (notably pimozide, sertindole, and thioridazine), cisapride, halofantrine, and sotalol, may increase the likelihood of ventricular arrhythmias when taken with TCA. This may be exacerbated where the interacting drug (such as quinidine or some antipsychotics) also reduces TCA metabolism. (290)

<u>Amitriptyline:</u>

- Is a substrate of CYP1A2 and CYP2D6 and of P-gp. (289)

11.12.8 Interactions: SNRI (venlafaxine)

- Increased risk of bleeding when associated with antithrombotic drugs, NSAIDs or acetylsalicylic acid. (289)
- Increased risk of hyponatraemia when associated with diuretics. (289)

Venlafaxine: is a substrate and inhibitor of CYP2D6 and a substrate of P-gp. (289)

11.12.9 Special precautions: TCA (amitriptyline)

- The antimuscarinic effects of TCA warrant care in patients with urinary retention, prostatic hyperplasia, or chronic constipation; caution has also been advised in untreated angle-closure glaucoma and in phaeochromocytoma. (290)
- The epileptogenic potential of TCA requires care in patients with a history of epilepsy. (290)
- Because of their potential cardiotoxicity, TCA should be used with caution in patients with cardiovascular disease and avoided in those with heart block, cardiac arrhythmias, or in the immediate recovery period after myocardial infarction. Caution has also been recommended in patients with hyperthyroidism as TCA may increase the risk of developing cardiac arrhythmias. (290)
- Blood-sugar concentrations may be altered in diabetic patients. (290)
- TCA may inhibit salivation and regular dental check-ups are recommended for patients on long-term therapy, particularly when taking those with marked antimuscarinic actions. (290)
- TCA should be withdrawn gradually to reduce the risk of withdrawal symptoms. (290) Suddenly stopping antidepressant therapy after regular use for 8 weeks or more may precipitate withdrawal symptoms. The symptoms associated with withdrawal of TCA appear to form 4 distinct syndromes:
    - gastrointestinal disturbances and generalised somatic symptoms such as malaise, chills, headache, and increased perspiration, which may also be accompanied by anxiety and agitation,
    - sleep disturbances characterised by insomnia followed by excessive and vivid dreams,
    - parkinsonism or akathisia,
    - hypomania or mania.

  TCA withdrawal has also resulted in cardiac arrhythmias in some patients. (290)

11.12.10 Special precautions : SNRI (venlafaxine)

- Check blood pressure during treatment. (290)
- Caution in case of history of convulsions, bleeding, mania. (290)
- Follow-up of patients with increased intra-ocular pressure or risk of closed-angle glaucoma. (290)

Venlafaxine:

- caution in case of moderate to severe liver or kidney failure. (290)
- Withdrawal reactions may be more common with venlafaxine than with some other serotonergic antidepressants (290)

11.12.11 Specific populations

11.12.11.1 Pregnancy and lactation, antidepressants in general

- Antidepressants should be avoided as much as possible during the entire duration of the pregnancy. (289)
- A teratogenic effect cannot be excluded for any antidepressant. Most of the data with reassuring results concern SSRIs and TCA (amitriptyline). (289)
- Problems with the newborn child when used shortly before delivery (289):
    - Respiratory problems, drinking problems, convulsions, persistent crying, muscle rigidity, risk of delivery haemorrhage (308)with maternal use of SSRIs and some other antidepressants (eg venlafaxine).
    - Anticholinergic effects (excitation, suction disorders and, less frequently, arrhythmias, intestinal motility disorders and urinary retention) when the mother uses anti-depressants with anticholinergic properties (including amitriptyline). (298)

11.12.11.2 Pregnancy and lactation, TCA (amitriptyline)

- No adverse effects have been demonstrated with amitriptyline use in the first and second trimester. (298)
- The safety profile of amitriptyline used in the third trimester is less clear. (298)
- Amitriptyline has anticholinergic properties. Its use shortly before delivery may result in anticholinergic side effects (excitement, sucking difficulties, and less frequently, cardiac arrhythmias, bowel motility disorder and urinary retention). (298)

- In general, only small amounts of tricyclic antidepressants are distributed into breast milk. Nevertheless, the American Academy of Pediatrics considers that the effect of all antidepressants, including tricyclics, on nursing infants is unknown but may be of concern. In addition, most manufacturers advise that tricyclics should be avoided by women during breast feeding. (290)

11.12.11.3 Pregnancy and lactation, SNRI (venlafaxine)

- Licensed product information recommends that venlafaxine should not be used during pregnancy unless clearly necessary. (290)
- Venlafaxine and its metabolite O-desmethylvenlafaxine are distributed into breast milk. (290)
- Licensed product information recommends that venlafaxine should not be used in women who are breast feeding. (290)

11.12.11.4 Children and adolescents, TCA (amitryptiline)

- Tricyclic antidepressants are not recommended in children under 6 years of age. (290)
- Withdrawal symptoms seem to be more common and more severe in children. (290)

11.12.11.5 Children and adolescents, SNRI (venlafaxine)

- Suicidal ideation has been reported, particularly in children when used for the treatment of depression in children and adolescents under 18 years old. (290)

11.12.11.6 Elderly, antidepressant in general

- Higher risk of hyponatraemia with risk of agitation and confusion, especially with SSRI's and venlafaxine. (289)

11.12.11.7 Elderly, TCA (amitriptyline)

- Elderly patients can be particularly sensitive to the adverse effects of tricyclic antidepressants and a reduced dose, especially initially, should be used. (290)
- Orthostatic hypotension and tachycardia can occur in patients without a history of cardiovascular disease, and may be particularly troublesome in the elderly. (290)

11.13 Anti-epileptics

11.13.1 Contra-indications: topiramate

- Pregnancy, especially when used as a prophylactic treatment for migraine in view of the alternatives. (289)

11.13.1.1 Contra-indications: valproate

- Pregnancy. (289)
- Increased risk of bleeding and bleeding disorders. (289)
- Certain mitochondrial diseases; therefore, do not use in young children with developmental disorders of unknown etiology. (289)
- Liver failure. (289)

11.13.2 Adverse events: anti-epileptics in general

- Anti-epileptics are drugs with a narrow therapeutic-toxic margin. (289)
- Frequent (289):
    - haematological disorders,
    - electrolyte disorders,
    - liver function disorders,
    - osteo-articular disorders,
    - especially in the elderly, cognitive disorders.
- Behavioral changes and mood disorders, including suicidal thoughts. (289)
- Cardiac arrhythmias or conduction disorders with multiple anti-epileptics. (289)
- Serious ocular problems (contraction of the peripheral field of vision, glaucoma, pigment deposit in the retina) with some anti-epileptics (including topiramate). (289)
- Tremor (especially with valproate), parkinsonian syndrome. (305)
- Stevens-Johnson syndrome and Lyell syndrome with multiple anti-epileptics. (289)
- Drug Reaction with Eosinophilia and Systemic Symptoms syndrome (DRESS syndrome, see DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome), especially with carbamazepine, phenobarbital, phenytoin and lamotrigine. (289)

11.13.2.1 Adverse events: topiramate

- Mostly cognitive impairment (e.g. word finding difficulties), drowsiness, fatigue, paresthesias, depression, tremor, ataxia, dizziness, headache, weight loss, nausea, diarrhoea, nasopharyngitis, renal lithiasis. (289)
- Agitation, anxiety, nervousness, emotional lability, and mood disorders may also occur. (290)

- Other reported adverse effects include abdominal pain, anorexia, asthenia, diplopia, leucopenia, nystagmus, insomnia, psychomotor retardation, impaired speech, altered taste, visual disturbances. (290)
- The risk of bleeding or of developing renal calculi is increased, especially in predisposed patients. (290)
- Rare: acute glaucoma and metabolic acidosis. (289)
- Also heat stroke by inhibition of carbonic anhydrase (resulting in decreased sweating and a diuretic effect). (298)

11.13.2.2 Adverse events: valproate

- Frequent:
  - gastrointestinal disorders such as nausea, vomiting and diarrhea (289),
  - increased appetite (290), weight gain (289).
- Less common adverse effects include oedema, headache. (290)
- Leucopenia and bone marrow depression have been reported. (290)
- Pancreatitis. (289)
- Hair loss (reversible). (289)
- Adverse effects on alertness and cognitive function. (289)
- Dizziness. (289)
- Tremor: valproate-related tremor is usually acute, but may also occur with chronic treatment, and is therefore a subacute or delayed abnormal movement. (305)
- Acute liver failure, especially in very young children with severe epilepsy and on polymedication (especially when taking phenytoin concomitantly), and most often in the first few weeks of treatment. (289)
- Thrombocytopenia with coagulation and haemostasis disorders (289)
- Clinical manifestation or aggravation of certain congenital mitochondrial diseases. (289)
- Also very rarely: gynecomastia. (299)
- Encephalopathy in case of abrupt dose increase. (289)
- Neurological adverse effects including ataxia, sedation, lethargy, confusion, have occasionally been reported, although these are often associated with too high a starting dose, increasing doses too rapidly, or use with other antiepileptics. (290)

11.13.2.3 Adverse events: lamotrigine

- Very frequent: rash; increased risk if dose is increased too rapidly or in combination with valproic acid/valproate. Rarely other skin lesions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS. (289)
  It is well known that lamotrigine can cause severe skin reactions, including Lyell's and Stevens-Johnson syndrome (incidence of severe skin reactions estimated at 1/1000 to 1/500 in adults, and 1/300 to 1/100 in children). (309)
- Nausea, headache, drowsiness, insomnia, agitation, dizziness, ataxia, tremor, diplopia. (289)
- Tics, nystagmus (290)
- Other adverse effects include angioedema, photosensitivity, blurred vision, conjunctivitis, tiredness, irritability and aggression, hallucinations and confusion. (290)
- Aggravation of certain types of myoclonus and certain epileptic syndromes. (289)
- Rare: lupus-like reactions (290), aseptic meningitis, arrhythmias. (289)

11.13.3 Interactions : anti-epileptics in general

- Excessive sedation when associated with other drugs with sedative effect or with alcohol. (289)

- Many anti-epileptic drugs are potent enzyme inducers, which can lead to numerous interactions with other drugs (including vitamin K antagonists), with vitamin D and with other anti-epileptic drugs. Important interactions include loss of efficacy of hormonal contraceptives (oral, transdermal, vaginal, implants) and oral emergency hormonal contraception. (289)
- Other anti-epileptic drugs are inhibitors. (289)

11.13.4 Interactions : topiramate

- Topiramate is an inhibitor of CYP2C19 and a substrate for CYP3A4 (289)
- At high doses (from 200 mg per day or more) :
    - Topiramate is an inducer of CYP3A4: an important interaction is the loss of efficacy of hormonal contraceptives (oral, transdermal, vaginal, implants) and oral emergency hormonal contraception. (289)
    - Topiramate may increase lithium toxicity (289)

11.13.5 Interactions: valproate

- Decreased plasma concentrations of valproic acid/valproate when combined with carbapenems. (289)
- Increased plasma concentrations of lamotrigine and phenobarbital when combined with valproic acid/valproate. (289)
- Increased risk of encephalopathy in combination with phenytoin, phenobarbital or topiramate. (289)
- Valproic acid is a substrate for CYP2C9 and CYP2C19. (289)

11.13.6 Interactions: lamaotrigine

- Increased risk of rash with concomitant valproic acid/valproate treatment. (289)
- Decreased plasma concentrations of lamotrigine when combined with inducers of UDP-glucuronyltransferase (e.g. carbamazepine, phenytoin, phenobarbital, primidone, rifampin). (289)
- Oral contraceptives may decrease plasma concentrations of lamotrigine, which may result in increased lamotrigine levels during the pill-free week, with the potential for toxicity. Pregnancy has been reported in women on oral hormonal contraceptives taking lamotrigine (no data are available for hormonal contraceptives administered by other routes). (289)
- Increased plasma concentrations of lamotrigine when combined with valproic acid/valproate. (289)

11.13.7 Special precautions, anti-epileptics in general

- Stopping suddenly or reducing the dose too quickly can trigger an epileptic seizure and can even result in a status epilepticus; reducing the dose should be done gradually. (289)

11.13.8 Special precautions, topiramate

- In patients with a history of renal lithiasis, the risk of lithiasis formation is high. (289)

11.13.9 Special precautions, valproate

- Transaminases, lipases and haemostasis (platelets, coagulation) should be measured before starting treatment, and checked every 3 months for the first year of treatment, and then annually. (289)
- In case of hypoalbuminemia, lower doses should be used, depending on the clinical effect. (289)

11.13.10 Special precautions, lamotrigine

- Lamotrigine should be given with caution to patients with hepatic or renal impairment. (290)
- All patients should be warned to see their doctor immediately if rashes or symptoms associated with hypersensitivity develop. To minimise the risk of developing serious skin reactions, dosage recommendations should not be exceeded. (290)
- Withdrawal of lamotrigine should be considered if rash, fever, flu-like symptoms, drowsiness, or worsening of seizure control occurs. Care is required when withdrawing lamotrigine therapy. Abrupt withdrawal should be avoided unless serious skin reactions have occurred. Lamotrigine should not be restarted in patients with previous hypersensitivity. (290)

11.13.11 Specific populations

11.13.11.1 Pregnancy and lactation: anti-epileptics general

- There is a risk of teratogenicity with many anti-epileptics. (289)
- Effective contraception is recommended for women of reproductive age using anti-epileptic drugs who do not wish to become pregnant, with attention to possible interactions. For women of reproductive age using anti-epileptic drugs who wish to become pregnant, evaluation of anti-epileptic treatment, in consultation with the woman, preferably long enough before conception, is important. (289)
- Long-term effects on the child's brain and behaviour have been described with some anti-epileptic drugs (especially valproic acid, phenobarbital and phenytoin); the risk seems highest with valproic acid. (289)
- Women on anti-epileptic treatment should be given 0.4 mg of folic acid per day from the time of stopping the contraception and certainly around conception. Higher doses (4 mg) are no longer routinely recommended for women with epilepsy, but may be prescribed if there is a history of neural tube defects in a previous pregnancy. (289)
- Antiepileptics are generally distributed into breast milk. (290)

11.13.11.2 Pregnancy and lactation: topiramate

- There is clear evidence of an increased risk of congenital malformations. (289)

11.13.11.3 Pregnancy and lactation: valproate

- Valproic acid should be avoided throughout pregnancy and should not be prescribed to women of childbearing age unless there is no alternative. It is associated with a greater risk of birth defects (particularly neural tube defects) than other anti-epileptic drugs and causes subsequent cognitive and behavioural problems in the child. (289)
- The prescription of valproic acid to women of childbearing age is subject to specific conditions. (289)
- Thrombocytopenic purpura and anaemia occurred in a breast-fed infant whose mother was being treated with valproic acid. (290)

11.13.11.4 Pregnancy and lactation: lamotrigine

- There is a theoretical risk of teratogenicity with lamotrigine because, like valproate, it is a folate antagonist. (290)
- Low-dose lamotrigine appears to be less toxic to the foetus than other anti-epileptic drugs. (289)
- Lamotrigine may accumulate in breast-fed infants, as the metabolic pathway for lamotrigine may not be fully developed in newborns. (290)
- Use of lamotrigine by mothers during breast feeding may be of concern, since there is the potential for therapeutic serum concentrations to occur in the infant. (290)

11.13.11.5 Children and adolescents: topiramate

- In children in particular, there is a risk of dehydration and heat stroke. (289)
- Reduced sweating with hyperthermia has occurred particularly in children. (290)

11.13.11.6 Children and adolescents: valproate

- In children, transaminases, lipases and haemostasis (platelets, coagulation) should be measured before starting treatment, and monitored monthly for the first 6 months. (289)
- Reports of nocturnal enuresis in children. (310)
- Irregular menstruation in adolescent girls. (289)

11.13.11.7 Children and adolescents: lamotrigine

- The incidence of severe skin reactions is estimated at 1/300 to 1/100 in children. (309)

11.13.11.8 Elderly: anti-epileptics in general

- Frequent : cognitive disorders with antiepileptic drugs, especially in the elderly. (289)
- Use lower doses of valproate in the elderly, depending on the clinical effect. (289)

11.14 Monoclonal antibodies

11.14.1 Adverse events

- Injection site reactions. (289)

- Constipation. (289)
- Pruritus. (289)
- Aggravation of Raynaud's phenomenon. (289)
- Severe hypersensitivity reactions (angioedema, anaphylactic reactions, urticaria,...) which may occur from a few minutes to one month after administration. (289)

Erenumab: also muscle spasms. (289)

Fremanezumab: also dizziness, bronchitis. (289)

Galcanezumab: also dizziness (289)

11.14.2 Special precautions

- Patients with certain severe cardiovascular diseases were excluded from the clinical studies. No safety data are available in these patients. (289)
- Post-marketing data suggest an increased risk of hypertension in some patients. This risk is mainly reported with erenumab, but cannot be excluded with galcanezumab and fremanezumab. (289)
- Treatment should be initiated by a neurologist or neuropsychiatrist. (289)

11.14.3 Specific populations

11.14.3.1 Pregnancy and lactation

No direct or indirect harmful effects have been established in animal studies, but as a precautionary measure, monoclonal antibodies should be avoided during pregnancy. (289)

11.15 Botulinum toxin

11.15.1 Contra-indications

- Muscle diseases such as myasthenia gravis. (289)
- Infection at the injection site. (289)
- Acute urinary retention in the treatment of bladder disorders. (289)

11.15.2 Adverse events

- Injections of botulinum toxins have been associated with a transient burning sensation, bruising at the injection site, and local weakness. (290) Exaggerated muscle weakness may occur with therapeutic doses. (290)
- Depending on the location of the injection (289) :
    - Blepharoptosis (289), hemifacial spasm, or strabismus, lachrymation, photophobia, ocular irritation, and facial swelling (290).
    - Dysphagia (289), dry mouth, paralysis of the vocal cords, and weakness of the neck muscles may also occur (290).
    - Falling, leg pain, and local and general weakness; lethargy and leg cramps. (290)

    - Headache is the most frequent adverse effect after injection into the muscles around the forehead in the treatment of glabellar (frown) lines. (290)
    - Other adverse effects frequently reported include ptosis, facial pain, muscle weakness, and nausea. (290)
- Rarely (289): anaphylactic reactions.
- Very rarely but can be fatal (289):
    - arrhythmias,
    - myocardial infarction
    - aspiration pneumonia.
- Also: urinary incontinence (sometimes slowly reversible).(310)

11.15.3 Specific populations

11.15.3.1 Pregnancy and lactation

- Botulinum toxin in chronic migraine: although this is a local treatment and botulinum toxin cannot cross the placental barrier, there is little clinical evidence to support its safe use in pregnancy. (298)
- Animal studies have demonstrated reproductive toxicity. (298)
- According to the SPC, the product should not be used during pregnancy unless absolutely necessary. (298)

11.16 Melatonin

11.16.1 Adverse events

- Psychomotor hyperactivity. (289)
- Nightmares. (289)
- Dizziness. (289)
- Hypertension. (289)
- Neurological disorders: syncope, drowsiness, headache, convulsions.(311) Melatonin may increase the frequency of convulsions in epileptic patients. (289)
- Psychological disorders: anxiety, depressive disorders.(311)
- Skin disorders: rash, maculopapular rash. (311)
- Digestive disorders: vomiting, constipation, acute pancreatitis (311), abdominal pain (289).
- Exacerbation of autoimmune disease has been reported in patients taking melatonin. (289)
- It is not clear whether there is tolerance to the effects of melatonin. (289)
- Ischaemic priapism. (312)
- In case of overdose (311)):
    - neurological side effects and tachycardia (in the context of a suicide attempt);
    - nausea, dizziness, vomiting and drowsiness (in case of chronic overuse).

11.16.2 Interactions

- Increased sedation when combined with other drugs with sedative effect or alcohol. (289)
- Melatonin is a CYP1A1 (290) and CYP1A2 (289, 290) substrate.

- Melatonin should not be taken with fluvoxamine, methoxsalen, cimetidine, or oestrogens, all of which increase melatonin concentrations through inhibition of its metabolism. (290)

11.16.3 Special precautions

- Normal-release preparation: take outside of mealtimes (minimum 2 hours before or after meals, 3 hours in diabetic patients). (289)
- Melatonin should not be used in patients with auto-immune disease or hereditary galactose intolerance disorders, LAPP lactase deficiency, or glucose-galactose malabsorption. Melatonin should not be used in patients with hepatic impairment because of reports of decreased clearance in such patients. (290)

11.16.4 Specific populations

11.16.4.1 Pregnancy and lactation

- Melatonin should be avoided during pregnancy and lactation due to the lack of data regarding its safety profile. (289)
- In animals, problems have been seen at high doses: bone damage, intrauterine growth retardation, embryonic loss, behavioural disorders. (311)

11.17 Folic acid

11.17.1 Contra-indications

- Vitamin B12 deficiency: treatment with high doses of folic acid may mask a vitamin B12 deficiency. In case of pernicious anaemia, folic acid alone corrects only the anaemia, but not the neurological disorders. (289)

11.17.2 Adverse events

- Folic acid is generally well tolerated. (290)
- Gastrointestinal disturbances and hypersensitivity reactions have been reported rarely. (290)

11.17.3 Interactions

- Increased toxicity of fluorouracil and its prodrugs (capecitabine and tegafur). (289)
- Decreased plasma concentrations of some anti-epileptic drugs (phenytoin, phenobarbital, primidone, possibly also carbamazepine and pheneturide) when taking high doses of folic acid (5 to 15 mg per day). (289)
- Folate deficiency states may be produced by drugs such as antiepileptics, oral contraceptives, antituberculous drugs, alcohol, glucarpidase, and folic acid antagonists such as methotrexate, pyrimethamine, triamterene, trimethoprim, and sulfonamides. In some instances, such as during methotrexate or antiepileptic therapy, replacement therapy with folinic acid or folic acid may become necessary in order to prevent megaloblastic anaemia developing; folate supplementation has reportedly decreased serum-phenytoin concentrations in a few cases and there is a possibility that such an effect could also occur with barbiturate antiepileptics. (290)

11.17.4 Special precautions

- Folic acid should never be given alone or with inadequate amounts of vitamin B12 for the treatment of undiagnosed megaloblastic anaemia, since folic acid may produce a haematopoietic response in patients with a megaloblastic anaemia due to vitamin B12 deficiency without preventing aggravation of neurological symptoms. This masking of the true deficiency state can lead to serious neurological damage, such as subacute combined degeneration of the spinal cord. (290)

11.18 Magnesium

11.18.1 Adverse events

- Mainly gastrointestinal (diarrhoea, abdominal pain). (289) Taking with food may decrease the incidence of diarrhoea. Chronic diarrhoea from long-term use may result in electrolyte imbalance. (290)
- For patients with renal failure, there is a risk of hypermagnesemia, with flushing, hypotension, loss of muscle reflexes, muscle weakness, sedation.(313)

1.18.2 Interactions

- Magnesium malabsorption with PPIs.(314)
- Oral magnesium salts decrease the absorption of tetracyclines and bisphosphonates, and doses should be separated by a number of hours. (290)

11.19 Riboflavin (vitamin B2)

11.19.1 Special precautions

- Large doses of riboflavin result in a bright yellow discoloration of the urine that may interfere with certain laboratory tests. (290)

11.20 Vitamin B12

11.20.1 Adverse events

- Allergic hypersensitivity reactions have occurred rarely after cyanocobalamin and hydroxocobalamin and include skin reactions such as rash and itching, and anaphylaxis. (290)
- Other adverse effects reported with cyanocobalamin and hydroxocobalamin include gastrointestinal disturbances, fever, chills, hot flushing, dizziness, malaise, acneform and bullous eruptions, and tremor. Headaches, paraesthesia, and chromaturia have occurred with hydroxocobalamin. (290)
- Arrhythmias secondary to hypokalaemia have occurred at the beginning of parenteral treatment with hydroxocobalamin. (290)

11.20.2 Interactions

Many of these interactions are unlikely to be of clinical significance but should be taken into account when performing assays for blood concentrations. (290)

- Absorption of vitamin B12 from the gastrointestinal tract may be reduced by neomycin, aminosalicylic acid, histamine H2-antagonists, omeprazole, and colchicine. (290)
- Serum concentrations may be decreased by use of oral contraceptives. (290)
- Vitamin b12 malabsorption with Ipps.(314)
- Parenteral chloramphenicol may attenuate the effect of vitamin B12 in anaemia. (290)

11.20.3 Special precautions

- Cyanocobalamin or hydroxocobalamin should, if possible, not be given to patients with suspected vitamin B12 deficiency without first confirming the diagnosis. (290)
- Regular monitoring of the blood is advisable. (290)
- Use of doses greater than 10 micrograms daily may produce a haematological response in patients with folate deficiency; indiscriminate use may mask the precise diagnosis. (290)
- Conversely, folate may mask vitamin B12 deficiency. (290)
- Cyanocobalamin should not be used for Leber's disease or tobacco amblyopia since these optic neuropathies may degenerate further. (290)

12 Appendix. Evidence tables. Acute treatment of migraine in adults.

12.1 Paracetamol

12.1.1 Paracetamol versus placebo for acute treatment of migraine in adults

Meta-analysis: VanderPluym 2021(1), Acute Treatments for Episodic Migraine in Adults A Systematic Review and Meta-analysis

Definition of migraine: the definition used in the original studies was accepted as long as it also fit the current *International Classification of Headache Disorders,*
Third Edition criteria for episodic migraine (defined as the presence of headache 14 or fewer days per month in someone whohas migraine).

Inclusion criteria: Eligible studies (1) included adult patients (≥18 years)with episodic migraine; (2) evaluated abortive pharmacologic therapy or noninvasive nonpharmacologic abortive therapy; (3) involved comparisons of the intervention with placebo, usual care, another pharmacologic therapy, noninvasive nonpharmacologic therapy, wait list, no treatment, or attention control, (4) reported short-term outcomes of interest (≤4 weeks after the end of treatments); and (5) were published in English.

Exclusion:
Invasive treatments (defined as surgically implanted), preventive treatments, in vitro studies, studies without original data, and single-group studies were excluded. Therapies in development, with terminated development, or unavailable in the United States were also excluded.
Studies that randomized migraine attacks instead of patients were not meta-analyzed because correlations between attacks could not be controlled.

Search strategy: EMBASE, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, PsycINFO, and Scopus from database inception to February 24, 2021, were searched. Clinical trial registries, governmentdatabasesandwebsites, conference proceedings, patient advocate groupwebsites, and medical society websites were also searched. Reference mining of existing systematic reviews/meta-analyses, clinical trial registries, and relevant primary studies was conducted to identify additional literature.

Assessment of quality of included trials: yes

Other methodological remarks:
All statistical analyses for RCTs involved analyzing participants according to their original allocation group. For crossover RCTs, outcomes before crossover were used in meta-analysis.8 Studies that randomized migraine attacks instead of patients were not meta-analyzed because correlations between attacks could not be controlled. DerSimonian-Laird random-effects model with Hartung- Knapp-Sidik-Jonkman variance correction was used to combine direct comparisons between treatments if the number of studies included in the analysis was larger than 3. The fixed-effect method based on the Mantel-Haenszel method was adopted when the number of studies was 3 or fewer.

Ref	Comparison	N/n	Outcomes	Result
VanderPluym2021 Design: SR+MA Search date: February 2021	Paracetamol Vs Placebo	N = 2 n = 729 (Lipton 2000, Prior 2010)	Pain free at 2h	Paracetamol: 57/366 Placebo: 30/363 **RR (95% CI): 1.89 (1.24 to 2.86)** **SS in favour of paracetamol** I^2= 0%
		N = 2 n = 729 (Lipton 2000, Prior 2010)	Pain free at 24h	Paracetamol: 124/366 Placebo: 69/363 **RR (95% CI): 1.78 (1.38 to 2.30)** **SS in favour of paracetamol** I^2=0.00%
		N = 2 n = 729 (Lipton 2000, Prior 2010)	Pain relief at 2h (Improvement of pain from moderate to severe at baseline to mild or none or pain scale improved at least 50% from baseline at defined assessment time)	Paracetamol: 177/366 Placebo: 109/363 **RR (95% CI):** 1.61 (1.33 to 1.95) **SS in favour of paracetamol** I^2=0.00%

		N = 2 n = 729 (Lipton 2000, Prior 2010)	Pain relief at 24h (Improvement of pain from moderate to severe at baseline to mild or none or pain scale improved at least 50% from baseline at defined assessment time)	Paracetamol: 196/366 Placebo: 114/363 **RR (95% CI):** 1.71 (1.43 to 2.04) **SS in favour of paracetamol** I^2=0.00%
		N = 2 n = 729 (Lipton 2000, Prior 2010)	Restored function at 2h (No restriction to perform work or usual activities)	Paracetamol: 76/366 Placebo: 42/363 **RR: 1.8; 95% CI: 1.27 to 2.54** **SS in favour of paracetamol** I^2= not provided
		N = 2 n = 729	Restored function at 24h (No restriction to perform work or usual activities)	Paracetamol: 155/366 Placebo: 88/363 **RR: 1.75; 95% CI: 1.41 to 2.17** **SS in favour of paracetamol** I^2= not provided
		N = 2 n = 729 (Lipton 2000, Prior 2010)	Pain scale at 2h	SMD (95% CI): 0.39 (0.25 to 0.54) **SS in favour of paracetamol** I^2= not provided
		N = 1 n = 351 (Lipton 2000)	Pain scale at 24h	SMD (95% CI): 0.31 (0.10 to 0.52) **SS in favour of paracetamol**

		N = 1 n = 378 (Prior 2010)	Function scale at 2h	SMD (95% CI): 0.38 (0.18 to 0.59) **SS in favour of paracetamol** -
		N = 2 n = 194 (Lipton 2000, Prior 2010)	Serious adverse events.	RR: 0.99; 95% CI 0.06 to 15.86 **NS** I^2= 0%
		N = 2 n = 729 (Lipton 2000, Prior 2010)	Total adverse events	RR: 0.82; 95% CI: 0.64 to 1.06; NS I2=0.00%
		N = 1 n = (Prior 2010)	Withdrawal due to adverse events	RR: 1.98; 95% CI: 0.18 to 21.64 NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Lipton 2000	351	Outpatients. Migraine ± aura (IHS 1988). Aged ≥ 18 years. Frequency 0.5 to 6 per month. Untreated severity ≥ moderate.	6h	Paracetamol Vs Placebo Paracetamol: 1000mg	Overall: Moderate risk of bias Randomization: Moderate risk Deviation from intended intervention: Low risk Missing outcome data: Low risk

		Excluded: require bedrest for >50%, or vomiting with >2 0% of attacks 15 % with aura Paracetamol: n = 176, 37.3 ± 10.4 years, 76.9% female, 23.8% African American, 75.5% White, 0.7% others Placebo: n = 175, 36 ± 9.3 years, 83.1% female, 28.9% African American, 69.7% white, 1.4% others		Oral, once Rescue medication after 2 h if necessary	Measurement of outcome: Low risk Selection of reported results: Low risk FOLLOW-UP: Not reported ITT: Not reported FUNDING: Not reported
Prior 2010	378	Outpatients. Episodic migraine ± aura (IHS 2004). Age ≥ 18 years. History of 0.5 to 6 attacks/month in past year and previous treatment with OTC medication. Untreated severity ≥ moderate. Excluded: require bedrest for > 50%, or vomiting with > 20% of attacks 22% with aura Paracetamol: n = 190, 38.1 ± 11 years, 80.8% female, 87% White Placebo: n = 188, 39.8 ± 11.8 years, 85.8%	3 days	Paracetamol Vs Placebo Paracetamol: 1000mg Oral, once Rescue medication after 2 h if necessary	Overall: Low risk of bias Randomization: Low risk Deviation from intended intervention: Low risk Missing outcome data: Low risk Measurement of outcome: Low risk Selection of reported results: Low risk FOLLOW-UP: Not reported ITT: Not reported FUNDING: Not reported

		female, 85.8% White			

Remarks:
Paracetamol 1000 mg was compared to placebo

12.2 Acetylsalicylic acid

12.2.1 Acetylsalicylic acid versus placebo for acute treatment of migraine attack of moderate to severe baseline pain intensity in adults

Meta-analysis: Kirthi 2010(16), Aspirin with or without an antiemetic for acute migraine headaches in adults

Definition of migraine: The diagnosis of migraine specified by the International Headache Society (IHS 1988; HIS 2004) was used, although other definitions were considered if they conformed in general to IHS diagnostic criteria.

Inclusion criteria: Randomised, double-blind, placebo or active-controlled studies using aspirin to treat a discrete migraine headache episode were included. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data. Studies reporting treatment of consecutive headache episodes were accepted if outcomes for the first, or each, episode were reported separately. Cross-over studies were accepted if there was adequate washout between treatments.

Population: Studies included adults (at least 18 years of age) with migraine. There were no restrictions on migraine frequency, duration or type (with or without aura). Participants taking stable prophylactic therapy to reduce the frequency of migraine attacks were accepted.
There were no restrictions on dose or route of administration, provided the medication was self-administered.

Studies to demonstrate prophylactic efficacy in reducing the number or frequency of migraine attacks were not included.

Search strategy: The following databases were searched: • Cochrane CENTRAL, Issue 1, 2010; • MEDLINE (via OVID), 10 March 2010;
• EMBASE (via OVID), 10 March 2010; • Oxford Pain Relief Database (Jadad 1996a).

Reference lists of retrieved studies and review articles were searched for additional studies. Grey literature and abstracts were not searched.

Assessment of quality of included trials: yes

Other methodological remarks:
We accepted randomisation to individual patient only.
The most likely source of missing data is in cross-over studies. Where this was an issue, only first-period data were used.
Relative risk of benefit or harm was calculated with 95% confidence intervals (CIs) using a fixed-effect model. NNT, NNTp and NNH with 95% CIs were calculated using the pooled number of events by the method of Cook and Sackett.
Some studies were inconsistent in the denominators reported and, for instance, reported on one or two patients fewer than the intention-to-treat population for some outcomes, but not for others, without giving a reason. As the denominators were always within a few patients of the intention-to-treat population, we used the denominators given.
Effect sizes were calculated and data combined for analysis only for comparisons and outcomes where there were at least two studies and 200 participants.

Ref	Comparison	N/n	Outcomes	Result
Kirthi 2010 Design: SR+MA Search date: March 2010	Acetylsalicylic acid Vs Placebo	N = 6 n = 2027 (Boureau 1994, Diener 2004a, Diener 2004b; Lange 2000, Lipton 2005, MacGregor 2002)	Pain free at 2h (PO)	Acetylsalicylic acid: 240/1008 (24%) Placebo: 117/1019 (11%) **RR (95% CI): 2.1 (1.7 to 2.6)** NNT (95% CI): 8.1 (6.4 to 11) **SS in favour of acetylsalicylic acid** I^2:0.0%

		N = 4 n = 1288 (Diener 2004a, Diener 2004b; Lipton 2005, MacGregor 2002)	Pain relief at 1 h (PO) (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	Acetylsalicylic acid: 236/641 (37%) Placebo: 99/647 (15%) **RR (95% CI): 2.4 (2.0 to 3.0)** NNT (95% CI): 4.7 (3.8 to 5.9) **SS in favour of acetylsalicylic acid** I^2:28%
		N = 6 n = 2027 (Boureau 1994, Diener 2004a, Diener 2004b; Lange 2000, Lipton 2005, MacGregor 2002)	Pain relief at 2h (PO) (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	Acetylsalicylic acid: 525/1008 (52%) Placebo: 23/1019 (32%) **RR (95% CI): 1.6 (1.5 to 1.8)** NNT (95% CI): 4.9 (4.1 to 6.2) **SS in favour of acetylsalicylic acid** I^2:0.0%
		N = 3 n = 1142 (Diener 2004a, Diener 2004b, Lipton 2005)	Sustained pain relief over 24h (PO) (Headache relief at 2 hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication)	Acetylsalicylic acid: 223/568 (39%) Placebo: 138/574 (24%) **RR (95% CI): 1.6 (1.4 to 2.0)** NNT (95% CI): 6.6 (4.9 to 10 **SS in favour of acetylsalicylic acid** I^2:0.0%

		N = 4 n = 878 (attack with symptoms) (Boureau 1994, Diener 2004a, Lange 2000 Lipton 2005)	Relief of nausea at 2h	Acetylsalicylic acid: 56% Placebo: 44% **RR (95% CI): 1.3 (1.1 to 1.4)** NNT (95% CI): 9.0 (5.6 to 22) **SS in favour of acetylsalicylic acid** I^2:84%
		N = 3 n = 139 (attack with symptoms) (Boureau 1994, Diener 2004b, Lange 2000)	Relief of vomiting at 2h	Acetylsalicylic acid: 73% Placebo: 66% RR (95% CI): 1.1 (0.94 to 1.3) NS **I^2:35%**
		N = 5 n = 1235 (attack with symptoms) (Diener 2004a, Diener 2004b; Lange 2000, Lipton 2005, MacGregor 2002)	Relief of photophobia at 2h	Acetylsalicylic acid: 47% Placebo: 33% **RR (95% CI): 1.4 (1.2 to 1.6)** NNT (95% CI): 7.7 (5.4 to 13) **SS in favour of acetylsalicylic acid** **I^2**:68%

		N = 5 n = 1217 (attack with symptoms) (Diener 2004a, Diener 2004b; Lange 2000, Lipton 2005, MacGregor 2002)	Relief of phonophobia at 2h	Acetylsalicylic acid: 49% Placebo: 34% **RR (95% CI): 1.4 (1.3 to 1.7)** NNT (95% CI): 6.6 (4.9 to 10) **SS in favour of acetylsalicylic acid** I^2:52%
		N = 1 n = 73 (MacGregor 2002)	Improvement of functional disability	Acetylsalicylic acid: 22/53 Placebo: (3/61) **RR (95% CI): 1.4 (1.3 to 1.7)** NNT (95% CI): 6.6 (4.9 to 10) **SS in favour of acetylsalicylic acid**
		N = 5 n = 1881 (Boureau 1994; Diener 2004a; Diener 2004b; Lange 2000; Lipton 2005)	Use of rescue medication	Acetylsalicylic acid: 44% Placebo: 63% **RR (95% CI): 0.67 (0.61 to 0.73)** NNT to prevent (95% CI): 4.8 (3.9 to 6.0) **SS in favour of acetylsalicylic acid** I^2:0.0%

		N = 5 n = 1892 (Boureau 1994; Diener 2004a; Diener 2004b; Lange 2000; Lipton 2005)	Adverse events over 24h	Acetylsalicylic acid: 12% Placebo: 9% **RR (95% CI): 1.3 (1.00 to 1.7)** **NS** I^2:4.0%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Boureau 1994 DB, PC, double-dummy, three-period CO RCT .	247	Aged 18-65 years, meeting IHS criteria for migraine without aura. At least 12-month history of migraine, with age of onset before 50 years and two to six attacks per month. Prophylaxis permitted if stable for ≥ 2 months Excluded participants with other types of headache. Included participants with 'slight' migraine at baseline, but reported primary outcomes for those with ≥ moderate pain separately 36.8% of randomised participants were taking prophylactic therapy	Assessment up to 2h	Aspirin 1000 mg Vs Paracetamol 400 mg + codeine 25 mg Vs placebo Single oral dose of each treatment for each of three migraine attacks If pain not controlled, participants asked to wait 2 hours before taking rescue medication	RANDOMIZATION: Unclear: Not described ALLOCATION CONCEALMENT: Unclear: Not described BLINDING: All outcomes: Yes: Double-dummy design

		n = 198 treated three attacks and analysed for efficacy Aspirin: n = 198 Paracetamol + codeine: n= 198 Placebo: n = 198 M = 57 F = 190 Mean age = 40 years			
Diener 2004a DB, three-arm, PG, double-dummy-RCT	433	Aged 18-65 years, meeting IHS criteria for migraine with and without aura. At least 12-month history of migraine, with one to six attacks per month. Acetylsalicylic acid: n = 146 Sumatriptan: n = 135 Placebo: n= 152 M = 66 F = 367 Mean age 42 years	Assessment up to 24h	Effervescent acetylsalicylic acid 1000 mg Vs Sumatriptan 50 mg Vs placebo Single oral dose Medication taken when migraine headache pain of moderate or severe intensity If pain not controlled, participants asked to wait 2 hours before taking rescue medication	RANDOMIZATION: Yes “Computer-generated randomisation list” ALLOCATION CONCEALMENT: Unclear: Not described BLINDING: All outcomes: Yes: “Matching effervescent or tablet placebo”
Diener 2004b DB, PC, double-dummy, three-period CO RCT	312	Aged 18-65 years, meeting IHS criteria for migraine with and without aura. At least 12-month history of migraine, with one to six attacks per month	Assessment up to 24h	Effervescent acetylsalicylic acid 1000 mg Vs Ibuprofen 400 mg Vs	RANDOMIZATION: Yes “Treatment was assigned by a predetermined randomisation code”

		Acetylsalicylic acid: n = 222 Ibuprofen: n = 212 Sumatriptan: n = 226 Placebo: n = 222 M = 59 F = 253 Mean age 38 years		Sumatriptan 50 mg Vs Placebo, Single oral dose per attack. Each participant treated three migraine attacks with different treatments medication taken when migraine headache pain of moderate or severe intensity. If pain not controlled, participants encouraged to wait 2 hours before taking rescue medication Participants instructed to leave a minimum of 48 hours between consecutive study treatments to ensure that new attack and not migraine recurrence was being treated	ALLOCATION CONCEALMENT: Unclear: Not described BLINDING: All outcomes: Yes: Double dummy design
Lange 2000 DB, PC, PG-RCT	374	Aged 18-65 years, meeting IHS criteria for migraine. At least 12-month history of migraine, with one to six attacks per month	Assessment up to 24h	Effervescent acetylsalicylic acid 2 × 500 mg vs Placebo	**RANDOMIZATION:** Unclear: Not described **ALLOCATION CONCEALMENT:** Unclear: Not described

		Excluded participants usually so incapacitated as to require bed rest during attacks, and those who vomited more than 20% of time during attacks n = 343 analysed for efficacy, 31 did not take medication Acetylsalicylic acid: n = 169 Placebo: n = 174 M = 62 F = 312 Mean age = 42 years		Single oral dose Participants instructed to take medication only if attack of at least moderate intensity, and within 6 hours of onset of symptoms. If pain not controlled, participants asked to wait 2 hours before taking rescue medication	**BLINDING: All outcomes:** Unclear: Not described
Lipton 2005 DB, PC, PG-RCT	409	Aged 18-50 years, meeting IHS criteria for migraine with and without aura. At least 12-month history of migraine, with one to six attacks per month of at least moderate pain intensity. Prophylaxis permitted if stable for ≥3 months 401 with confirmed migraine Aspirin: n = 205 Placebo: n = 204	Assessment up to 24h	Aspirin 1000 mg Vs Placebo Single oral dose Medication administered when migraine headache pain of moderate or severe intensity	**RANDOMIZATION:** Unclear: Not described **ALLOCATION CONCEALMENT:** Unclear: Not described **BLINDING: All outcomes:** Yes "Matched placebo"
MacGregor 2002 DB, PC, two period CO-RCT	101	Aged > 18 years, meeting IHS criteria for migraine with and without aura. At least 12-month history of migraine, with one to six attacks per month within previous three months	Assessment up to 6h	Mouth-dispersible aspirin 900 mg Vs Placebo	RANDOMIZATION: Unclear: Not described ALLOCATION CONCEALMENT: Unclear: Not described

		Excluded: participants who vomited during the majority of their migraine attacks; participants who regularly used NSAIDs or other drugs that could interact with trial medications 73 treated two attacks and analysed for efficacy Mouth-dispersible aspirin: n = 73 Placebo: n = 73 M = 11, F = 90 Mean age 44 years		Single oral dose of each medication for each of two attacks Medication administered when migraine headache pain of moderate or severe intensity	BLINDING: All outcomes: Yes ““Placebo tablets formulated and manufactured to be indistinguishable from aspirin tablets, with respect to appearance, taste and dispersion in mouth”

Remarks:

- Studies using a single dose of aspirin in established pain of at least moderate intensity were analysed separately from studies in which medication was taken before pain was well established or in which a second dose of medication was permitted. All treatments were administered orally, and when the headache was of moderate or severe intensity, except in Boureau 1994, where up to 15% of participants had “slight” headache at baseline. No studies specifically investigated early treatment of attacks while pain intensity was still mild.
- Acetylsalicylic acid doses of 900 mg and 1000 mg were considered sufficiently similar to combine for analysis. Different formulations were used: oral tablet, mouth dispersible or effervescent formulations.
- For studies in which participants were asked to treated consecutive headaches with different study medication, if more than one attack was treated with the same medication, or if a second dose of study medication was permitted if there was an inadequate response to the first, authors have used data for the first attack only, where these data were reported separately, for efficacy outcomes to avoid problems of double counting participants and repeated measures for the same individuals; for use of rescue medication and adverse event data, we have accepted data from multiple attacks in the absence of first-attack data in order to be inclusive and provide conservative estimates.
- Pain intensity or pain relief was measured by the patient (not the investigator or carer). Pain measures accepted for the primary outcomes were: (1) Pain intensity (PI): 4-point categorical scale, with wording equivalent to none, mild, moderate and severe; or 100 mm VAS (2) Pain relief (PR): 5-point categorical scale, with wording equivalent to none, a little, some, a lot, complete; or 100 mm VAS.

Author's conclusions:
"Aspirin 900 mg or 1000 mg is an effective treatment for acute migraine headaches, with participants in these studies experiencing reduction in both pain and associated symptoms, such as nausea and photophobia. Overall, slightly more participants experienced adverse events with either aspirin alone or aspirin plus metoclopramide than with placebo, but the difference barely reached statistical significance."

12.2.2 Acetylsalicylic acid versus ibuprofen for acute treatment of migraine attack of moderate to severe baseline pain intensity in adults

Meta-analysis: Kirthi 2010(16), Aspirin with or without an antiemetic for acute migraine headaches in adults

Definition of migraine: The diagnosis of migraine specified by the International Headache Society (IHS 1988; HIS 2004) was used, although other definitions were considered if they conformed in general to IHS diagnostic criteria.

Inclusion criteria: Randomised, double-blind, placebo or active-controlled studies using aspirin to treat a discrete migraine headache episode were included. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data. Studies reporting treatment of consecutive headache episodes were accepted if outcomes for the first, or each, episode were reported separately. Cross-over studies were accepted if there was adequate washout between treatments.

Population: Studies included adults (at least 18 years of age) with migraine. There were no restrictions on migraine frequency, duration or type (with or without aura). Participants taking stable prophylactic therapy to reduce the frequency of migraine attacks were accepted. Medication was self-administered.

Studies to demonstrate prophylactic efficacy in reducing the number or frequency of migraine attacks were not included.

Search strategy: The following databases were searched: • Cochrane CENTRAL, Issue 1, 2010; • MEDLINE (via OVID), 10 March 2010; • EMBASE (via OVID), 10 March 2010; • Oxford Pain Relief Database.
Reference lists of retrieved studies and review articles were searched for additional studies. Grey literature and abstracts were not searched.

Assessment of quality of included trials: yes

Other methodological remarks:
We accepted randomisation to individual patient only. Authors have used data for the first attack only. For use of rescue medication and adverse event data, we have accepted data from multiple attacks in the absence of first-attack data in order to be inclusive and provide conservative estimates
The most likely source of missing data is in cross-over studies. Where this was an issue, only first-period data were used.
Relative risk of benefit or harm was calculated with 95% confidence intervals (CIs) using a fixed-effect model. NNT, NNTp and NNH with 95% CIs were calculated using the pooled number of events by the method of Cook and Sackett.
Some studies were inconsistent in the denominators reported and, for instance, reported on one or two patients fewer than the intention-to-treat population for some outcomes, but not for others, without giving a reason. As the denominators were always within a few patients of the intention-to-treat population, we used the denominators given.
Effect sizes were calculated and data combined for analysis only for comparisons and outcomes where there were at least two studies and 200 participants.

Ref	Comparison	N/n	Outcomes	Result
Kirthi 2010 Design: SR+MA Search date: March 2010	Acetylsalicylic acid Vs ibuprofen	N = 1 n = 212 (Diener 2004b)	Pain free at 2h (PO) Six studies (2027 participants) provided data on the proportion of patients pain-free at 2 hours.	Acetylsalicylic acid: 60/221 Ibuprofen: 70/211 **Insufficient data for analysis**
		N = 1 n = 212 (Diener 2004b)	Pain relief at 1 h (PO) (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	Acetylsalicylic acid: 76/221 Ibuprofen: 65/211 **Insufficient data for analysis**
		N = 1 n = 212 (Diener 2004b)	Pain relief at 2h (PO) (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	Acetylsalicylic acid: 116/221 Ibuprofen: 127/211 **Insufficient data for analysis**

		N = 1 n = 212 (Diener 2004b)	Use of rescue medication	Acetylsalicylic acid: 99/221 Ibuprofen: 87/211 **Insufficient data for analysis**
		N = 1 n = 212 (Diener 2004b)	Adverse events	Acetylsalicylic acid: 36/221 Ibuprofen: 26/211 **Insufficient data for analysis**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Diener 2004b DB, PC, double-dummy, three-period CO-RCT	312	Aged 18-65 years, meeting IHS criteria for migraine with and without aura. At least 12-month history of migraine, with one to six attacks per month Acetylsalicylic acid: n = 222 Ibuprofen: n = 212 Sumatriptan: n = 226 Placebo: n = 222 M = 59 F = 253 Mean age 38 years	Assessment up to 24h	Effervescent acetylsalicylic acid 1000 mg Vs Ibuprofen 400 mg Vs Sumatriptan 50 mg Vs Placebo Single oral dose per attack. Each participant treated three migraine attacks with different treatments medication taken when migraine headache pain of	RANDOMIZATION: Yes “Treatment was assigned by a predetermined randomisation code” ALLOCATION CONCEALMENT: Unclear: Not described BLINDING: All outcomes: Yes: Double dummy design

				moderate or severe intensity. If pain not controlled, participants encouraged to wait 2 hours before taking rescue medication Participants instructed to leave a minimum of 48 hours between consecutive study treatments to ensure that new attack and not migraine recurrence was being treated	

Remarks:

- Authors calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants. As only one study was found in SR for the comparison acetylsalicylic acid to ibuprofen, no data analysis was performed.
- Studies using a single dose of aspirin in established pain of at least moderate intensity were analysed **separately** from studies in which medication was taken before pain was well established or in which a second dose of medication was permitted. All treatments were administered orally, and when the headache was of moderate or severe intensity.
- Pain intensity or pain relief was measured by the patient (not the investigator or carer). Pain measures accepted for the primary outcomes were: (1) Pain intensity (PI): 4-point categorical scale, with wording equivalent to none, mild, moderate and severe; or 100 mm VAS (2) Pain relief (PR): 5-point categorical scale, with wording equivalent to none, a little, some, a lot, complete; or 100 mm VAS.

Author's conclusions:

"Aspirin 900 mg or 1000 mg is an effective treatment for acute migraine headaches, with participants in these studies experiencing reduction in both pain and associated symptoms, such as nausea and photophobia. Overall, slightly more participants experienced adverse events with either aspirin alone or aspirin plus metoclopramide than with placebo, but the difference barely reached statistical significance."

12.2.3 Acetylsalicylic acid versus sumatriptan for acute treatment of migraine attack of moderate to severe baseline pain intensity in adults

Meta-analysis: Kirthi 2010(16), Aspirin with or without an antiemetic for acute migraine headaches in adults

Definition of migraine: The diagnosis of migraine specified by the International Headache Society (IHS 1988; HIS 2004) was used, although other definitions were considered if they conformed in general to IHS diagnostic criteria.

Inclusion criteria: Randomised, double-blind, placebo or active-controlled studies using aspirin to treat a discrete migraine headache episode were included. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data. Studies reporting treatment of consecutive headache episodes were accepted if outcomes for the first, or each, episode were reported separately. Cross-over studies were accepted if there was adequate washout between treatments.

Population: Studies included adults (at least 18 years of age) with migraine. There were no restrictions on migraine frequency, duration or type (with or without aura). Participants taking stable prophylactic therapy to reduce the frequency of migraine attacks were accepted.

Studies to demonstrate prophylactic efficacy in reducing the number or frequency of migraine attacks were not included.

Search strategy: The following databases were searched: • Cochrane CENTRAL, Issue 1, 2010; • MEDLINE (via OVID), 10 March 2010; • EMBASE (via OVID), 10 March 2010; • Oxford Pain Relief Database (Jadad 1996a).
Reference lists of retrieved studies and review articles were searched for additional studies. Grey literature and abstracts were not searched.

Assessment of quality of included trials: yes

Other methodological remarks:
We accepted randomisation to individual patient only.
The most likely source of missing data is in cross-over studies. Where this was an issue, only first-period data were used.
Relative risk of benefit or harm was calculated with 95% confidence intervals (CIs) using a fixed-effect model.
NNT, NNTp and NNH with 95% CIs were calculated using the pooled number of events by the method of Cook and Sackett.

Some studies were inconsistent in the denominators reported and, for instance, reported on one or two patients fewer than the intention-to-treat population for some outcomes, but not for others, without giving a reason. As the denominators were always within a few patients of the intention-to-treat population, we used the denominators given. Effect sizes were calculated and data combined for analysis only for comparisons and outcomes where there were at least two studies and 200 participants.

Ref	Comparison	N/n	Outcomes	Result
Kirthi 2010 Design: SR+MA Search date: March 2010	Acetylsalicylic acid Vs Sumatriptan	N = 2 n = 726 (Diener 2004a; Diener 2004b)	Pain free at 2h (PO)	Acetylsalicylic acid: 97/367 (26%) Sumatriptan: 116/359 (32%) RR (95% CI): 0.82 (0.65 to 1.03) NS I^2:48%
		N = 2 n = 726 (Diener 2004a; Diener 2004b)	Pain relief at 1 h (PO) (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	Acetylsalicylic acid: 138/367 (38%) Sumatriptan: 85/359 (24%) **RR (95% CI): 1.6 (1.3 to 2.0)** NNT (95% CI) 7.2 (4.9 to 14) **SS in favour of acetylsalicylic acid** I^2:16%
		N = 2 n = 726 (Diener 2004a; Diener 2004b)	Pain relief at 2h (PO) (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	Acetylsalicylic acid: 188/367 (51%) Sumatriptan: 191/359 (53%) RR (95% CI): 0.96 (0.84 to 1.1) NS I^2:0.0%
		N = 2	Relief of photophobia at 2h	Acetylsalicylic acid: 60% Sumatriptan 66% RR (95% CI): 0.91 (0.80 to 1.03)

		n = 575 (attacks with symptoms) (Diener 2004a; Diener 2004b)		NS I^2:0.0%
		N = 2 n = 540 (attack with symptom) (Diener 2004a; Diener 2004b)	Relief of phonophobia at 2h	Acetylsalicylic acid: 63% Sumatriptan 65% RR (95% CI): 0.98 (0.86 to 1.1) NS I^2:0.0%
		N = 2 n = 726 (Diener 2004a; Diener 2004b)	Use of rescue medication	Acetylsalicylic acid: 44% Sumatriptan: 40% RR (95% CI): 1.1 (0.92 to 1.3) NS I^2:0.0%
		N = 2 n = 730 (Diener 2004a; Diener 2004b)	Adverse events over 24h	Acetylsalicylic acid: 55/369 (15%) Sumatriptan: 64/361 (18%) RR (95% CI): 0.85 (0.61 to 1.2) NS I^2:0.0%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology

Diener 2004a DB, three-arm, PG, double-dummy-RCT	433	Aged 18-65 years, meeting IHS criteria for migraine with and without aura. At least 12-month history of migraine, with one to six attacks per month. Acetylsalicylic acid: n = 146 Sumatriptan: n = 135 Placebo: n= 152 M = 66 F = 367 Mean age 42 years	Assessment up to 24h	Effervescent acetylsalicylic acid 1000 mg Vs Sumatriptan 50 mg Vs placebo Single oral dose Medication taken when migraine headache pain of moderate or severe intensity If pain not controlled, participants asked to wait 2 hours before taking rescue medication	RANDOMIZATION: Yes "Computer-generated randomisation list" ALLOCATION CONCEALMENT: Unclear: Not described BLINDING: All outcomes: Yes: "Matching effervescent or tablet placebo"
Diener 2004b DB, PC, double-dummy, three-period CO RCT	312	Aged 18-65 years, meeting IHS criteria for migraine with and without aura. At least 12-month history of migraine, with one to six attacks per month Acetylsalicylic acid: n = 222 Ibuprofen: n = 212 Sumatriptan: n = 226 Placebo: n = 222 M = 59 F = 253 Mean age 38 years	Assessment up to 24h	Effervescent acetylsalicylic acid 1000 mg Vs Ibuprofen 400 mg Vs Sumatriptan 50 mg Vs Placebo, Single oral dose per attack. Each participant treated three migraine attacks	RANDOMIZATION: Yes "Treatment was assigned by a predetermined randomisation code" ALLOCATION CONCEALMENT: Unclear: Not described BLINDING: All outcomes: Yes: Double dummy design

				with different treatments medication taken when migraine headache pain of moderate or severe intensity. If pain not controlled, participants encouraged to wait 2 hours before taking rescue medication Participants instructed to leave a minimum of 48 hours between consecutive study treatments to ensure that new attack and not migraine recurrence was being treated	

Remarks:

- Studies using a single dose of aspirin in established pain of at least moderate intensity were analysed separately from studies in which medication was taken before pain was well established or in which a second dose of medication was permitted. All treatments were administered orally, and when the headache was of moderate or severe intensity.

- Acetylsalicylic acid doses of 900 mg and 1000 mg were considered sufficiently similar to combine for analysis. Different formulations were used: oral tablet, mouth dispersible or effervescent formulations and compared to sumatriptan 50 mg.
- Pain intensity or pain relief was measured by the patient (not the investigator or carer). Pain measures accepted for the primary outcomes were: (1) Pain intensity (PI): 4-point categorical scale, with wording equivalent to none, mild, moderate and severe; or 100 mm VAS (2) Pain relief (PR): 5-point categorical scale, with wording equivalent to none, a little, some, a lot, complete; or 100 mm VAS.

- For studies in which participants were asked to treated consecutive headaches with different study medication, if more than one attack was treated with the same medication, or if a second dose of study medication was permitted if there was an inadequate response to the first, authors have used data for the first attack only, where these data were reported separately, for efficacy outcomes to avoid problems of double counting participants and repeated measures for the same individuals; for use of rescue medication and adverse event data, we have accepted data from multiple attacks in the absence of first-attack data in order to be inclusive and provide conservative estimates.

Author's conclusions:

"Aspirin 1000 mg is an effective treatment for acute migraine headaches, similar to sumatriptan 50 mg or 100 mg. Adverse events were mainly mild and transient, and were slightly more common with aspirin than placebo, but less common than with sumatriptan 100 mg.
The MA analyses also reported data from two other studies comparing acetylsalicylic acid plus metoclopramide to sumatriptan 100mg. From these two studies, authors concluded: single doses of aspirin, with or without metoclopramide, did not cause significantly more or fewer adverse events in these studies than did placebo or comparator treatments, with the exception of sumatriptan 100 mg, where for every eight individuals treated with sumatriptan, one would experience adverse events who would not have done with aspirin plus metoclopramide."

12.3 NSAID

12.3.1 Diclofenac versus placebo for acute treatment of migraine attack of moderate to severe baseline pain intensity in adults

Meta-analysis: Derry 2013(23), Diclofenac with or without an antiemetic for acute migraine headaches in adults (Review)

Definition of migraine: We used the definition of migraine specified by the International Headache Society (IHS 1988; IHS 2004).

Inclusion criteria: We included randomised, double-blind, placebo-controlled or active-controlled studies, or both, using diclofenac to treat a migraine headache episode. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data for at least one of the outcomes specified below. We accepted studies reporting treatment of consecutive headache episodes if outcomes for the first, or each, episode were reported separately; we used first-attack data preferentially. We accepted cross-over studies if there was adequate (at least 24 hours) washout between treatments.

Population: Studies included adults (at least 18 years of age) with migraine. There were no restrictions on migraine frequency, duration, or type (with or without aura). We accepted studies including participants taking stable prophylactic therapy to reduce the frequency of migraine attacks.

We excluded studies designed to demonstrate prophylactic efficacy in reducing the number or frequency of migraine attacks.

Search strategy: For the original review we searched the following databases to 27 September 2011: • the Cochrane Central Register of Controlled Trials (CENTRAL)
(Issue 10). • MEDLINE (via Ovid). • EMBASE (via Ovid). • Oxford Pain Relief Database.
For the update we searched: • the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 1, 2013); • MEDLINE (via Ovid) from January 2011 to 15 February 2013; • EMBASE (via Ovid) from January 2011 to 15 February 2013.
For the original review we searched reference lists of retrieved studies and review articles for additional studies (we identified two unpublished studies). We also searched online databases of clinical trials (clinicaltrials.gov and novctrd.com). We made written requests to Novartis, who manufacture Voltarol Rapid tablets, and Nautilus Neurosciences, who manufacture Cambia, asking for details of any randomised controlled trials (RCTs) known to them involving diclofenac for acute treatment of migraine.

Assessment of quality of included trials: yes

Other methodological remarks:

We accepted randomisation at the individual patient level only. For all outcomes we carried out analyses, as far as possible, on a modified intention-to-treat (ITT) basis, i.e. we included all participants who were randomised and received an intervention. Where sufficient information was reported, we re-included missing data in the analyses we undertook. We excluded data from outcomes where data from T 10% of participants were missing with no acceptable reason provided or apparent. For analysis of studies with more than one treatment arm contributing to any one analysis (e.g. two formulations of the same dose of diclofenac in the same study with a single placebo group), we split the placebo group equally between the two treatment arms so as not to double-count placebo participants. The most likely source of missing data was in cross-over studies; we planned to use only first-period data where possible, but where that was not provided, we treated the results as if they were parallel group results. We calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants. We calculated relative risk of benefit or harm with 95% confidence intervals (CIs) using a fixed effect model. We calculated NNT, NNTp, and NNH with 95% CIs, where possible, using the pooled number of events by the method of Cook and Sackett.

Ref	Comparison	N/n	Outcomes	Result
Derry 2013 Design: SR+MA Search date: September 2011+February 2013 (update)	Diclofenac Vs Placebo	N = 2 n = 1477 (Diener 2006, Lipton 2010)	Pain free at 2h (PO)	Diclofenac: 195/873 (22%) Placebo: 67/604 (11%) **RR (95% CI): 2.0 (1.6 to 2.6)** NNT (95% CI): 8.9 (6.7 to 13) **SS in favour of diclofenac** I^2: 40%
		N = 2 n = 1477	Pain relief at 2h (PO)	Diclofenac : 482/873 (55%) Placebo: 236/604 (39%) **RR (95% CI): 1.5 (1.3 to 1.7)**

		(Diener 2006, Lipton 2010)	(Pain reduced from moderate or severe to none or mild without the use of rescue medication)	NNT (95% CI): 6.2 (4.7 to 9.1) **SS in favour of diclofenac** I^2: 0.0%
		N = 2 n = 1578 (Diener 2006, Lipton 2010)	Sustained pain free over 24h (PO) (headache relief at 2 hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication)	Diclofenac : 175/932 (19%) Placebo: 53/646 (8.2%) **RR (95% CI): 2.3 (1.7 to 3.0)** NNT (95% CI): 9.5 (7.2 to 14) **SS in favour of diclofenac** I^2: 0%
		N = 2 n = 873 (DKSMSG 1999, Lipton 2010)	Improvement of functional disability	Diclofenac : 143/431 Placebo: 62/442 **RR (95% CI): 2.36 (1.8 to 3.08)** NNT (95% CI): 5.2 (4.1 to 7.3) **SS in favour of diclofenac** I^2: 0%
		N = 3 n = 1578 (Diener 2006, Lipton 2010,	Adverse events	Diclofenac : 109/596 (18%) Placebo: 78/479 (16%) **RR (95% CI): 1.1 (0.86 to 1.5)** **NS**

		DKSMSG 1999)		I^2: 20%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
DKSMSG 1999 DB, double-dummy, PC, CO-RCT	156	Migraine ± aura (IHS 1988). History: 2 to 6 attacks/month in previous 6 months Exclusions: participants experiencing non-migrainous interval headaches or other types of migraine Diclofenac-K 50 mg: n = 115 Diclofenac-K 100 mg: n = 115 Sumatriptan: n = 115 Placebo: n = 115 Beta-blockers allowed if dose stable M: 37 F: 119 Median age 33 years, range 19 to 70 years Median time since first diagnosis 15 years	Assessment up to 8 h	Diclofenac-K 50 mg Vs Diclofenac-K 100 mg Vs Sumatriptan 100 mg Vs Placebo, n = 115 Single oral dose of each medication to treat each of 4 separate attacks; each patient was to receive all 4 treatments during the course of the trial. Medication taken at first sign of pain and attacks separated by > 48 hours If pain not controlled, participants asked to wait 2 hours before taking rescue medication (paracetamol)	RANDOMIZATION: Unclear risk Not described ALLOCATION CONCEALMENT: Unclear risk Not described BLINDING (performance bias and detection bias, all outcomes) Low risk "Double dummy" INCOMPLETE OUTCOME: Low risk Drop-outs described. Completer analysis for efficacy, but did not contribute to efficacy analyses. Safety analysis on all participants receiving treatment.

Diener 2006 DB, double-dummy, PC, CO-RCT	317	Migraine with or without aura (IHS 1988). History: 2 to 6 migraine attacks/month in previous 3 months Exclusions: participants with interval headaches between attacks, other types of migraine, pregnancy or lactation or inadequate contraception, known hypersensitivity to study or related medications, significant systemic disease Diclofenac-K sachet: n = 291 Diclofenac-K tablet: n = 298 Placebo: n = 299 Prophylactic treatment allowed with a single agent if stable M: 44 F: 273 Mean age: 39 years	Assessment up to 8 h	Diclofenac-K sachet 50 mg Vs Diclofenac-K tablet 50 mg Vs Placebo Single dose of each treatment for each of three separate migraine attacks, with at least 48 hours between attacks. Medication taken at the first sign of a migraine attack If pain not controlled, participants asked to wait 2 hours before taking rescue medication	RANDOMIZATION: Unclear risk Not described ALLOCATION CONCEALMENT: Low risk Remote allocation BLINDING (performance bias and detection bias, all outcomes) Low risk "Double dummy" INCOMPLETE OUTCOME DATA: Low risk Drop-outs described
Lipton 2010 DB, double-dummy, PC, PG-RCT	690	Migraine with or without aura (IHS 2004). History: at least one migraine attack/month in previous year Exclusions: participants experiencing vomiting in 20% of attacks or needing bed rest with most attacks, pregnancy, lactation or inadequate contraception, hypersensitivity to study or related medication,	Assessment up to24 h	Diclofenac-K oral solution 50mg Vs Placebo Single dose of each medication to treat a single migraine attack, with at least 48 h of treating previous	RANDOMIZATION: Unclear risk Not described ALLOCATION CONCEALMENT: Unclear risk Not described BLINDING (performance bias and detection bias, all outcomes) Low risk Both treatments made up to clear solution INCOMPLETE OUTCOME DATA:

		traumatic injury to head or neck within 6 months, other significant medical history Diclofenac: n = 343 Placebo: n = 347 Prophylactic treatment allowed if dose stable for > 3 months M: 105 F: 585 Mean age: 40 years, range: 18 to 65 Migraine with aura 13%		migraine. Trial medication was to be taken at the earliest sign of a migraine attack, when migraine of moderate or severe intensity. If pain not controlled, participants asked to wait 2 hours before taking rescue medication.	Low risk Drop-outs described. ITT: yes
Vecsei 2007 DB, PC, CO-RCT	266	Migraine without aura. History: 1 to 6 migraine attacks/month in the 12 months prior to enrolment Exclusions: participants usually experiencing severe attacks, known hypersensitivity to study medication, concomitant treatment with drugs that interact with diclofenac, serious psychiatric disease, drug abuse headache Diclofenac: n = 133 Placebo: n = 133 M: 14 F: 119 Mean age 42 years	Assessment up to24 h	Diclofenac epolamine (DHEP) 65 mg sachet Vs Placebo Single oral dose of each treatment for four consecutive migraine attacks, with at least 48 h between consecutive treatments Medication to be taken at the earliest sign of migraine attack, and a second tablet could be taken 1	RANDOMIZATION: Low risk "Computer-generated using validated software" ALLOCATION CONCEALMENT: Unclear risk Not described BLINDING: Unclear risk Not described INCOMPLETE OUTCOME DATA: Unclear risk Data missing for 22/155 participants without adequate reason ITT: yes

				hour later if relief was judged insufficient by the participant "In the case of a migraine attack recurring within 48 hours, the patient was allowed to treat this attack with his 'usually used attack medicine'	

Remarks:

- Authors analysed studies using a single dose of diclofenac in established pain of at least moderate intensity **separately** from studies in which medication was taken before pain became well established, or in which a second dose of medication was permitted. In one study (Lipton 2010) participants were instructed to wait until pain intensity was moderate or severe before taking study medication.
  - In Diener 2006, DKSMSG 1999 and Vecsei 2007 they were asked to take medication at the first sign of pain.
  - Diener 2006 and Vecsei 2007 reported efficacy separately for participants with moderate or severe pain at baseline, and despite instructions to treat early, the vast majority (94% and 89% respectively) had at least moderate pain at baseline, so this subset was analysed together with Lipton 2010.
  - For the outcome sustained pain free over 24h Diener 2006 reported data for all included participants, a proportion (around 11%) of whom had mild baseline pain. The total number of participants in this comparison was 1578.
  - DKSMG 1999 (in which 144 participants were asked to take study medication at the first sign of pain) there were **no data suitable for analysis** for the primary outcomes (only group mean data); in addition the attrition rate was of 20%.
  - In Vecsei 2007 participants were instructed to take diclofenac at the earliest sign of a migraine attack with an optional dose at one hour if needed, rather than waiting until pain was moderate or severe. The majority of participants took the second dose (63% with diclofenac 50 mg, and 87% with placebo). The majority of attacks appear to have been of moderate or severe intensity at baseline. Authors **did not combine** the different dosing regimens for analysis. The authors also mentioned that 22 participants were excluded because they had missing data for "various reasons" (unspecified). We are not reporting this study because this constitutes a different dosage regiment which does not meet our inclusion criteria.

- Pain intensity or pain relief had to be measured by the patient (not the investigator or care giver). Pain measures accepted for the main efficacy outcomes were:
  - Pain intensity (PI): 4-point categorical scale, with wording equivalent to none, mild, moderate and severe; or 100 mm VAS), where < 30 mm was considered equivalent to mild or no pain and T 30 mm equivalent to moderate or severe pain;
  - Pain relief (PR): 5-point categorical scale, with wording equivalent to none, a little, some, a lot, complete; or 100 mm VAS, where < 30 mm was considered equivalent to none or a little, and T 30 mm equivalent to some, a lot or complete
- Results presented in the MA report results for diclofenac potassium 50 mg. There were insufficient data for analysis of the 100 mg dose compared with placebo. Included studies used oral diclofenac as the potassium salt taken either in a standard tablet formulation or as a powder to be dissolved in water just before ingestion. In the study Vecsei 2007, that was not pooled for other methodological reasons, the powdered epolamine salt to be dissolved in water just before ingestion was used.
- Vecsei 2007 included only participants who experienced migraine without aura and excluded participants if they usually experienced migraine of 'severe intensity'
- Lipton 2010 excluded participants if they experienced vomiting in 20% of attacks or needed bed rest with most attacks.

Author's conclusions:
"Oral diclofenac potassium 50 mg is an effective treatment for acute migraine, providing relief from pain and associated symptoms, although only a minority of patients experience pain-free responses. Adverse events are mostly mild and transient and occur at the same rate as with placebo. »
"…While the NNTs for headache relief at two hours, pain-free at two hours and sustained pain-free during the 24 hours post dose are of borderline clinical utility, the 50 mg dose achieves these three outcomes in 55%, 22%, and 19%, respectively, of patients who treat moderate or severe pain."

12.3.2 Ibuprofen versus placebo for acute treatment of migraine attack of moderate to severe pain intensity in adults

Meta-analysis: Rabbie 2013(28), Ibuprofen with or without an antiemetic for acute migraine headaches in adults.

Definition of migraine: We used the definition of migraine specified by the International Headache Society (IHS 1988, IHS 2004). We accepted diagnostic criteria equivalent to IHS 1988, where a specific reference was not provided.

Inclusion criteria: We included randomised, double-blind, placebo-controlled or active-controlled studies, or both, using ibuprofen to treat a migraine headache episode. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data for at least one of the outcomes specified below. We accepted studies reporting treatment of consecutive headache episodes if outcomes for the first, or each, episode were reported separately; we used first-attack data preferentially. We accepted cross-over studies if there was adequate (at least 24 hours) washout between treatments.
Population: Studies included adults (at least 18 years of age) with migraine. There were no restrictions on migraine frequency, duration, or type (with or without aura). We accepted studies including participants taking stable prophylactic therapy to reduce the frequency of migraine attacks.
We excluded studies designed to demonstrate prophylactic efficacy in reducing the number or frequency of migraine attacks.

Search strategy: The following electronic databases were searched for the original review: • The Cochrane Central Register of Controlled Trials (CENTRAL), last search 22 April 2010. • MEDLINE (via Ovid) last search 22 April 2010. • EMBASE (via Ovid) last search 22 April 2010. • Oxford Pain Relief Database (Jadad 1996a).
For the update we searched: • The Cochrane Central Register of Controlled Trials (CENTRAL)
(Issue 1, 2013); • MEDLINE (via Ovid) from 1 January 2010 to 14 February 2013; • EMBASE (via Ovid) from 1 January 2010 to 14 February 2013.
We searched reference lists of retrieved studies and review articles for additional studies, and for the update we searched http://clinicaltrials.gov for information about both published and unpublished data, but no additional studies were identified. Grey literature and abstracts were not searched.

Assessment of quality of included trials: yes

Other methodological remarks:
We accepted randomisation at the individual patient level only.
The most likely source of missing data was cross-over studies; we planned to use only first-period data where possible, but where that was not provided, we treated the results as if they were parallel group results.
For all outcomes we carried out analyses, as far as possible, on a modified intention-to-treat (ITT) basis, i.e. we included all participants who were randomised and received an intervention. Where sufficient information was reported, we re-included missing data in the analyses we undertook. We excluded data from outcomes where data from ≥ 10% of participants were missing with no acceptable reason provided or apparent.
We calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants.
We calculated relative risk of benefit or harm with 95% confidence intervals (CIs) using a fixed effect model. We calculated NNT, NNTp and NNH with 95% CIs using the pooled number of events by the method of Cook and Sackett.

Ref	Comparison	N/n	Outcomes	Result

Rabbie 2013 Design: SR+MA Search date: April 2010 +February 2013 (update)	Ibuprofen 200 mg Vs Placebo	N = 2 n = 777 (Codispoti 2001, Kellstein 2001)	Pain free at 2h (PO)	Ibuprofen: 84/414 (20%) Placebo: 36/363 (10%) RR (95% CI): **2.0 (1.4 to 2.8)** NNT (95% CI): 9.7 (6.5 to 18) **SS in favour of ibuprofen** I^2: 0%
		N = 2 n = 777 (Codispoti 2001, Kellstein 2001)	Pain relief at 2h (PO) (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	Ibuprofen: 217/414 (52%) Placebo: 133/363 (37%) RR (95% CI): **1.4 (1.2 to 1.6)** NNT (95% CI): 6.3 (4.4 to 11) **SS in favour of ibuprofen** I^2: 0%
		N = 2 n = 777 (Codispoti 2001, Kellstein 2001)	Pain relief at 1h (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	Ibuprofen: 141/414 (34%) Placebo: 83/363 (23%) RR (95% CI): **1.5 (1.2 to 1.8)** NNT (95% CI): 8.9 (5.7 to 20) **SS in favour of ibuprofen** I^2: 0%
		N = 1 n = 340 (Kellstein 2001)	Sustained pain relief over 24h (headache relief at 2 hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication)	Ibuprofen: 54% Placebo: 35% **No analysis provided**

		N = 2 n = 429 (Codispoti 2001, Kellstein 2001)	Relief of nausea at 2h	Ibuprofen: 115/234 Placebo: 70/195 RR (95% CI): 1.33 (1.06 to 1.67) **SS in favour of ibuprofen** I^2: 0%
		N = 2 n = 751 (Codispoti 2001, Kellstein 2001)	Relief of photophobia at 2h	Ibuprofen: 102/401 Placebo: 62/350 RR (95% CI): **1.4 (1.05 to 1.85)** **SS in favour of ibuprofen** I^2: 0%
		N = 2 n = 724 (Codispoti 2001, Kellstein 2001)	Relief of phonophobia at 2h	Ibuprofen: 113/386 Placebo: 68/338 RR (95% CI): **1.4 (1.08 to 1.82)** **SS in favour of ibuprofen** I^2: 0%
		N = 2 n = 757 (Codispoti 2001, Kellstein 2001)	Improvement of functional disability	Ibuprofen: 187/406 Placebo: 104/351 RR (95% CI): **1.4 (1.18 to 1.66)** **SS in favour of ibuprofen** I^2: 0%
		N = 2 n = 777	Use of rescue medication	Ibuprofen: 112/414 Placebo: 1147/363 RR (95% CI): **0.7 (0.58,0.86)**

		(Codispoti 2001, Kellstein 2001)		**SS in favour of ibuprofen** I^2: 55%
		N = 2 n = 780 (Codispoti 2001, Kellstein 2001)	Adverse events over 24h	Ibuprofen: 90/416 (22%) Placebo: 101/364 (28%) RR (95% CI): **0.85 (0.67 to 1.1)** **NS** I^2: 0%

* Characteristics of included studies: see below

Ref	Comparison	N/n	Outcomes	Result
Rabbie 2013 Design: SR+MA Search date: April 2010 +February 2013 (update)	Ibuprofen 400 mg Vs Placebo	N = 6 n = 2575 (Codispoti 2001, Diener 2004, Goldstein 2006, Misra 2007, Saper 2006, Kellstein 2001)	Pain free at 2h (PO)	Ibuprofen: 401/1553 (26%) Placebo: 128/1042 (12%) RR (95% CI): 1.9 (1.6 to 2.3) NNT (95% CI): 7.2 (5.9 to 9.2) **SS in favour of ibuprofen** I^2: 81%
		N = 7 n = 1815 (Codispoti 2001, Diener	Pain relief at 2h (PO) (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	Ibuprofen: 528/931 (57%) Placebo: 224/884 (25%) RR (95% CI): 2.2 (1.9 to 2.5) NNT (95% CI): 3.2 (2.8 to 3.7) SS in favour of ibuprofen

		2004, Misra 2004, Misra 2007, Saper 2006, Kellstein 2001, Sandrini 1998)		I^2: 90%
		N = 4 n = 1269 (Codispoti 2001, Diener 2004, Kellstein 2001, Sandrini 1998)	Pain relief at 1h (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	Ibuprofen: 226/655 (35%) Placebo: 108/614 (18%) RR (95% CI): 1.9 (1.5 to 2.3) NNT (95% CI): 5.9 (4.6 to 8.2) SS in favour of ibuprofen I^2: 77%
		N = 1 n = 376 (Saper 2006)	Sustained pain free over 24h (headache relief at 2 hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication)	Ibuprofen: 18% Placebo: 3% No analysis provided
		N = 4 n = 879 (Misra 2004, Misra 2007, Saper 2006, Kellstein 2001)	Sustained pain relief over 24h (headache relief at 2 hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication)	Ibuprofen: 208/467 (45%) Placebo: 80/412 (19%) RR (95% CI): 2.2 (1.8 to 2.7) NNT (95% CI): 4.0 (3.2 to 5.2) SS in favour of ibuprofen I^2: 75%

		N = 3 n = 336 (Codispoti 2001, Saper 2006, Kellstein 2001)	Relief of nausea at 2h	Ibuprofen: 170/328 Placebo: 102/306 RR (95% CI): 1.54 (1.27 to 1.86) SS in favour of ibuprofen I^2: 30%
		N = 2 n = 93 (Diener 2004, Saper 2006)	Relief of vomiting at 2h	Ibuprofen: 40/44 Placebo: 30/49 RR (95% CI): 1.53 (1.21 to 1.92) SS in favour of ibuprofen I^2: 86%
		N = 4 n = 1328 (Codispoti 2001, Diener 2004, Saper 2006, Kellstein 2001)	Relief of photophobia at 2h	Ibuprofen: 260/689 Placebo: 159/639 RR (95% CI): 1.51 (1.29 to 1.77) SS in favour of ibuprofen I^2: 43%
		N = 4 n = 1261 (Codispoti 2001, Diener 2004, Saper 2006, Kellstein 2001)	Relief of phonophobia at 2h	Ibuprofen: 274/652 Placebo: 159/609 RR (95% CI): 1.63 (1.39 to 1.90) SS in favour of ibuprofen I^2: 21%

		N = 3 n = 114 (Codispoti 2001, Saper 2006, Kellstein 2001)	Improvement of functional disability	Ibuprofen: 245/583 Placebo: 129/531 RR (95% CI): 1.61 (1.38 to 1.89) SS in favour of ibuprofen I^2: 78%
		N = 7 n = 1815 (Codispoti 2001, Diener 2004, Misra2004, Misra 2007, Saper 2006, Sandrini 1998, Kellstein 2001)	Use of rescue medication	Ibuprofen: 353/931 Placebo: 516/884 RR (95% CI): **0.67 (0.61 to 0.74)** SS in favour of ibuprofen I^2: 66%
		N = 7 n = 1767 (Codispoti 2001, Diener 2004, Goldstein 2006, Misra 2007, Saper 2006, Sandrini 1998,	Adverse events over 24h	Ibuprofen: 231/1557 (15%) Placebo: 206/1079 (19%) RR (95% CI): 0.97 (0.82 to 1.2) NS I^2: 0%

		Kellstein 2001)		

* Characteristics of included studies: see below

Ref	Comparison	N/n	Outcomes	Result
Rabbie 2013 Design: SR+MA Search date: April 2010 +February 2013 (update)	Ibuprofen 600 mg Vs Placebo	N = 1 n = 340 (Kellstein 2001)	Pain free at 2h (PO)	Ibuprofen: 58/198 Placebo: 19/142 RR (95% CI): **2.19 (1.37 to 3.51)** SS in favour of ibuprofen
		N = 1 n = 340 (Kellstein 2001)	Pain relief at 2h (PO) (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	Ibuprofen: 142/198 Placebo: 71/142 RR (95% CI): 1.43 (1.19 to 1.73) SS in favour of ibuprofen I^2:

Ref + design	n	Population	Duration	Comparison	Methodology
Codispoti 2001 DB, PC, PG, RCT	660	Migraine with/without aura (IHS 1988) of at least moderate severity. History: 0.5 to 6 episodes/month in the year before study entry Excluded participants with > 50% episodes requiring bedrest or > 20% including vomiting Ibuprofen 200 mg: n = 216 Ibuprofen 400 mg: n = 223 Placebo: n = 221 M 104 F 556 Mean age 39 years History of aura: 27%	Assessment up to 6 h	Ibuprofen 200 mg Vs Ibuprofen 400 mg Vs Placebo Single oral dose Medication taken when migraine of moderate or severe intensity If pain not controlled, participants asked to wait 2 hours before taking rescue medication (of participant's choice) Prophylactic medication continued unchanged, if stable	**RANDOMIZATION:** Low risk "computer-generated randomization code" **ALLOCATION CONCEALMENT:** Low risk "unopened treatment-blinding tear-off portion of winged label was affixed to the patient's case report form" **BLINDING:** performance bias and detection bias, all outcomes: Low risk All participants "received a blister card containing two tablets that were identical in colour, size, and shape" **INCOMPLETE OUTCOME DATA: all outcomes:** Low risk Drop-outs described
Diener 2004 DB, double-dummy, PC, CO-RCT	312 (cross-over trial, 882 attacks)	Migraine with or without aura (IHS 1988). History: 1 to 6 attacks/month in previous year Ibuprofen 400 mg: n = 212 ASA 2 x 500 mg: n = 222	Assessment up to24h	Ibuprofen 400 mg Vs Acetylsaysilic acid 2 x 500 mg Vs Sumatriptan 50 mg Vs	**RANDOMIZATION:** Low risk "predetermined randomization code" **ALLOCATION CONCEALMENT:** Unclear risk Not described **BLINDING:** performance

		Sumatriptan 50 mg: n = 226 Placebo: n = 222 M 59 F 253 Mean age 38 years History of aura: 21%		Placebo Single oral dose of each treatment for each of three migraine attacks, with at least 48 hours between consecutive treatments Medication taken within 6 hours of onset, when migraine of moderate or severe intensity, and not improving If pain not controlled, participants asked to wait 2 hours before taking rescue medication (of participant's choice - 12 hours if triptan or ergot)	bias and detection bias, all outcomes: Low risk All participants "double-dummy" method with "matching placebo" for each treatment **INCOMPLETE OUTCOME DATA: all outcomes:** Low risk Drop-outs described
Goldstein 2006 DB, double-dummy, PC, PG-RCT	1559	Migraine with and without aura (IHS 1988). History: attack at least once every 2 months during past year. Untreated attacks R moderate severity Ibuprofen: n = 669 Paracetamol + aspirin + caffeine: n = 669 Placebo: n = 221	Assessment up to4h	Ibuprofen 2 x 200 mg VS Paracetamol + aspirin + caffeine 2 x 250/250/65 mg Vs Placebo, n = 221 Single oral dose	**RANDOMIZATION:** Unclear risk Not described **ALLOCATION CONCEALMENT:** Unclear risk Not described **BLINDING:** performance bias and detection bias, all outcomes: Low risk All participants "double-dummy" method” **INCOMPLETE OUTCOME DATA: all outcomes:** Low risk Drop-outs described

		M 306 F 1249 Mean age 38 years History of aura: 21%		Medication taken when migraine of moderate or severe intensity If pain not controlled, participants asked to wait 2 hours before taking rescue medication (of participant's choice)	
Kellstein 2001 DB, PC, PG-RCT	729	Migraine with/without aura (IHS 1988). At least 12-month history of migraine with/without aura, average frequency of 0.5 to 8 attacks/month in the previous year. Untreated attacks R moderate severity. Previous experience of some relief from OTC analgesics Excluded participants with headaches that were usually severely disabling or incapacitating, or R 20% accompanied by vomiting Ibuprofen liquigel 200 mg: n = 198 Ibuprofen liquigel 400 mg: n = 191 Ibuprofen liquigel 600 mg: n = 198 Placebo: n = 142 M 179 F 550 Mean age 37 years (35 participants were 12 to 19 years)	Assessment up to24h	Ibuprofen liquigel 200 mg Vs Ibuprofen liquigel 400 mg Vs Ibuprofen liquigel 600 mg Vs Placebo Single oral dose Medication taken when migraine of moderate or severe intensity Rescue medication allowed, but no details reported	**RANDOMIZATION:** Unclear risk Not described **ALLOCATION CONCEALMENT:** Unclear risk Not described **BLINDING:** performance bias and detection bias, all outcomes: Low risk All participants "matching placebo" **OUTCOME DATA: all outcomes:** Low risk Drop-outs described

		History of aura: 12%			
Misra 2004 DB, PC, PG-RCT	124	Migraine with and without aura (IHS 1988). History: at least 12-month history of migraine with/without aura, no more than 6 attacks/month. Untreated attacks R moderate severity Excluded participants with headaches usually needing bedrest, or R 20% accompanied by vomiting n = 101 analysed Ibuprofen 400 mg: n = 35 Rofecoxib 25 mg: n = 33 Placeb: n = 33 M 18 F 83 Mean age 32 years History of aura: not reported	Assessment up to24h	Ibuprofen 400 mg Vs Rofecoxib 25 mg Vs Placebo Single oral dose/attack (R 2 attacks treated) Medication taken when migraine of moderate or severe intensity If moderate or severe headache persisted after 2 hours, rescue medication allowed (sumatriptan 100 mg or piroxicam 20 mg)	**Study does not correspond to our methodology (n < 40 per study group)**
Misra 2007 DB, PC, PG-RCT	155	Migraine (IHS 1988). History: < 8 attacks/month. Untreated attacks > moderate severity Excluded participants with headaches associated with recurrent vomiting Ibuprofen 400 mg: n = 52	Assessment up to24h	Ibuprofen 400 mg Vs Rizatriptan 10 mg Vs Placebo Single oral dose/attack (> 2 attacks treated)	**RANDOMIZATION:** Low risk "computer-generated random numbers" **ALLOCATION CONCEALMENT:** Unclear risk Randomisation done by one investigator and responses evaluated by the other, but no details about method of concealment

		Rizatriptan 10 mg: n = 53 Placebo: n = 50 M 59 F 106 Mean age 30 years History of aura: not reported		Medication taken when migraine of moderate or severe intensity If moderate or severe headache persisted after 2 hours, rescue medication allowed (sumatriptan 100 mg or piroxicam 20 mg)	**BLINDING:** performance bias and detection bias, all outcomes: Unclear risk Medication "provided in identical packets" **OUTCOME DATA: all outcomes:** Low risk Drop-outs described
Sandrini 1998 DB, double-dummy, PC, CO, RCT	34	Migraine headache (IHS 1988). History: R 2 months, without aura, 2 to 6 headache episodes/month n = 29 analysed for efficacy Ibuprofen arginine 400 mg: n = 34 Placebo: n = 34 M 8 F 26 Mean age 34 years	Assessment up to6h	Ibuprofen arginine 400 mg Vs Placebo Single oral dose of each treatment for each of two migraine attacks - time between consecutive treated attacks not specified Medication taken when pain was R 60 mm If pain not controlled, participants asked to wait 2 hours before taking rescue medication	**Study does not correspond to our methodology (n < 40 per study group)**
Saper 2006 DB, triple-dummy, PC,PG-RCT	783	Migraine with and without aura (IHS 1988). History: 1 to 8 migraine attacks/month in the 6 months before enrolment	Assessment up to24h	Ibuprofen 400 mg Vs Rofecoxib 25 mg Vs Rofecoxib 50 mg Vs	**RANDOMIZATION:** Low risk "computer-generated random numbers" **ALLOCATION CONCEALMENT:** Low risk Remote allocation **BLINDING:** performance

		Ibuprofen 400 mg: n = 199 (189 analysed for efficacy) Rofecoxib 25 mg: n = 194 (187 analysed for efficacy) Rofecoxib 50 m: n = 196 (188 analysed for efficacy) Placebo: n = 194 (187 analysed for efficacy) M 108 F 675 Mean age 40 years History of aura: 12%		Placebo Single oral dose Medication taken when migraine of moderate or severe intensity, and not resolving spontaneously. If pain not controlled, participants asked to wait 2 hours before taking rescue medication	bias and detection bias, all outcomes: Placebo tablets visually matched the three active treatments **OUTCOME DATA: all outcomes:** Unclear risk_ 5% drop-outs in each group, with no reasons given **Follow up:** 32 participants took medication but were excluded from efficacy analyses - probably due to protocol violations or lack of post-baseline data.

* Characteristics of included studies: see below

Remarks:

- Authors analysed studies using a single dose of ibuprofen in established pain of at least moderate intensity **separately** from studies in which medication was taken before pain was well established or in which a second dose of medication was permitted. All data were pooled. No studies investigated treating attacks when pain was mild, and none compared different dosing strategies or treatment regimens.
- Misra 2004 and Misra 2007 included participants as young as 16 years, and just under 5% of participants in Kellstein 2001 were aged 16 to 19 years.
- Misra 2004 and Misra 2007 treated two or more attacks with single doses of the same study medication. It is not clear how the data for multiple attacks were combined in these studies. In Diener 2004 participants treated three separate attacks with single doses of three different study medications, while in Sandrini 1998 participants treated two consecutive attacks with single doses of two different study medications. Neither study reported data for the first attack only.
- Different doses of ibuprofen were used: 200mg, 400mg, or 600 mg and analysed separately. Kellstein 2001 used an oral liquigel formulation (solubilised ibuprofen potassium), and Sandrini 1998 used oral ibuprofen arginine. Other studies used standard oral tablet.

- Four studies (Codispoti 2001, Kellstein 2001, Misra 2004, Misra 2007) excluded participants who experienced headaches that were usually severely disabling or incapacitating, and/or accompanied at least 20% of the time by vomiting, while Goldstein 2006 specifically did not exclude such participants.

Author's conclusions:
"'Ibuprofen is an effective treatment for acute migraine headaches, providing pain relief in about half of sufferers, but complete relief from pain and associated symptoms for only a minority. NNTs for all efficacy outcomes were better with 400 mg than 200 mg in comparisons with placebo, and soluble formulations provided more rapid relief. Adverse events were mostly mild and transient, occurring at the same rate as with placebo."
"Participants treated with ibuprofen had better relief of migraine associated symptoms compared with those treated with placebo. There was a non-significant trend for better relief of nausea, photophobia and phonophobia with ibuprofen 400 mg than 200 mg."
"Ibuprofen 400 mg would seem to be a good first-line therapy for acute migraine headaches in this population."

12.3.3 Naproxen versus placebo for acute treatment of migraine attack of moderate to severe baseline pain intensity in adults

Meta-analysis: Law 2013(37), Naproxen with or without an antiemetic for acute migraine headaches in adults.

Definition of migraine: We used the definition of migraine specified by the International Headache Society (IHS 1988; IHS 2004), although we accepted diagnostic criteria equivalent to those of IHS 1988 where a specific reference was not provided.

Inclusion criteria: We included randomised, double-blind, placebo- and/or active controlled studies using naproxen to treat a migraine headache episode. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data for at least one of the outcomes specified below. We accepted studies reporting treatment of consecutive headache episodes if outcomes for the first, or each, episode were reported separately; ; first-attack data were used preferentially. Cross-over studies were accepted if there was adequate washout (> 24 hours) between treatments.

Population : Studies enrolled adults (at least 18 years of age) with migraine. There were no restrictions on migraine frequency, duration, or type (with or without aura). Participants taking stable prophylactic therapy to reduce migraine frequency were accepted. All included studies used one or more of these standard scales (reported in remarks) and reported outcomes as defined above.
We considered only data obtained directly from the patient.

Exclusion: We excluded studies designed to demonstrate prophylactic efficacy in reducing the number or frequency of migraine headaches.

Search strategy: We searched the following electronic databases. • The Cochrane Central Register of Controlled Trials (CENTRAL), (The Cochrane Library), Issue 4 of 12, 2013. • MEDLINE (via Ovid),1947 to 22 May 2013. • EMBASE (via Ovid), 1974 to 22 May 2013. • Oxford Pain Relief Database, searched on 22 May 2013 (Jadad 1996a).
We searched for additional studies in reference lists of retrieved studies and review articles, and in two clinical trials databases (www.clinicaltrials.gov and www.gsk-clinicalstudyregister.com). We did not search grey literature and short abstracts.
We applied no language restrictions

Assessment of quality of included trials: yes

Other methodological remarks:
We accepted randomisation at the individual patient level only.
The most likely source of missing data was in cross-over studies; we planned to use only first-period data where possible, but no included studies used a cross-over design. Where there were substantial missing data in any study, we commented on this and performed sensitivity analyses to investigate their effect.
For all outcomes, we carried out analyses, as far as possible, on a modified intention-to-treat basis. Where sufficient information was reported, we re-included missing data in the analyses we undertook. We would exclude data from outcomes where results from 10% or greater of participants were missing with no acceptable reason provided or apparent.
We calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants. We calculated relative risk of benefit or harm with 95% confidence intervals (CIs) using a fixed effect model. We calculated NNT, NNTp, and NNH with 95% CIs using the pooled number of events by the method of Cook and Sackett.

Ref	Comparison	N/n	Outcomes	Result

Law 2013 Design: SR+MA Search date: May 2013	Naproxen Vs Placebo	N = 4 n = 2149 (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005; Wentz 2008)	Pain free at 2 h (PO)	Naproxen: 17% (183/1064) Placebo: 8.5% (92/1085) **RR (95% CI): 2.0 (1.6 to 2.6)** NNT (95%CI): 11 (8.7 to 17) **SS in favour of naproxen** I^2: 59%
		N = 4 n = 2149 (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005; Wentz 2008)	Pain relief at 2 h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	Naproxen: 45% (482/1064) Placebo: 29% (311/1085) **RR (95% CI): 1.6 (1.4 to 1.8)** NNT (95%CI): 6 (4.8 to 7.9) **SS in favour of naproxen** I^2: 0%
		N = 4 n = 2149 (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005; Wentz 2008)	Sustained pain-free over 24h (PO) (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	Naproxen: 12% (129/1064) Placebo: 6.7% (73/1085) **RR (95% CI): 1.8 (1.4 to 2.4)** NNT (95%CI): 19 (13 to 34) **SS in favour of naproxen** I^2: 62%

		N = 4 n = 2149 (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005; Wentz 2008)	Sustained pain relief over 24 h (PO) (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.)	Naproxen: 30% (315/1064) Placebo: 18% (190/1085) **RR (95% CI): 1.7 (1.5 to 2.0)** NNT (95%CI): 8.3 (6.4 to 12) **SS in favour of naproxen** I^2: 0%
		N = 3 n = 782 (Brandes 2007 Study 1; Brandes 2007 Study 2; Wentz 2008)	Relief of nausea at 2h	Naproxen: 156/398 Placebo: 88/384 **RR (95% CI): 1.73 (1.38 to 2.16)** **SS in favour of naproxen** I^2: 70%
		N = 3 n = 1342 (Brandes 2007 Study 1; Brandes 2007 Study 2; Wentz 2008)	Relief of photophobia at 2h	Naproxen: 215/666 Placebo: 126/676 **RR (95% CI): 1.73 (1.43 to 2.10)** **SS in favour of naproxen** I^2: 0

		N = 3 n = 1313 (Brandes 2007 Study 1; Brandes 2007 Study 2; Wentz 2008)	Relief of phonophobia at 2h	Naproxen: 221/637 Placebo: 140/676 **RR (95% CI): 1.68 (1.40 to 2.01)** **SS in favour of naproxen** I^2: 0%
		N = 2 n = 1346 (Brandes 2007 Study 1; Brandes 2007 Study 2)	Relief of functional disability at 2h	Naproxen: 131/667 Placebo: 62/679 **RR (95% CI): 2.14 (1.62 to 2.84)** **SS in favour of naproxen** I^2: 0%
		N = 4 n = 2174 (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005; Wentz 2008)	Adverse events	Naproxen: 15% (165/1078) Placebo: 12% (128/1096) **RR (95% CI): 1.3 (1.1 to 1.6)** NNH (95%CI): 28 (15 to 132) **SS in favour of placebo (more adverse events with naproxen)** I^2: 48%

		N = 4 n = 2149 (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005; Wentz 2008)	Use of rescue medication	Naproxen: 440/1064 Placebo: 630/1085 **RR (95% CI): 0.71 (0.65 to 0.78)** **SS in favour of naproxen (less rescue medication with naproxen)** I^2: 48%

Ref + design	n	Population	Duration	Comparison	Methodology
Brandes 2007 Study 1 and Study 2 DB, PC, PG-RCT	 <u>Study 1:</u> 1461	Migraine ± aura (IHS 2004), aged 18-65 years. History: > 6 months with frequency of 2-6 per month and untreated severity ≥ moderate Excluded: uncontrolled hypertension, cardio- or cerebrovascular disease, using MAOI, ergot, SJW, or NSAID <u>Study 1:</u> Sumatriptan 85 mg/naproxen 500 mg, n = 370 (364 analysed for efficacy) Sumatriptan 85 mg, n = 365 (361 for efficacy)	Assessment up to 24 h	Sumatriptan 85 mg/naproxen 500 mg Vs Sumatriptan 85 mg Vs Naproxen 500 mg Vs Placebo Single dose to treat a single attack Medication taken when PI ≥ moderate	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** Not reported INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs described

	Study 2: 1495	Naproxen 500 mg, n = 361 (365 for efficacy) Placebo, n = 365 (360 for efficacy) F = 86% Mean age 40 years 72% without aura Study 2: Sumatriptan 85 mg/naproxen 500 mg, n = 367 (362 for efficacy) Sumatriptan 85 mg, n = 370 (362 for efficacy) Naproxen 500 mg, n = 371 (364 for efficacy) Placebo, n = 387 (382 for efficacy)		Rescue medication allowed after 2 h if necessary (as prescribed by physician but not ergot-containing, serotonin agonist, or NSAID-containing medications)	
Smith 2005 DB, double dummy, PG-RCT	972	Migraine ± aura (IHS 2004), aged ≥ 18 years. History ≥ 1 year with 2-6 attacks per month, and able to tolerate oral triptan or ergot derivative Sumatriptan 50 mg + naproxen 500 mg, n = 251 Sumatriptan 50 mg, n = 229 Naproxen 500 mg, n = 250 Placebo, n = 242 F = 91% Mean age 42 years Without aura: > 70%	Assessment up to 24 h	Sumatriptan 50 mg + naproxen 500 mg Vs Sumatriptan 50 mg Vs Naproxen 500 mg Vs Placebo Single dose to treat a single attack Medication taken when pain ≥ moderate	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Low risk** Double dummy INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs described

				Rescue medication allowed after 2 h if necessary (not specified)	
Wentz 2008 DB, PC, PG-RCT	284	Migraine ± aura (IHS 2004), aged 18-65 years. History > 6 months Frequency 6/month with untreated severity ≥ moderate Excluded if > 15 headache days/month, associated disease, or if on acute or prophylactic medication 28 for efficacy Naproxen 825 mg, n = 109 Placebo, n = 117 111 participants were also treated with an experimental COX-2 inhibitor (GW406381), which is not marketed F = 81% Mean age 41 years Without aura: > 80%	Assessment up to 4 h	Naproxen 825 mg Vs Placebo Single dose to treat a single attack Medication taken when PI ≥ moderate Rescue medication allowed after 2 h (patient's usual medication)	RANDOMIZATION: **Low risk** Randomised by computer-generated sequence ALLOCATION CONCEALMENT: **Low risk** No concealment of allocations prior to assignments BLINDING: performance bias and detection bias, all outcomes: **Low risk** Double dummy INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs accounted for

Remarks:

- Authors analysed studies using a single dose of naproxen in established pain of at least moderate intensity s**eparately** from studies in which medication was taken before pain was well established or in which a second dose of medication was permitted. In all studies, medication was to be taken orally when the PI was of at least moderate intensity. No studies employed multiple dosing strategies for individual attacks.
- Three studies gave naproxen 500mg (Brandes 2007 Study 1, Brandes 2007 Study 2; Smith 2005) while Wentz 2008 gave naproxen 825 mg as this is the recommended maximum dose in Europe for acute migraine treatment. For analysis of the placebo-controlled studies, authors chose to combine results from the three using naproxen 500 mg with the one using naproxen 825 mg.

- Since there was no obvious relationship between numbers of participants with adverse events and the time over which the data were collected, we have combined data from the different time periods for analysis of the placebo-controlled studies.
- PI or PR had to be measured by the participant(not the investigator or care giver).
    - PI: 4-point categorical scale, with wording equivalent to none, mild, moderate, and severe; or 100 mm visual analogue scale (VAS)), where less than 30 mm was considered equivalent to mild or no pain and 30 mm or greater equivalent to moderate or severe pain (Collins 1997);
    - PR: 5-point categorical scale, with wording equivalent to none, a little, some, a lot, complete; or 100 mm VAS, where less than 30 mm was considered equivalent to none or a little, and 30 mm or greater equivalent to some, a lot, or complete.
- Data on relief of associated symptoms were reported but not in a consistent way; only one study reported data for calculation of relief of vomiting (Wentz 2008), while specific relief of nausea, photophobia, and phonophobia were available from three out of the four placebo controlled studies (Brandes 2007 Study 1; Brandes 2007 Study 2; Wentz 2008).

Author's conclusions:
"Naproxen is statistically superior to placebo in the treatment of acute migraine, but the NNT of 11 for pain-free response at two hours suggests that it is not a clinically useful treatment. Other Cochrane reviews examining alternative monotherapies, such as aspirin, ibuprofen, paracetamol, or sumatriptan have reported better (lower) NNT results for the same outcome, so are effective in more people."
"Naproxen is not clinically useful as a stand-alone analgesic in acute migraine, as it is effective in fewer than 2 people in 10."

12.3.4 Diclofenac versus sumatriptan for acute treatment of migraine attack in adults

Meta-analysis: Xu 2016(41), Network meta-analysis of migraine disorder treatment by NSAIDs and triptans

Definition of migraine:

Inclusion criteria: Articles were included if they: (1) were randomized clinical trials (RCTs); (2) were categorized as double blind; (3) included relevant clinical outcomes and treatments; (4) contained comparisons between different treatments.

Search strategy: We employed search strategies to explore the medical literature for relevant studies in PubMed and EMBASE systematically, and 2,967 records were identified using the following terms: "migraine disorders", "tryptans", "non-steroidal anti-inflammatory agents", "ergot alkaloids", "opioid analgesics", "sumatriptan", "zolmitriptan", "almotriptan", "rizatriptan", "naratriptan", "ibuprofen", "eletriptan", "diclofenac-potassium" and "aspirin" in PubMed. Reviewers also provided 3 additional references.

Assessment of quality of included trials: yes

Other methodological remarks:
We initially carried out a conventional pair-wise meta-analysis which directly compares each pair of treatments.
The corresponding odds ratios (ORs) and 95% confidence intervals (CIs) for each study were pooled in order to obtain the overall effect size. Furthermore, a NMA was performed for each endpoint with a Bayesian framework using R 3.2.3 software.

Ref	Comparison	N/n	Outcomes	Result
Xu 2016 Design: SR+MA Search date:	Diclofenac Vs Sumatriptan	N = 1 n = 115 (DKSMSG)	Pain free at 1 h	**OR (95% CI):** 1.19 (0.54 to 2.63) **NS**
		N = 1 n = 115 (DKSMSG)	Absence of nausea at 2 h	**OR (95% CI):** 1.25 (0.87 to 1.81) **NS**
		N = 1 n = 115 (DKSMSG)	Migraine recurrence	**OR (95% CI):** 0.88 (0.54 to 1.43) **NS**

		N = 1 n = 115 (DKSMSG)	Adverse events	**OR (95% CI):** 0.43 (0.26 to 0.71) **SS in favour of diclofenac (less with diclofenac)**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
DKSMSG 1999 DB, double-dummy, PC, CO-RCT	156	Migraine ± aura (IHS 1988). History: 2 to 6 attacks/month in previous 6 months Exclusions: participants experiencing non-migrainous interval headaches or other types of migraine Diclofenac-K 50 mg: n = 115 Diclofenac-K 100 mg: n = 115 Sumatriptan: n = 115 Placebo: n = 115 Beta-blockers allowed if dose stable M: 37 F: 119 Median age 33 years, range 19 to 70 years Median time since first diagnosis 15 years	Assessment up to 8 h	Diclofenac-K 50 mg Vs Diclofenac-K 100 mg Vs Sumatriptan 100 mg Vs Placebo, n = 115 Single oral dose of each medication to treat each of 4 separate attacks; each patient was to receive all 4 treatments during the course of the trial. Medication taken at first sign of pain and attacks separated by > 48 hours If pain not controlled, participants asked to wait 2 hours before taking	RANDOMIZATION: Unclear risk Not described ALLOCATION CONCEALMENT: Unclear risk Not described BLINDING (performance bias and detection bias, all outcomes) Low risk "Double dummy" INCOMPLETE OUTCOME: Low risk Drop-outs described. Completer analysis for efficacy, but did not contribute to efficacy analyses. Safety analysis on all participants receiving treatment.

				rescue medication (paracetamol)	

Remarks:

- Authors initially carried out a conventional pair-wise meta-analysis which directly compares each pair of treatments. The corresponding odds ratios (ORs) and 95% confidence intervals (CIs) for each study were pooled in order to obtain the overall effect size. Furthermore, a NMA was performed for each endpoint with a Bayesian framework using R 3.2.3 software. In the present document we only reported results from the pair-wise comparison
- In the study, 144 participants were randomised to treat four consecutive attacks each with a single dose of the different study medications, only 115 patients had four attacks, giving an attrition rate of 20% (12% for reasons other than lack of qualifying headache).

12.3.5 Ibuprofen versus rizatriptan for acute treatment of migraine attack in adults

Meta-analysis: Xu 2016(41), Network meta-analysis of migraine disorder treatment by NSAIDs and triptans

Definition of migraine:

Inclusion criteria: Articles were included if they: (1) were randomized clinical trials (RCTs); (2) were categorized as double blind; (3) included relevant clinical outcomes and treatments; (4) contained comparisons between different treatments.

Search strategy: We employed search strategies to explore the medical literature for relevant studies in PubMed and EMBASE systematically, and 2,967 records were identified using the following terms: “migraine disorders”, “tryptans”, “non-steroidal anti-inflammatory agents”, “ergot alkaloids”, “opioid analgesics”, “sumatriptan”, “zolmitriptan”, “almotriptan”, “rizatriptan”, “naratriptan”, “ibuprofen”, “eletriptan”, “diclofenac-potassium” and “aspirin” in PubMed. Reviewers also provided 3 additional references.

Assessment of quality of included trials: yes

Other methodological remarks:
We initially carried out a conventional pair-wise metaanalysis which directly compares each pair of treatments.
The corresponding odds ratios (ORs) and 95% confidence intervals (CIs) for each study were pooled in order to obtain the overall effect size. Furthermore, a NMA was performed for each endpoint with a Bayesian framework using R 3.2.3 software.

Ref	Comparison	N/n	Outcomes	Result
Xu 2016 Design: SR+MA Search date:	Ibuprofen Vs Rizatriptan	N = 1 n = 155 (Misra 2007)	Pain free at 2 h	OR (95% CI): 0.86 (0.40 to 1.85) NS
		N = 1 n = 155 (Misra 2007)	Pain relief at 2h	OR (95% CI): 0.72 (0.39 to 1.35) NS
		N = 1 n = 155 (Misra 2007)	Use of rescue medication	OR (95% CI): 1.75 (0.82, 3.74) NS
		N = 1 n = 155 (Misra 2007)	Adverse events	OR (95% CI): 0.91 (0.33, 2.53) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Misra 2007 DB, PC, PG-RCT	155	Migraine (IHS 1988). History: < 8 attacks/month. Untreated attacks > moderate severity Excluded participants with headaches associated with recurrent vomiting Ibuprofen 400 mg: n = 52 Rizatriptan 10 mg: n = 53 Placebo: n = 50 M 59 F 106 Mean age 30 years	Assessment up to24h	Ibuprofen 400 mg Vs Rizatriptan 10 mg Vs Placebo Single oral dose/attack (> 2 attacks treated) Medication taken when migraine of moderate or severe intensity If moderate or severe headache persisted after 2 hours, rescue medication allowed (sumatriptan 100 mg or piroxicam 20 mg)	**RANDOMIZATION:** Low risk "computer-generated random numbers" **ALLOCATION CONCEALMENT:** Unclear risk Randomisation done by one investigator and responses evaluated by the other, but no details about method of concealment **BLINDING:** performance bias and detection bias, all outcomes: Unclear risk Medication "provided in identical packets" **OUTCOME DATA: all outcomes:** Low risk Drop-outs described (As rated in Rabbie 2013)

Remarks:

- Authors initially carried out a conventional pair-wise meta-analysis which directly compares each pair of treatments. The corresponding odds ratios (ORs) and 95% confidence intervals (CIs) for each study were pooled in order to obtain the overall effect size. Furthermore, a NMA was performed for each endpoint with a Bayesian framework using R 3.2.3 software. In the present document we only reported results from the pair-wise comparison
- Misra 2007 included participants as young as 16 years.
- Misra 2007 described itself as double-blind, but used treatments that were potentially distinguishable if directly compared.
- Misra 2007 treated two or more attacks with single doses of the same study medication. It is not clear how the data for multiple attacks were combined in these studies.

Author's conclusions:

"We can derive that rizatriptan and eletriptan tend to show effective performance with respect to outcomes including 1 h-pain-relief and rescue medication."

12.3.6 Ibuprofen versus sumatriptan for acute treatment of migraine attack in adults

Meta-analysis: Xu 2016(41), Network meta-analysis of migraine disorder treatment by NSAIDs and triptans

Definition of migraine:

Inclusion criteria: Articles were included if they: (1) were randomized clinical trials (RCTs); (2) were categorized as double blind; (3) included relevant clinical outcomes and treatments; (4) contained comparisons between different treatments.

Search strategy: We employed search strategies to explore the medical literature for relevant studies in PubMed and EMBASE systematically, and 2,967 records were identified using the following terms: "migraine disorders", "tryptans", "non-steroidal anti-inflammatory agents", "ergot alkaloids", "opioid analgesics", "sumatriptan", "zolmitriptan", "almotriptan", "rizatriptan", "naratriptan", "ibuprofen", "eletriptan", "diclofenac-potassium" and "aspirin" in PubMed. Reviewers also provided 3 additional references.

Assessment of quality of included trials: yes

Other methodological remarks:
We initially carried out a conventional pair-wise metaanalysis which directly compares each pair of treatments.
The corresponding odds ratios (ORs) and 95% confidence intervals (CIs) for each study were pooled in order to obtain the overall effect size. Furthermore, a NMA was performed for each endpoint with a Bayesian framework using R 3.2.3 software.

Ref	Comparison	N/n	Outcomes	Result
Xu 2016 Design: SR+MA Search date:	Ibuprofen Vs Sumatriptan	N = 1 n = 882 attacks (Diener 2004)	Pain free at 1 h	OR (95% CI): 1.87 (0.90 to 3.89) NS
		N = 1 n = 882 attacks (Diener 2004)	Pain relief at 1 h	OR (95% CI): 1.30 (0.87 to 1.96) NS
		N = 1 n = 882 attacks (Diener 2004)	Pain free at 2h	OR (95% CI): 0.90 (0.62 to 1.30) NS
		N = 1 n = 882 attacks (Diener 2004)	Pain relief at 2h	OR (95% CI): 1.09 (0.80 to 1.49) NS
		N = 1 n = 882 attacks (Diener 2004)	Use of rescue medication	OR (95% CI): 1.01 (0.71 to 1.43) NS
		N = 1	Migraine recurrence	OR (95% CI): 0.84 (0.53 to 1.32)

		n = 882 attacks (Diener 2004)		NS
		N = 1 n = 882 attacks (Diener 2004)	Adverse events	OR (95% CI): 1.07 (0.07 to 17.2) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Diener 2004 DB, double-dummy, PC, CO-RCT	312 (cross-over trial, 882 attacks)	Migraine with or without aura (IHS 1988). History: 1 to 6 attacks/month in previous year Ibuprofen 400 mg: n = 212 ASA 2 x 500 mg: n = 222 Sumatriptan 50 mg: n = 226 Placebo: n = 222 M 59 F 253 Mean age 38 years History of aura: 21%	Assessment up to24h	Ibuprofen 400 mg Vs Acetylsaysilic acid 2 x 500 mg Vs Sumatriptan 50 mg Vs Placebo Single oral dose of each treatment for each of three migraine attacks, with at least 48 hours between consecutive treatments Medication taken within 6 hours of onset, when	**RANDOMIZATION:** Low risk "predetermined randomization code" **ALLOCATION CONCEALMENT:** Unclear risk Not described **BLINDING:** performance bias and detection bias, all outcomes: Low risk All participants "double-dummy" method with "matching placebo" for each treatment **INCOMPLETE OUTCOME DATA: all outcomes:** Low risk Drop-outs described

				migraine of moderate or severe intensity, and not improving If pain not controlled, participants asked to wait 2 hours before taking rescue medication (of participant's choice - 12 hours if triptan or ergot)	

Remarks:

- Auhtors initially carried out a conventional pair-wise meta-analysis which directly compares each pair of treatments. The corresponding odds ratios (ORs) and 95% confidence intervals (CIs) for each study were pooled in order to obtain the overall effect size. Furthermore, a NMA was performed for each endpoint with a Bayesian framework using R 3.2.3 software. In the present document we only reported results from the pair-wise comparison

12.3.7 Naproxen versus sumatriptan for acute treatment of migraine attack of moderate to severe baseline pain intensity in adults

Meta-analysis: Law 2013(37), Naproxen with or without an antiemetic for acute migraine headaches in adults. Definition of migraine: We used the definition of migraine specified by the International Headache Society (IHS 1988; IHS 2004), although we accepted diagnostic criteria equivalent to those of IHS 1988 where a specific reference was not provided. Inclusion criteria: We included randomised, double-blind, placebo- and/or active controlled studies using oral sumatriptan to treat a migraine headache episode. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data for at least one of the outcomes specified

below. We accepted studies reporting treatment of consecutive headache episodes if outcomes for the first, or each, episode were reported separately; ; first-attack data were used preferentially. Cross-over studies were accepted if there was adequate washout (> 24 hours) between treatments.

Population : Studies enrolled adults (at least 18 years of age) with migraine. There were no restrictions on migraine frequency, duration, or type (with or without aura). Participants taking stable prophylactic therapy to reduce migraine frequency were accepted. All included studies used one or more of these standard scales (reported in remarks) and reported outcomes as defined above.

Exclusion: We excluded studies designed to demonstrate prophylactic efficacy in reducing the number or frequency of migraine headaches.

Search strategy: We searched the following electronic databases. • The Cochrane Central Register of Controlled Trials (CENTRAL), (The Cochrane Library), Issue 4 of 12, 2013. • MEDLINE (via Ovid),1947 to 22 May 2013. • EMBASE (via Ovid), 1974 to 22 May 2013. • Oxford Pain Relief Database, searched on 22 May 2013 (Jadad 1996a).
We searched for additional studies in reference lists of retrieved studies and review articles, and in two clinical trials databases (www.clinicaltrials.gov and www.gsk-clinicalstudyregister.com). We did not search grey literature and short abstracts.
We applied no language restrictions

Assessment of quality of included trials: yes

Other methodological remarks:
We accepted randomisation at the individual patient level only.
The most likely source of missing data was in cross-over studies; we planned to use only first-period data where possible, but no included studies used a cross-over design. Where there were substantial missing data in any study, we commented on this and performed sensitivity analyses to investigate their effect.
For all outcomes, we carried out analyses, as far as possible, on a modified intention-to-treat basis. Where sufficient information was reported, we re-included missing data in the analyses we undertook. We would exclude data from outcomes where results from 10% or greater of participants were missing with no acceptable reason provided or apparent.
We calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants. We calculated relative risk of benefit or harm with 95% confidence intervals (CIs) using a fixed effect model. We calculated NNT, NNTp, and NNH with 95% CIs using the pooled number of events by the method of Cook and Sackett.

Ref	Comparison	N/n	Outcomes	Result

Law 2013 Design: SR+MA Search date: May 2013	Naproxen Vs Sumatriptan	N = 1 n = 474 (Smith 2005)	Pain free at 2 h (PO)	Naproxen: 45/248 (18%) Sumatriptan: 45/226 (20%) NS
		N = 1 n = 474 (Smith 2005)	Pain relief at 2 h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	Naproxen: 114/248 (46%) Sumatriptan: 111/226 (49%) NS
		N = 1 n = 474 (Smith 2005)	Sustained pain-free over 24h (PO) (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	Naproxen: 30/248 (12%) Sumatriptan: 25/226 (11%) NS
		N = 1 n = 474 (Smith 2005)	Sustained pain relief over 24 h (PO) (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.)	Naproxen: 62/248 (25%) Sumatriptan: 66/226 (29%) NS
		N = 1 n = 474 (Smith 2005)	Use of rescue medication	Naproxen: 129/248 Sumatriptan: 115/226 NS
		N = 1 n = 479 (Smith 2005)	Adverse events within 24 h	Naproxen: 43/250 (17%) Sumatriptan: 55/229 (24%) NS

Ref + design	n	Population	Duration	Comparison	Methodology
Smith 2005 DB, double dummy, PG-RCT	972	Migraine ± aura (IHS 2004), aged ≥ 18 years. History ≥ 1 year with 2-6 attacks per month, and able to tolerate oral triptan or ergot derivative Sumatriptan 50 mg + naproxen 500 mg, n = 251 Sumatriptan 50 mg, n = 229 Naproxen 500 mg, n = 250 Placebo, n = 242 F = 91% Mean age 42 years Without aura: > 70%	Assessment up to 24 h	Sumatriptan 50 mg + naproxen 500 mg Vs Sumatriptan 50 mg Vs Naproxen 500 mg Vs Placebo Single dose to treat a single attack Medication taken when pain ≥ moderate Rescue medication allowed after 2 h if necessary (not specified)	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Low risk** Double dummy INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs described

Remarks:

- Authors analysed studies using a single dose of naproxen in established pain of at least moderate intensity separately from studies in which medication was taken before pain was well established or in which a second dose of medication was permitted. In all studies, medication was to be taken orally when the PI was of at least moderate intensity. No studies employed multiple dosing strategies for individual attacks.
- Smith 2005 gave naproxen 500mg vs sumatriptan 50 mg. Two studies (Brandes 2007 study and study 2) also used naproxen 500 mg and sumatriptan 85 mg and were not reported for this comparison. 85mg sumatriptan is the dosage used for combination with naproxen.
- Authors calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants. As only one study was used for this comparison, no analysis of the data was performed.
- PI or PR had to be measured by the participant (not the investigator or care giver):

PI: 4-point categorical scale, with wording equivalent to none, mild, moderate, and severe; or 100 mm visual analogue scale (VAS)), where less than 30 mm was considered equivalent to mild or no pain and 30 mm or greater equivalent to moderate or severe pain (Collins 1997);
PR: 5-point categorical scale, with wording equivalent to none, a little, some, a lot, complete; or 100 mm VAS, where less than 30 mm was considered equivalent to none or a little, and 30 mm or greater equivalent to some, a lot, or complete.

12.3.8 Naproxen versus naratriptan for acute treatment of migraine attack in adults

Meta-analysis: Law 2013(37), Naproxen with or without an antiemetic for acute migraine headaches in adults.

Definition of migraine: We used the definition of migraine specified by the International Headache Society (IHS 1988; IHS 2004), although we accepted diagnostic criteria equivalent to those of IHS 1988 where a specific reference was not provided.

Inclusion criteria: We included randomised, double-blind, placebo- and/or active controlled studies using oral sumatriptan to treat a migraine headache episode. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data for at least one of the outcomes specified below. We accepted studies reporting treatment of consecutive headache episodes if outcomes for the first, or each, episode were reported separately; ; first-attack data were used preferentially. Cross-over studies were accepted if there was adequate washout (> 24 hours) between treatments.

Population : Studies enrolled adults (at least 18 years of age) with migraine. There were no restrictions on migraine frequency, duration, or type (with or without aura). Participants taking stable prophylactic therapy to reduce migraine frequency were accepted. All included studies used one or more of these standard scales (reported in remarks) and reported outcomes as defined above.
We considered only data obtained directly from the patient.

Exclusion: We excluded studies designed to demonstrate prophylactic efficacy in reducing the number or frequency of migraine headaches.

Search strategy: We searched the following electronic databases. • The Cochrane Central Register of Controlled Trials (CENTRAL), (The Cochrane Library), Issue 4 of 12, 2013. • MEDLINE (via Ovid),1947 to 22 May 2013. • EMBASE (via Ovid), 1974 to 22 May 2013. • Oxford Pain Relief Database, searched on 22 May 2013 (Jadad 1996a).
We searched for additional studies in reference lists of retrieved studies and review articles, and in two clinical trials databases (www.clinicaltrials.gov and www.gsk-clinicalstudyregister.com). We did not search grey literature and short abstracts.
We applied no language restrictions

Assessment of quality of included trials: yes

Other methodological remarks:
We accepted randomisation at the individual patient level only.
The most likely source of missing data was in cross-over studies; we planned to use only first-period data where possible, but no included studies used a cross-over design. Where there were substantial missing data in any study, we commented on this and performed sensitivity analyses to investigate their effect.
For all outcomes, we carried out analyses, as far as possible, on a modified intention-to-treat basis. Where sufficient information was reported, we re-included missing data in the analyses we undertook. We would exclude data from outcomes where results from 10% or greater of participants were missing with no acceptable reason provided or apparent.
We calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants.
We calculated relative risk of benefit or harm with 95% confidence intervals (CIs) using a fixed effect model. We calculated NNT, NNTp, and NNH with 95% CIs using the pooled number of events by the method of Cook and Sackett.

Remarks:

- Two studies were head-to-head comparisons of a low dose (275 mg) of naproxen with naratriptan (S2WA4003; S2WA4004).
- The two active-controlled studies comparing naproxen 275 mg with naratriptan 2.5 mg did not report any of our prespecified efficacy outcomes (S2WA4003; S2WA4004); they did report numbers of participants experiencing our prespecified adverse event and withdrawal outcomes, but combined data for all attacks over a 12- week period without any explanation of how it was done, so we were unable to use them in analyses.

No data were provided

Not enough evidence

12.4 Associations with caffeine

12.4.1 APC versus placebo for acute treatment of migraine attack of in adults

Meta-analysis: Diener 2022(42), Aspirin, paracetamol (acetaminophen) and caffeine for the treatment of acute migraine attacks: A systemic review and meta-analysis of randomized placebo-controlled trials.

Definition of migraine: /

Inclusion criteria: Randomized, blinded, placebo-controlled studies investigating patients experiencing episodic migraines, and using APC or placebo to treat a migraine attack, were identified. Studies using one dose of APC in a migraine attack with at least moderate headache intensity were included.

Search strategy: An electronic search in the Embase database with the search terms "((‘paracetamol'/exp OR ‘paracetamol’ OR ‘acetaminophen'/exp OR ‘acetaminophen’) AND (‘aspirin'/exp OR ‘aspirin’) AND (‘caffeine'/exp OR ‘caffeine’) AND (‘migraine'/exp OR migraine)) AND (‘clinicaltrial'/de OR ‘controlled clinical trial'/de OR ‘randomized controlled trial'/de) AND (‘article'/it OR ‘conference abstract'/it OR ‘conference paper'/it)" was conducted on 25 August 2020.
In addition, electronic searches with the search terms aspirin AND paracetamol AND caffeine AND migraine were performed using the following data sources: (i) US clinical trial registry (https:// clini caltr ials.gov/); (ii) European Union clinical trial registry (https://eudra ct.ema.europa.
eu); (iii) Chinese clinical trial registry (http://www.chictr.org.cn); (iv) Indian clinical trial registry (http://ctri.nic.in/Clini caltr ials/login.
php); (v) Pan African clinical trial registry (https://pactr.samrc.ac.za)

Assessment of quality of included trials: yes

Other methodological remarks:
The RRs of benefit or harm, with 95% CIs, were computed using Mantel–Haenszel statistics.
Random-effect meta-analysis models were used because heterogeneity was expected due to the known variation in pain assessments used in different patient and study settings.

Ref	Comparison	N/n	Outcomes	Result

Diener 2022 Design: SR+MA Search date: August 2020	APC Vs Placebo	N = 6 n = 2934 (Diener 2005, Novartis 2012, Goldstein 2006, Lipton 1998 studies 1, 2, 3)	Pain free at 2 h (PO) (Pain reduced from “severe” or “moderate” to “no pain” pain reduced by 90% from baseline)	APC: 567/1879 ; median:19.6% (95% CI: 12.9 to 29.9) Placebo: 141/1055 ; median: 9% **RR: 2.2 (95% CI: 1.5 to 3.1)** NNT: 9.4 (95% CI 4.8–25.6) **SS in favour of APC** I^2: 82%
		N = 5 n = 1771 (Diener 2005, Lipton 1998 studies 1, 2, 3, Goldstein 2005)	Headache relief at 2 h (PO) (Pain reduced from “severe” or “moderate” to “mild” or “no pain”, or pain reduced by 50% from baseline)	APC: 679/1025 ; median: 54.3% (95% CI: 48.7 to 60.2) Placebo: 265/746 ; median: 31.2% **RR: 1.7 (95% CI: 1.6 to 1.9)** NNT: 4.3 (95% CI: 3.4 to 5.7) **SS in favour of APC** I^2: 0%
		N = 5 n = 2565 (Diener 2005, Goldstein 2006, Lipton 1998 studies 1, 2, 3)	Pain free at 1 h (Pain reduced from “severe” or “moderate” to “no pain” pain reduced by 90% from baseline)	APC: 159/1631 ; median: 7.4% (95% CI: 5.1 to 10.6) Placebo: 36/934 ; median : 4.1% RR: 1.80 (95% CI: 1.25 to 2.58) **SS in favour of APC** I^2: 0%
		N = 5 n = 2565 (Diener 2005, Goldstein 2006, Lipton	Pain free at 4 h (Pain reduced from “severe” or “moderate” to “no pain” pain reduced by 90% from baseline)	APC: 863/1631 ; median: 43.8 (95% CI: 32.6–58.7) Placebo : 235/934 ; median: 22% **RR: 1.99 (95% CI: 1.48 to 2.67)** **SS in favour of APC**

		1998 studies 1, 2, 3)		I^2: 83%
		N = 5 n = 1771 (Diener 2005, Lipton 1998 studies 1, 2, 3, Goldstein 2005)	Headache relief at 1 h (Pain reduced from “severe” or “moderate” to “mild” or “no pain”, or pain reduced by 50% from baseline)	APC: 420/1025 ; median: 36.3 (95 % CI: 30.6to 43.1) Placebo: 142/746 ; median: 17.8 **RR: 2.04 (95 % CI: 1.72 to 2.42)** **SS in favour of APC** I^2: 0%
		N = 5 n = 1771 (Diener 2005, Lipton 1998 studies 1, 2, 3, Goldstein 2005)	Headache relief at 4 h (Pain reduced from “severe” or “moderate” to “mild” or “no pain”, or pain reduced by 50% from baseline)	APC: 828/1025 ; median: 76.4 (95 % CI: 70.6 to 82.8) Placebo: 371/746 ; median: 49% **RR: 1.56 (95 % CI: 1.44 to 1.69)** **SS in favour of APC** I^2: 0%
		N = 4 n = 1691 (Diener 2005, Lipton 1998 studies 1, 2, 3)	No/little functional disability at 2 h	APC: 542/975 Placebo: 237/716 **RR: 1.74 (95% CI: 1.53 to 1.98)** **SS in favour or APC** I^2: 0%
		N = 4 n = 1587 (Novartis 2012, Lipton	No nausea at 2h	APC: 552/850 Placebo: 426/737 RR:1.10 (95% CI:1.00 to 1.20) **p = 0.04** **SS in favour or APC**

		1998 studies 1, 2, 3)		I^2: 26 %
		N = 4 n = 1587 (Novartis 2012, Lipton 1998 studies 1, 2, 3)	No photophobia at 2h	APC: 328/849; median: 30.1% (95% CI: 20.6–44.2) Placebo: 153/738 ; median: 17.0% **RR: 1.77 (1.21 to 2.60)** **SS in favour of APC** I^2: 81%
		N = 4 n = 1586 (Novartis 2012, Lipton 1998 studies 1, 2, 3)	No phonophobia at 2h	APC: 351/849 ; median: 33.0% (95% CI: 23.9 to 45.8) Placebo: 173/737 ; median:19.9% **RR: 1.66 (95% CI: 1.20 to 2.30)** **SS in favour of APC** I^2: 78%
		N = 4 N=1323 (Lipton 1998 studies 1, 2, 3, Goldstein 2005)	Use of rescue medication	No pooled data: <u>Lipton 1998: (3 studies)</u> APC: 12.5% Placebo: 27.2% $p < 0.001$ **SS in favour of APC** <u>Goldstein 2005: 1 study</u> APC: 1.5% Placebo: 14.3% $p = 0.043$

				SS in favour of APC
		N = 6 n = 3202 (Diener 2005, Novartis 2012, Goldstein 2006, Lipton 1998 studies 1, 2, 3)	Adverse events	APC: 226/2078 ; median: 18.5% (95%-CI: 14.5 to 23.48) Placebo: 88/1124 ; media: 10.8% **RR: 1.71 (95%CI: 1.3 to 2.2)** RD: 7.7% (95%-CI: 3.7–12.6) **SS in favour of placebo** I^2: 0%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Lipton 1998 **(3 studies)** <u>Study 1:</u>	<u>Study 1:</u>	IHS diagnosis migraine with or without aura; at least 18 years old; good general health; at least on migraine headache every 2 months, but not more than 6 per month; headache of at least moderate intensity when untreated Main exclusion criteria: Patients usually incapacitated (i. e. requiring bed rest for their attacks); patients experiencing vomiting 20% or more of the time <u>Study 1:</u> APC, n = 187	Assessment up to 6h	APC Vs Placebo 2 tablets 500/500/130 mg	RANDOMIZATION: **Low risk**, "… qualified patients were randomly assigned (1:1 ratio), according to a computer-generated randomization schedule, to receive a bottle of double-blinded study medication containing either 2 tablets of unbranded ACP or 2 identical-appearing placebo tablets…" Randomization process outlined; allocation concealment is given; baseline data comparisons show balanced groups. BLINDING:

DB, PC, PG-RCT Single-centre <u>Study 2:</u> DB, PC, PG-RCT Multi-centre <u>Study 3:</u> DB, PC, PG-RCT Multi-centre	378 <u>Study 2:</u> 427 <u>Study 3:</u> 415	Placebo, n = 191 <u>Study 2:</u> APC, n = 206 Placebo, n = 221 <u>Study 3:</u> APC, n = 209 Placebo, n = 206			**Low risk**, patients and study personnel were not aware of the medication; the larger percentage of rescue medication in the placebo group induces an underestimation of the treatment effect MISSING OUTCOME DATA: **Low risk**, Only 30/1250 ITT patients are excluded from evaluable patients set, balanced in both groups (16 in ACP, 14 in placebo group) REPORTING: **Low risk**, All primary endpoints and endpoints needed for these meta-analyses are reported
Goldstein 2005 DB, PC, PG-RCT Multi-centre	170	Main inclusion criteria: IHS diagnosis migraine with or without aura; 1 to 8 migraine attacks per month; headache of at least moderate intensity when untreated Main exclusion criteria: Patients requiring bed rest during more than 50% of their attacks; patients experiencing vomiting 20% or more of the time APC, n = 68 Sumatriptan, n = 67	Assessment up to 4 h	APC Vs Sumatriptan Vs Placebo 2 tablets 500/500/130 mg	! methodology (<n= 40 /study group)

		Placebo, n = 35			
Diener 2005 DB, PC, PG-RCT Multi-centre	1210	IHS diagnosis migraine with or without aura, and/or tension-type headache (only data of migraine attacks were used for this analysis); at least 18 years old; at least 2 headache episodes in the previous 3 months; headache history of at least 12 months Only data of treated migraine attacks were used for the meta-analysis. Data were provided by the study sponsor.) Exclusion: Use of prescription-only medication to treat headache; headache on more than 10 days per month; usual headache episode lasting shorter than 4 h; menstrual migraine APC: 373 Aspirin/Paracetamol: 358 Aspirin: 188 Paracetamol: 191 Caffeine: 99 Placebo: 101	Assessment up to 4 h	APC Vs Aspirin + paracetamol Vs Aspirin Vs Paracetamol Vs Caffeine Vs Placebo 2 tablets 500/400/100 mg	RANDOMIZATION: **Low risk**, *Patients qualifying for this double-blind treatment phase were randomly allocated to one of the six treatment groups ….. The randomization list was generated using a 4 : 4 : 2 : 2 : 1 : 1 scheme (ASA + PAR + CAF : ASA + PAR : ASA : PAR : CAF : PL) in blocks of 14 with the commercial program ClinPro/LBL, version 6.0* BLINDING: **Low risk**, patients and study personnel were not aware of the medication; the larger percentage of rescue medication in the placebo (10%) vs. (4%) in the APC group induces an underestimation of the treatment effect, i.e. the potential bias is in the conservative direction. MISSING OUTCOME DATA: **Low risk**, Only 3 ITT patients are excluded because of missing VAS data. REPORTING: **Low risk**, all data necessary for this meta-Analysis are available.

Goldstein 2006 DB, PC, PG-RCT Multi-centre	1555	Main inclusion criteria: IHS diagnosis migraine with or without aura; at least 18 years old; at least on migraine headache every 2 months, but not more than 6 per month during the prior 12 months; headache of at least moderate intensity when untreated Main exclusion criteria: Analgesic use on more than 12 days per month APC: 669 Ibuprofen: 666 Placebo: 220	Assessment up to 4 h	APC Vs Ibuprofen Vs Placebo 2 tablets 500/500/130 mg	RANDOMIZATION: **Low risk**, *patients were randomly assigned (3:3:1 ratio)….* Randomization process outlined; allocation concealment is given; baseline data comparisons show balanced groups. BLINDING: **Low risk**, patients and study personnel were not aware of the medication; the larger percentage of rescue medication in the placebo vs. in the APC (“ At 2 hours after treatment, the proportion of patients who required rescue medication was significantly higher in the IB (P = .025) and placebo (P < .001) treatment groups than for the AAC treatment group induces an underestimation of the treatment effect, i.e. the potential bias is in the conservative direction. MISSING OUTCOME DATA: **Low risk**, Only 2 ITT patients (1 in each group) are excluded. REPORTING: ***Low risk***, The results for the primary endpoint “weighted sum of pain relief (PAR) scores at 2 h (TOTPAR2)” demonstrate a clear superiority; among the secondary endpoints, - all in a clear favour

					of APC – only the data for pain-free are reported, not the data for pain relief.
Novartis 2012 DB, PC, PG-RCT Multi-centre	625	Main inclusion criteria: 18 years and over; IHS diagnosis of migraine without aura or typical aura with migraine headache; history of experiencing at least 1, but not more than 8, acute migraine attacks monthly during the previous year; history of at least moderate migraine pain intensity, if left untreated. Main exclusion criteria: Routine use (≥ 10 days per month, on average) of any medication having the potential to interfere with the pharmacologic effects or evaluation of the study medications (e.g., narcotic and non-narcotic analgesic products (prescription or over-the-counter); ergotamine-containing and ergot-type medication, anxiolytics, hypnotics, sedatives, 5HT-1 agonists, anti-emetics, or prokinetic drugs); history of vomiting during more than 20% of migraine episodes or confined to bedrest for more than 50% of migraine episodes. APC: 248 Sumatriptan: 256	Assessment up to 4 h	APC Vs Sumatriptan Vs Placebo 2 tablets 500/500/130 mg	RANDOMIZATION: **Low risk**, *Allocation: Randomized; Intervention Model: Parallel Assignment; Masking: Double (Participant, Investigator);…* Randomization mentioned; allocation concealment is given; baseline data comparisons show balanced groups. BLINDING: **Low risk**, patients and study personnel were not aware of the medication MISSING OUTCOME DATA: **Low risk**, Only 8/256 and 4/125 ITT patients are excluded REPORTING: **Low risk**, The results for the primary endpoint “pain-free at 2h” are reported; also for the secondary endpoints “free of nausea at 2h” and “free of phonophobia at 2h”, and photophobia demonstrate superiority”.

		Placebo: 121			

Remarks:

- The following definitions were used: “severe”,“moderate” or mild defined on four-point; or % pain defined on100-mm visual analogue scale [VAS].
- The studies investigated two tablets of usual APC combinations, corresponding to 500/400/100 mg aspirin/paracetamol/caffeine (Diener 2005), or 500/500/130 mg for the other.
- In all studies, medications were taken when the pain of the treated migraine attack was moderate or severe.
- The Novartis study (NCT01248468) reported its results on Clinicaltrials.gov, but has not been published in a scientific journal.
- One study Diener 2005 investigated tension-type headache as well as migraine. Only data on treated migraine attacks were used for the meta-analysis (data were provided by the study sponsor).
- As reported by authors: “In two studies, significant positive outcomes for APC compared to placebo were mentioned (pain relief, improvement of functional ability, phonophobia and photophobia (Goldstein 2006 and 2005), but the results were not reported in detail and could therefore not be included in the analysis.” Data were not provided.
- All included studies made some mention of AEs, but did not always report the numbers of participants in each treatment group who experienced at least one AE. The incidence of AEs varied considerably among studies, which might be explained by differences in study procedures to collect these data (e.g., a diary vs. spontaneous reporting), or by contamination with migraine-associated symptoms.

Author’s conclusions:

“In conclusion, the present meta-analysis demonstrates good efficacy for APC versus placebo in terms of both the International Headache Society-recommended primary outcome, “rate of pain-free patients at 2 h” and the secondary outcome, “rate of pain relief at 2 h”. The tolerability was good and indicates that APC is an effective and well-tolerated OTC treatment for acute migraine attacks.”

12.4.2 APC vs paracetamol + ASA for the treatment of a migraine attack in adults

Study details	n/Population	Comparison	Outcomes	Methodological
Diener 2005	n= 1983		Efficacy	RANDO:

RCT (BD, PG) Assessments at 30 min, 1h, 2h, 3h, and 4h	1743 patients for ITT Mean age: 38 Age range: 16-72 F76% 84% of the patients usually suffered from migraine headache, 13% from episodic tension-type headache and 3% could not be classified Pain severity: severe 62% moderate 37% At baseline the headache pain intensity had to be greater than 30 mm. Definition of migraine : Usual headaches had to meet International Headache Society (1) criteria for episodic	Paracetamol 400mg + acetylsalicylic acid 500mg + caffeine 100mg (n=482) vs paracetamol 400mg + acetylsalicylic acid 500mg (n=498) Two headache episodes were treated, six treatment groups for both treatment phases ASA+PAR+CAF ASA+PAR ASA	Time to 50% pain relief (PO) (pain intensity recorded on a 100 mm visual analogue scale)	PAR+ASA+CAF: 1h5min PAR+ASA: 1h13min p = 0.0181 **SS in favour of PAR+ASA+CAF**	Adequate ALLOCATION CONC: Unclear: in sequential order of entry BLINDING : Participants: yes Personnel: yes Assessors: unclear Reported as doubled blind, expert is blinded for diagnosis but no other description. FOLLOW-UP: Lost-to follow-up, Drop-out and Exclusions: 94 did not take study medication., 146 patients did not return any diaries, all data given per group • Described: yes • Balanced across groups: yes Both PP and ITT: Yes: Data missing for any scheduled efficacy evaluation was replaced by the last observation carried forward procedure.
			Time until reduction of pain intensity to 10 mm VAS(PI).	PAR+ASA+CAF: 1h56min PAR+ASA: 2h25min **SS in favour of PAR+ASA+CAF**	
			Pain intensity difference at 2h relative to baseline (mm on a 100 mm visual analogue scale)	PAR+ASA+CAF: 44.7 PAR+ASA: 40.2 Difference: -4.6 (-7.4 to -1.7) *p* = 0.0019 **SS in favour of PAR+ASA+CAF**	
			% patients with impairment of daily activities at 2h (somewhat, greatly, impossible activity)	PAR+ASA+CAF: 34.6%, 10.6%, 0.8% PAR+ASA: 39.4%, 10%, 1.2% p = 0.0813 **NS**	
			Safety		
			% of patients with any adverse events	PAR+ASA+CAF: 8% PAR+ASA: 7.8% No statistics provided	
			% patients with palpitation	PAR+ASA+CAF: 0.4% PAR+ASA: 0.2% No statistics provided	

	tension-type headache (2.1) and/or migraine with or without aura Additional medication: rescue medication 4 h after the administration of the trial medication <u>Inclusion</u>: male or female outpatients (18–65 years), They must have experienced these headaches for at least 12 months with a minimum of two headache episodes within the previous 3 months <u>Exclusion:</u> patient treats their headache with prescription analgesics or migraine drugs,requires higher single doses of non-prescription analgesics, normally treats their headache	PAR CAF PL The trial medication was to be taken as a single dose when the headache occurred, and when the patients would normally have taken their usual analgesic.			SELECTIVE REPORTING: yes A lot of outcomes are not reported and particularly % of patient with pain relief Sponsor: Boehringer Ingelheim Thomapyrin Study/CRA Team for their work in conducting and data handling of this study

	with non-prescription analgesics in effervescent tablet form, headache occurs on more than 10 days per month or lasts untreated normally less than 4 h, menstrual migraine,. concomitant treatment with prescription-only and/or non-prescription analgesics, antidepressants or antipsychotic medication, antirheumatic or anti-inflammatory drugs, drugs containing ASA paracetamol or caffeine, migraine prophylaxis, drug overuse, alcohol or drug abuse, pregnancy and lactation, gastrointestinal ulcers, pathologically				

	increased bleeding tendency, glucose- 6-phosphate dehydrogenase deficiency, bronchial asthma, concomitant treatment with anticoagulants, chronic or recurrent gastrointestinal symptoms, liver disorders, pre-existing renal damage, Gilbert's syndrome, or hyperthyroidism.				

12.4.3 APC vs paracetamol for the treatment of a migraine attack in adults

Study details	n/Population	Comparison	Outcomes		Methodological
Diener 2005 (45) RCT (BD, PG)	n= 1983 1743 patients for ITT Mean age: 38 Age range: 16-72 F76%	Paracetamol 400mg + acetylsalicylic acid 500mg + caffeine 100mg	Efficacy		RANDO: Adequate ALLOCATION CONC: Unclear: in sequential order of entry BLINDING :
			Time to 50% pain relief (PO) (pain intensity recorded on a 100 mm visual analogue scale)	PAR+ASA+CAF: 1h5min PAR: 1h21min p = 0.0016 **SS in favour of PAR+ASA+CAF**	

Assessments at 30 min, 1h, 2h, 3h, and 4h	84% of the patients usually suffered from migraine headache, 13% from episodic tension-type headache and 3% could not be classified Pain severity: severe 62% moderate 37% At baseline the headache pain intensity had to be greater than 30 mm. Definition of migraine : Usual headaches had to meet International Headache Society (1) criteria for episodic tension-type headache (2.1) and/or migraine with or without aura Additional medication: rescue medication 4 h after the	(n=482) vs paracetamol 1000mg (n=251) Two headache episodes were treated, six treatment groups for both treatment phases ASA+PAR+CAF ASA+PAR ASA PAR CAF PL	Time until reduction of pain intensity to 10 mm VAS(PI).	PAR+ASA+CAF: 1h56min PAR: 2h35min **SS in favour of PAR+ASA+CAF**	Participants: yes Personnel: yes Assessors: unclear Reported as doubled blind, expert is blinded for diagnosis but no other description. FOLLOW-UP: Lost-to follow-up, Drop-out and Exclusions: 94 did not take study medication., 146 patients did not return any diaries, all data given per group • Described: yes • Balanced across groups: yes Both PP and ITT: Yes: Data missing for any scheduled efficacy evaluation was replaced by the last observation carried forward procedure. SELECTIVE REPORTING: yes
			Pain intensity difference at 2h relative to baseline (mm on a 100 mm visual analogue scale)	PAR+ASA+CAF: 44.7 PAR: 39.5 Difference: -5.2 (-8.7 to -1.7) p = 0.0032 **SS in favour of PAR+ASA+CAF**	
			% patients with impairment of daily activities at 2h (somewhat, greatly, impossible activity)	PAR+ASA+CAF: 34.6%, 10.6%, 0.8% PAR : 39%, 11.2%, 1.2% p = 0.0765 **NS**	
			Safety		
			% of patients with any adverse events	PAR+ASA+CAF: 8% PAR: 5.8% No statistics provided	
			% patients with palpitation	PAR+ASA+CAF: 0.4% PAR: / No statistics provided	

	administration of the trial medication Inclusion: male or female outpatients (18–65 years), They must have experienced these headaches for at least 12 months with a minimum of two headache episodes within the previous 3 months Exclusion: patient treats their headache with prescription analgesics or migraine drugs, requires higher single doses of non-prescription analgesics, normally treats their headache with non-prescription analgesics in effervescent tablet form, headache occurs on more than 10 days per month or	The trial medication was to be taken as a single dose when the headache occurred, and when the patients would normally have taken their usual analgesic.			A lot of outcomes are not reported and particularly % of patient with pain relief Sponsor: Boehringer Ingelheim Thomapyrin Study/CRA Team for their excellent work in conducting and data handling of this study

	lasts untreated normally less than 4 h, menstrual migraine,. concomitant treatment with prescription-only and/or non-prescription analgesics, antidepressants or antipsychotic medication, antirheumatic or anti-inflammatory drugs, drugs containing ASA paracetamol or caffeine, migraine prophylaxis, drug overuse, alcohol or drug abuse, pregnancy and lactation, gastrointestinal ulcers, pathologically increased bleeding tendency, glucose- 6-phosphate dehydrogenase deficiency, bronchial asthma, concomitant				

	treatment with anticoagulants, chronic or recurrent gastrointestinal symptoms, liver disorders, pre-existing renal damage, Gilbert's syndrome, or hyperthyroidism.				

12.4.4 APC vs ASA acid for the treatment of a migraine attack in adults

Study details	n/Population	Comparison	Outcomes		Methodological
Diener 2005 (45) RCT (BD, PG) Assessments at 30 min, 1h, 2h, 3h, and 4h	n= 1983 1743 patients for ITT Mean age: 38 Age range: 16-72 F76% 84% of the patients usually suffered from migraine headache, 13% from episodic tension-type headache and 3% could not be classified Pain severity: severe 62% moderate 37% At baseline the headache pain intensity had to be greater than 30 mm. Definition of migraine :	Paracetamol 400mg + acetylsalicylic acid 500mg + caffeine 100mg (n=482) vs acetylsalicylic acid 1000mg (n=252) Two headach episodes were treated, six treatment groups for both treatment phases ASA+PAR+CAF ASA+PAR	Efficacy		RANDO: Adequate ALLOCATION CONC: Unclear: in sequential order of entry BLINDING : Participants: yes Personnel: yes Assessors: unclear Reported as doubled blind, expert is blinded for diagnosis but no other description. FOLLOW-UP: Lost-to follow-up, Drop-out and Exclusions: 94 did not take study medication., 146 patients did not return any diaries, all data given per group • Described: yes • Balanced across groups: yes
			Time to 50% pain relief (PO) (pain intensity recorded on a 100 mm visual analogue scale)	PAR+ASA+CAF: 1h5min ASA: 1h19min p = 0.0398 **SS in favour of PAR+ASA+CAF**	
			Time until reduction of pain intensity to 10 mm VAS(PI)	PAR+ASA+CAF: 1h56min ASA: 2h31min **SS in favour of PAR+ASA+CAF**	
			Pain intensity difference at 2h relative to baseline (mm on a 100 mm visual analogue scale)	PAR+ASA+CAF: 44.7 PAR: 40.7 Difference: -4.0 (-7.5 to -0.6) p = 0.0228 **SS in favour of PAR+ASA+CAF**	
			% patients with impairment of daily activities at 2h (somewhat, greatly, impossible activity)	PAR+ASA+CAF: 34.6%, 10.6%, 0.8% ASA: 37.3%, 12.7%, 1.6% p = 0.0446 **SS in favour of PAR+ASA+CAF**	
			Safety		

	Usual headaches had to meet International Headache Society (1) criteria for episodic tension-type headache (2.1) and/or migraine with or without aura Additional medication: rescue medication 4 h after the administration of the trial medication <u>Inclusion</u>: male or female outpatients (18–65 years), They must have experienced these headaches for at least 12 months with a minimum of two headache episodes within the previous 3 months <u>Exclusion:</u> patient treats their headache with prescription analgesics or migraine drugs, requires higher	ASA PAR CAF PL The trial medication was to be taken as a single dose when the headache occurred, and when the patients would normally have taken their usual analgesic.	% of patients with any adverse events	PAR+ASA+CAF: 8% ASA: 9.7% No statistics provided	Both PP and ITT: Yes: Data missing for any scheduled efficacy evaluation was replaced by the last observation carried forward procedure. SELECTIVE REPORTING: yes A lot of outcomes are not reported and particularly % of patient with pain relief Sponsor: Boehringer Ingelheim Thomapyrin Study/CRA Team for their excellent work in conducting and data handling of this study
			% patients with palpitation	PAR+ASA+CAF: 0.4% ASA: / No statistics provided	

	single doses of non-prescription analgesics, normally treats their headache with non-prescription analgesics in effervescent tablet form, headache occurs on more than 10 days per month or lasts untreated normally less than 4 h, menstrual migraine,. concomitant treatment with prescription-only and/or non-prescription analgesics, antidepressants or antipsychotic medication, antirheumatic or anti-inflammatory drugs, drugs containing ASA paracetamol or caffeine, migraine prophylaxis, drug overuse, alcohol or				

	drug abuse, pregnancy and lactation, gastrointestinal ulcers, pathologically increased bleeding tendency, glucose- 6-phosphate dehydrogenase deficiency, bronchial asthma, concomitant treatment with anticoagulants, chronic or recurrent gastrointestinal symptoms, liver disorders, pre-existing renal damage, Gilbert's syndrome, or hyperthyroidism.				

12.4.5 APC vs ibuprofen for the treatment of a migraine attack in adults

Study details	n/Population	Comparison	Outcomes		Methodological
AGoldstein 2006 Design:	n= 1714 Mean age: 38.3 F80.3%	Paracetamol 500mg+ acetylsalicylic	Efficacy		RANDO: Unclear: not described ALLOCATION CONC: Unclear: not described
			Sum of pain relief score at 2 h (PO)	PAR +ASA +CAF: 2.7 Ibuprofen: 2.4 P < 0.03	

RCT (DB, PG) Assessments at 15, 30, 45, 60, 90, 120, 180, and 240 minutes	79.3% with aura Baseline pain intensity: Moderate: 57.6% Severe: 42.4% Definition of migraine : International Headache Society (IHS) diagnostic criteria for migraine without aura (IHS 1.1) or migraine with aura (IHS 1.2). <u>Inclusion:</u> at least 18 years old, was in good general health, and had experienced a migraine attack at least once every 2 months—but no more than 6 times monthly—during the prior 12 months. Untreated attacks were of at least	acid 500mg + caffeine 130 mg (n=669) Vs Ibuprofen 400mg (n=666) If the headache symptom profile met the criteria for migraine and was of at least moderate intensity, patients were instructed to take study medication.	(on a 5-point scale (0 = no relief; 1 = a little relief; 2 = some relief; 3 = a lot of relief; and 4 = complete relief))	**SS in favour of PAR + ASA + CAF**	BLINDING : Participants: yes Personnel: probably yes Assessors: probably yes All treatment information remained blinded until all queries were resolved and the database was locked. FOLLOW-UP: Lost-to follow-up:36, 38, 15 Drop-out and Exclusions:0, 3, 1 • Described: yes • Balanced across groups: yes ITT: Yes SELECTIVE REPORTING: only significant values reported Sponsor:
			Sum of pain relief score at 4 h	PAR +ASA +CAF: 7.8 Ibuprofen: 7.1 P < 0.007 **SS in favour of PAR + ASA + CAF**	
			Time to meaningful pain relief	PAR +ASA +CAF: 128.4 min Ibuprofen: 147.9 min p = 0.036 **SS in favour of PAR + ASA + CAF**	
			Sum of pain intensity difference relative to baseline at 2h (on a 4-point scale (0 = no pain; 1 = mild pain; 2 = moderate pain; and 3 = severe pain))	PAR +ASA +CAF: 1.5 Ibuprofen: 1.4 P < 0.045 **SS in favour of PAR + ASA + CAF**	
			Sum of pain intensity difference relative to baseline at 4h	PAR +ASA +CAF: 4.6 Ibuprofen: 4.2 p < 0.012	

	moderate pain intensity. Exclusion: headache symptoms may have been caused or aggravated by recent head or neck trauma and patients with cluster headache, specific migraine variants, or other serious nonmigraine causes of headache, using analgesic drug products for headache on more than 12 days per month			**SS in favour of PAR + ASA + CAF**	
			% patients with pain reduced to mild or none at 2h	PAR +ASA +CAF: 67% Ibuprofen: 62% p < 0.046 **SS in favour of PAR + ASA + CAF**	
			% patients pain free at 4 h	Raw data not reported p < 0.035 **SS in favour of PAR + ASA + CAF**	
			Functional disability	Raw data not reported **NS**	
			Associate nausea	Raw data not reported **NS**	
			Associated vomiting	Raw data not reported **NS**	
			Associated photophobia	Raw data not reported **NS**	
			Associated phonophobia	Raw data not reported **NS**	

			Safety		
			% patients with any adverse events	PAR +ASA +CAF: 9.7% Ibuprofen: 5.1% No statistic provided	
			% patients with cardiovascular event (palpitation or tachycardia)	PAR +ASA +CAF: 0.3% Ibuprofen: no event No statistic provided	

12.4.6 APC vs sumatriptan for the treatment of a migraine attack in adults

Study details	n/Population	Comparison	Outcomes		Methodological
Goldstein 2005 (44) Design: RCT (DB, PG) Assessments at 0.25, 0.5,	n= 188 170 for ITT analysis Age38.1 F81% 0.5% with aura Baseline pain intensity: Moderate: 34.7% Severe: 65.3% **(72%) of subjects reported moderate or**	Paracetamol 500mg+ acetylsalicylic acid 500mg + caffeine 130 mg Vs Sumatriptan 50 mg **take the study medication**	Efficacy		RANDO: yes ALLOCATION CONC: yes BLINDING : Participants: yes Personnel: no reported Assessors: not reported All treatment information remained blinded until all queries were resolved and the database was locked.
			Sum of pain intensity difference relative to baseline at 4h (PO) (on a 4-point scale (0 = no pain; 1 = mild pain; 2 = moderate pain; and 3 = severe pain))	PAR +ASA +CAF: 3.9 Sumatriptan: 2.1 p = 0.014 **SS in favour of PAR + ASA + CAF**	
			Pain intensity difference at 2h	PAR +ASA +CAF: 1.1 Sumatriptan: 0.6 p < 0.05 **SS in favour of PAR + ASA + CAF**	

0.75, 1, 1.5, 2, 3, and 4 hours	**severe pain intensity at dosing** IHS diagnostic criteria for migraine with or without aura <u>Inclusion:</u> 1to 8 migraine episodes of at least moderate intensity if left untreated <u>Exclusion:</u> Subjects who reported vomiting during more than 20% of migraine episodes or who required bedrest during more than 50% of migraine episodes were excluded.	**when the first symptoms usually recognized as the beginning of a migraine attack occurred.**			FOLLOW-UP: Lost-to follow-up:1 Drop-out and Exclusions:/ • Described: yes • Balanced across groups: yes ITT: Yes SELECTIVE REPORTING: unclear for several outcomes only significant values reported Sponsor:
			Pain relief score at 2 h (on a 5-point scale (0 = no relief; 1 = a little relief; 2 = some relief; 3 = a lot of relief; and 4 = complete relief))	PAR +ASA +CAF: 2.5 Sumatriptan: 1.9 p < 0.05 **SS in favour of PAR + ASA + CAF**	
			Sum of pain relief score at 4 h	PAR +ASA +CAF: 8.9 Sumatriptan: 6.9 p = .022 **SS in favour of PAR + ASA + CAF**	
			% patients with pain reduced to mild or none at 30 min	PAR +ASA +CAF: 6% Sumatriptan: 29% P = 0.012 **In favour of sumatriptan**	
			% patients with pain reduced to mild or none at 2 h	PAR +ASA +CAF: 84% Sumatriptan: 65% P≤.027 **SS in favour of PAR + ASA + CAF**	

			% patients with pain reduced to mild or none at 4 h	PAR +ASA +CAF: 98% Sumatriptan: 72% P≤.027 **SS in favour of PAR + ASA + CAF**	
			Pain recurrence after 2h	PAR +ASA +CAF: 10% Sumatriptan: 6.5% **NS**	
			Use of rescue medication at 4h	PAR +ASA +CAF: 1.5% Sumatriptan: 11.9% **SS in favour of PAR + ASA + CAF (less with PAR + ASA + CAF)**	
			% patient without functional disability at 4h	PAR +ASA +CAF: 81% Sumatriptan: 62% P = 0.044 **SS in favour of PAR +ASA +CAF**	
			Associated nausea	Raw data not reported **NS**	
			Associated vomiting	Raw data not reported	

				NS	
			Associated photophobia at 90 min	Raw data not reported P ≤ .015 **SS in favour of PAR +ASA +CAF**	
			Associated phonophobia at 2 h	Raw data not reported P ≤ .044 **SS in favour of PAR +ASA +CAF**	
			Safety		
			% patients with cardiovascular event (palpitation or tachycardia)	No events	

12.4.7 Paracetamol 1000 mg + caffeine 130 mg vs Sumatriptan 50 mg for the treatment of a migraine attack in adults

Study details	n/Population	Comparison	Outcomes		Methodological
Pini 2012 (48) Design: RCT (DB, double dummy, CO) Phase IV	n= 108 (92 for efficacy, 264 attacks) Mean age:M 33.6y ± 10.5, F 35,6y ± 9.6 Pain intensity: Mild 20 (22 %) Moderate 49 (53 %)	Paracetamol 1000 mg + caffeine 130 mg Vs Sumatriptan 50 mg required to treat three	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: unclear not reported Assessors: unclear not reported, described as double blind
			Pain intensity difference at 4h (between pre and post dose) (on a 4-point scale: 0 'absent', 1 'mild', 2 'moderate', 3 'severe')	Paracetamol + caffeine: 3.2 ± 3.8 Sumatriptan: 3.2 ± 3.7 p = 0.88 NS	
			Total pain relief at 4h	Paracetamol + caffeine: 7.0 ± 3.6 Sumatriptan: 7.4 ± 3.6	

Assessments: At the end of 4-h measurement interval or at the time of use of rescue medication, the patients had to record the presence and intensity of AEs.	Severe 23 (25 %) Definition of migraine : Diagnosis of migraine ICHD-II criteria for migraine with or without aura, 2–8 attacks per month. Additional medication: rescue medication (usual medication for each patient), to be taken 3 h after the administration of the trial medication, if the pain lasted over the 2 h. <u>Inclusion:</u> volunteers (age 18–62) with a clinical history of episodic migraine • If female, adequate contraception in women of fertile age. • Daily consumption of at least two cups of coffee.	subsequent consecutive migraine attacks with the investigational study medications, (one PCF and two SUM, or two PCF and one SUM in a randomized sequence treatment) The trial medication was to be taken when the headache occurred, and when the patients would normally have taken their usual analgesic.	(sum of hourly assessments) (on a 5-point scale: 0 'no relief', 1 'little relief', 2 'some relief', 3 'much relief', 4 'complete relief')	p = 0.48 NS	FOLLOW-UP: Lost-to follow-up: Drop-out and Exclusions: 17% • Described: yes • Balanced across groups: not reported ITT: Yes: patients who took at least one of the treatments (intention-to-treat, ITT) were evaluated. SELECTIVE REPORTING: no Sponsor: This work was supported by a grant from the Italian League of Cephalalgic Patients (LIC-Onlus) a no-profit association of patients.
			% patients with complete relief at 4h	Paracetamol + caffeine: 74.1% Sumatriptan: 72.2% NS	
			Safety		
			% patients with no adverse event	Paracetamol + caffeine: 52.7% Sumatriptan: 42.1% NS	
			palpitation	Paracetamol + caffeine: 9.1% Sumatriptan: 11.6% NS	

	• Medical history and clinical parameters inconsistent with organic or psychiatric disorders associated with headaches. <u>Exclusion:</u> • Declared hypersensitivity or allergy to paracetamol or sumatriptan. • Presence of chronic migraine or headache, or medication overuse headache. • Post-traumatic headache. • Past or present earth ischemia or myocardial infarction, cerebral ischemic attacks, peripheral vascular diseases, hepatic or renal diseases, mail, severe or uncontrolled hypertension, phenylketonuria, hemolytic anemia.				

	• Treatment with anticoagulants or antiplatelet drugs. • Drugs and alcohol abuse, or psychiatric diseases. • Coagulation disorders, peptic ulcer disease, pancreatic disease, clinically significant renal or hepatic disease, blood hypertension, mild/moderate kidney or liver failure, Gilbert's syndrome.				

12.5 Anti-emetics

12.5.1 Metoclopramide versus placebo for acute treatment of migraine in adults

Meta-analysis: VanderPluym 2021(1), Acute Treatments for Episodic Migraine in Adults A Systematic Review and Meta-analysis

Definition of migraine: the definition used in the original studies was accepted as long as it also fit the current *International Classification of Headache Disorders, Third Edition* criteria for episodic migraine (defined as the presence of headache 14 or fewer days per month in someone who has migraine).

Inclusion criteria: Eligible studies (1) included adult patients (≥18 years)with episodic migraine; (2) evaluated abortive pharmacologic therapy or noninvasive nonpharmacologic abortive therapy; (3) involved comparisons of the intervention with placebo, usual care, another pharmacologic therapy, noninvasive nonpharmacologic therapy, wait list, no treatment, or attention control, (4) reported short-term outcomes of interest (≤4 weeks after the end of treatments); and (5) were published in English.

Exclusion: Invasive treatments (defined as surgically implanted), preventive treatments, in vitro studies, studies without original data, and single-group studies were excluded. Therapies in development, with terminated development, or unavailable in the United States were also excluded.
Studies that randomized migraine attacks instead of patients were not meta-analyzed because correlations between attacks could not be controlled.

Search strategy: EMBASE, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, PsycINFO, and Scopus from database inception to February 24, 2021, were searched. Clinical trial registries, government databases and websites, conference proceedings, patient advocate group websites, and medical society websites were also searched. Reference mining of existing systematic reviews/meta-analyses, clinical trial registries, and relevant primary studies was conducted to identify additional literature.

Assessment of quality of included trials: yes

Other methodological remarks:
All statistical analyses for RCTs involved analyzing participants according to their original allocation group. For crossover RCTs, outcomes before crossover were used in meta-analysis.8 Studies that randomized migraine attacks instead of patients were not meta-analyzed because correlations between attacks could not be controlled.
DerSimonian-Laird random-effects model with Hartung- Knapp-Sidik-Jonkman variance correction was used to combine direct comparisons between treatments if the number of studies included in the analysis was larger than 3. The fixed-effect method based on the Mantel-Haenszel method was adopted when the number of studies was 3 or fewer.

Ref	Comparison	N/n	Outcomes	Result

VanderPluym2021 Design: SR+MA Search date: February 2021	Metoclopramide Vs Placebo	N = 3 n = 268 (Coppola 1995, Dogan 2019, Tek 1990)	Pain relief (2h) (Improvement of pain from moderate to severe at baseline to mild or none or pain scale improved at least 50% from baseline at defined assessment time)	Metoclopramide: 85/122 Placebo: 45/124 RR (95% CI): 1.91 (1.47 to 2.48) **SS in favour of metoclopramide** I^2=67.30%
		N = 2 n = 198 (Dogan 2019, Tek 1990)	Pain scale	SMD (95% CI): -0.12 (-0.40 to 0.17) NS I^2=90.46%
		N = 2 n = 124 (Dogan 2019, Tek 1990)	Total adverse events	Rate Ratio: 1.21 95% CI: 0.37 to 4.03 NS I^2=N/A

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Coppola 1995 RCT	70	Emergency department patients	2 days after discharge	Metoclopramide IV, 10 mg in 2 mL Vs Prochlorperazine IV, 10 mg in 2 mL Vs Placebo: normal saline IV, 2 mL	RCT did not meet our inclusion criteria (sample size per group)

				Once for 2 minutes	
Dogan 2019 RCT	74	Emergency department patients Patients aged 33 ± 13.3 years, 62.2% female	1-3 days	Metoclopramide IV, 10 mg in 100 mL normal saline solution Vs Placebo IV, 100 mL normal saline Once for 10 minute	RCT did not meet our inclusion criteria (sample size per group)
Jones 1996	86	Emergency department patients Patients aged 32.1 ± 2.1 years, 73% female	2 days	Prochlorperazine edisylate IM, 10 mg Vs Metoclopramide Hydrochloride IM, 10 mg Vs Placebo IM, 2 mL	RCT did not meet our inclusion criteria (sample size per group)
Tek 1990 RCT	50	Emergency department patients Age range 18-60	2 days	Metoclopramide IV, 10 mg Vs Placebo IV, 2 mL	RCT did not meet our inclusion criteria (sample size per group)

Remarks:

- The MA included 3 RCTs for metoclopramide compared to placebo examining intravenous administration and 1 RCT using intramuscular formulation.
- The 4 RCTs reported in this MA for metoclopramide vs placebo were realized in emergency department setting.
- Other comparisons were reported for metoclopramide that were not included in our search criteria.

Author's conclusions:

"In particular, use of triptans, NSAIDs, acetaminophen, dihydroergotamine, calcitonin generelated peptide antagonists, lasmiditan, and remote electrical neuromodulation was associatedwith improved pain and function with relatively robust SOE."

12.5.2 Paracetamol versus metoclopramide for acute treatment of migraine in adults

Meta-analysis: VanderPluym 2021(1), Acute Treatments for Episodic Migraine in Adults A Systematic Review and Meta-analysis

Definition of migraine: the definition used in the original studies was accepted as long as it also fit the current *International Classification of Headache Disorders, Third Edition* criteria for episodic migraine (defined as the presence of headache 14 or fewer days per month in someone whohas migraine).

Inclusion criteria: Eligible studies (1) included adult patients (≥18 years)with episodic migraine; (2) evaluated abortive pharmacologic therapy or noninvasive nonpharmacologic abortive therapy; (3) involved comparisons of the intervention with placebo, usual care, another pharmacologic therapy, noninvasive nonpharmacologic therapy, wait list, no treatment, or attention control, (4) reported short-term outcomes of interest (≤4 weeks after the end of treatments); and (5) were published in English.

Exclusion:
Invasive treatments (defined as surgically implanted), preventive treatments, in vitro studies, studies without original data, and single-group studies were excluded. Therapies in development, with terminated development, or unavailable in the United States were also excluded.
Studies that randomized migraine attacks instead of patients were not meta-analyzed because correlations between attacks could not be controlled.

Search strategy: EMBASE, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, PsycINFO, and Scopus from database inception to February 24, 2021, were searched. Clinical trial registries, governmentdatabasesandwebsites, conference proceedings, patient advocate groupwebsites, and medical society websites were also searched. Reference mining of existing systematic reviews/meta-analyses, clinical trial registries, and relevant primary studies was conducted to identify additional literature.

Assessment of quality of included trials: yes

Other methodological remarks:
All statistical analyses for RCTs involved analyzing participants according to their original allocation group. For crossover RCTs, outcomes before crossover were used in meta-analysis.8 Studies that randomized migraine attacks instead of patients were not meta-analyzed because correlations between attacks could not be controlled.

DerSimonian-Laird random-effects model with Hartung- Knapp-Sidik-Jonkman variance correction was used to combine direct comparisons between treatments if the number of studies included in the analysis was larger than 3. The fixed-effect method based on the Mantel-Haenszel method was adopted when the number of studies was 3 or fewer.

Remarks:
One study was included in the MA, evaluating paracetamol vs metoclopramide in 98 patients. The study only used I.V. formulations for both drugs and therefore does not meet our inclusion criteria for the present report.

12.6 Triptans

12.6.1 Almotriptan versus placebo for acute treatment of migraine attack in adults

Meta-analysis: Chen 2007(53), Meta-Analysis Examining the Efficacy and Safety of Almotriptan in the Acute Treatment of Migraine

Definition of migraine: criteria defined by the International Headache Society (IHS)

Inclusion criteria: double-blind RCTs including patients diagnosed with typical migraine with or without aura according to the criteria defined by the International Headache Society (IHS). Trials were included if they used a single oral dose of almotriptan in treating a single acute migraine attack. Multiple-dose (multiple attack) trials were included if outcomes for the first migraine attack were available.

Search strategy: MEDLINE (1966 to March 2007), EMBASE (1980 to March 2007), the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials (2007, Issue 2); using a structured electronic search strategy. This was supplemented by searching the reference lists of all retrieved studies, review articles, conference reports, and proceedings of the relevant Food and Drug Administration (FDA) advisory panels and the online Pharmaceutical Research and Manufacturers of American Clinical Study Result Database.

Assessment of quality of included trials: yes

Other methodological remarks:
We fitted a random-effects meta-analysis model to allow for possible heterogeneity between studies.

Ref	Comparison	N/n	Outcomes	Result
Chen 2007 Design: SR+MA Search date: March 2007	Almotriptan 12.5 mg Vs Placebo	N = 5 n = 1590 (Pascual 2000, Dahlof 2001, Dowson 2002, Diener 2005, Mathew 2007)	Pain free at 2h (PO)	Almotriptan: 351/981 Placebo: 102/609 **RR (95% CI): 2.15 (1.64 to 2.80)** NNT (95%CI): 5.2 (4.0, 7.2) **SS in favour of almotriptan** I^2: 40%
		N = 5 n = 1429 (Pascual 2000, Dahlof 2001, Dowson 2002, Diener 2005, Mathew 2007)	Pain relief at 2h (PO) Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.	Almotriptan: 555/880 Placebo: 195/549 **RR (95% CI): 1.68 (1.42 to 1.98)** NNT (95%CI) : 4.0 (3.2 to 5.3) **SS in favour of almotriptan** I^2: 42%
		N = 4	Pain free at 1h	**RR (95% CI): 1.77 (1.19 to 2.63)**

		n = Not reported Studies not reported		**SS in favour of almotriptan**
		N = 4 n = Not reported Studies not reported	Pain relief at 1h Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.	**RR (95% CI): 1.47 (1.21 to 1.79)** **SS in favour of almotriptan**
		N = 5 n = 1617 calculated (Pascual 2000, Dahlof 2001, Dowson 2002, Diener 2005, Mathew 2007)	Sustained pain-free over 24h (Defined as patients who were pain free at 2 hours post-dose and did not experience any pain from 2 to 24 hours post-dose as well as no use of rescue medication.)	**RR (95% CI): 2.12 (1.64 to 2.75)** NNT (95% CI): 7.0 (5.6 to 9.5) **SS in favour of almotriptan**
		N = 5 n = 1617 calculated (Pascual 2000, Dahlof 2001, Dowson	Adverse events over 24h	**RR(95% CI): 1.10 (0.87 to 1.40)** NS

		2002, Diener 2005, Mathew 2007)		

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Pascual 2000	ITT patients: 912	Adults with moderate or severe migraine Almotriptan 6.25 mg: n = 363 Almotriptan 12.5 mg: n = 373 Placebo: n = 176	3 attacks	Almotriptan 6.25 mg Vs Almotriptan 12.5 mg Vs Placebo	Reported Jadad score according to Chen 2007: 5 ITT: yes
Dahlof 2001	ITT patients: 572	Adults with moderate or severe migraine Almotriptan 6.25 mg: n = 167 Almotriptan 12.5 mg: n = 164 Almotriptan 25 mg: n = 161 Placebo: n = 80	1 attack	Almotriptan 6.25 mg Vs Almotriptan 12.5 mg Vs Almotriptan 25 mg Vs Placebo	Reported Jadad score according to Chen 2007: 3 ITT: yes
Dowson 2002	ITT patients: 475	Adults with moderate or severe migraine Almotriptan 12.5 mg: n = 183 Sumatriptan 100mg: n = 193 Placebo: n = 99	1 attack	Almotriptan 12.5 mg Vs Sumatriptan 100mg Vs Placebo	Reported Jadad score according to Chen 2007: 3 ITT: yes
Diener 2005	ITT patients: 198	Adults with moderate or severe migraine and who responded poorly to sumatriptan Almotriptan 12.5 mg: n = 99	1 attack	Almotriptan 12.5 mg Vs Placebo	Reported Jadad score according to Chen 2007: 3 ITT: yes

		Placebo: n = 99			
Mathew 2007		Adults with mild, moderate or severe migraine Almotriptan 12.5 mg: n = 174 Placebo: n = 173	3 attacks	Almotriptan 12.5 mg Vs Placebo	Reported Jadad score according to Chen 2007: 4 ITT: yes

Remarks:

- One trial (Diener 2005) was conducted on patients who had unsatisfactory responses to sumatriptan on at least two occasions.
- For several outcomes, studies included in the MA were not reported. It was therefore not possible to determine the n of participants included in the MA for these outcomes.
- For adverse events and sustained pain relief, the number of participants included in the MA was not reported. We have evaluated the number of participant based on the ITT population reported in the characteristic of the included studies.
- The SR also identified and reported on studies comparing almotriptan 6.25 mg to placebo. We have not reported this comparison in the present report because it is not available /recommend dosage in BE.

Author's conclusions:

"The results of this meta-analysis have shown that almotriptan 12.5 mg is an effective treatment for an acute migraine attack and its safety profile was similar to placebo in terms of clinically relevant adverse events."

12.6.2 Eletriptan versus placebo for acute treatment of migraine attack in adults

Meta-analysis: Pascual 2007(59), Marketed Oral Triptans in the Acute Treatment of Migraine: A Systematic Review on Efficacy and Tolerability

Definition of migraine: moderate and/or severe acute migraine attack, with or without aura and had been diagnosed according to the International Headache Society (IHS).

Inclusion criteria: All Adult: 19+ years, English, Publication list 2007/02/22, Randomized Controlled Trial, Humans.

Study at least 1 commercially available triptan, study triptans administered orally as tablets or as orally disintegrating formulations, include patients with symptomatic relief of an acute migraine attack.
Whatever the trial design, parallel or crossover, single or multiple attacks, to avoid data heterogeneity and to homogenize clinical conditions, the trials were only included provided that separate data were available for the first attack treated and for the first treatment administered.

Search strategy: The search was conducted using the Pubmed/MEDLINE electronic database and the Cochrane Central Register of Controlled Trials. Furthermore, a search of articles cited in the selected publications was performed.

Assessment of quality of included trials: yes

Other methodological remarks:
The studied population is defined by the intent-to-treat (ITT) population (andomized patients who suffered a migraine attack and received active treatment or a placebo).
A random-effects model was selected.

Ref	Comparison	N/n	Outcomes	Result
Pascual 2007 Design: SR+MA Search date: February 2007	Eletriptan 40 mg Vs Placebo	N = 9 n = 4380 (Diener 2002, Garcia-Ramos 2003, Goadsby 2000, Mathew 2003, Sakai 2004, Sandrini 2002, Sheftell 2003, Stark	Pain free at 2 h	**RR (95% CI): 4.83 (3.05 to 7.66)** **SS in favour of eletriptan** *P* < 0.001 for heterogeneity

		2002, Steiner 2003)		
		N = 8 n = 4096 (Diener 2002, Goadsby 2000, Mathew 2003, Sakai 2004, Sandrini 2002, Sheftell 2003, Stark 2002,Steiner 2003)	Headache relief at 2 h (response)	**RR (95% CI): 2.48 (1.99 to 3.11)** **SS in favour of eletriptan** *P* < 0.001 for heterogeneity
		N = 4 n = 2647 (Mathew 2003, Sandrini 2002,	Pain free at 1 h	**RR (95% CI): 7.94 (2.88 to 21.87)** **SS in favour of eletriptan** p = 0.3 for heterogeneity

		Sheftell 2003, Steiner 2003)		
		N = 2 n = 866 (Garcia-Ramos 2003, Sheftell 2003)	Headache relief at 30 min (response)	**RR (95% CI): 1.17 (0.29 to 4.80)** NS p = 0.04 for heterogeneity
		N = 6 n = 3247 (Diener 2002, Garcia-Ramos 2003, Mathew 2003, Sandrini 2002, Sheftell 2003, Steiner 2003)	Headache relief at 1h (response)	**RR (95% CI): 2.54 (1.95 to 3.31)** **SS in favour of eletriptan** p = 0.07 for heterogeneity
		N = 6 n = 1680 (Goadsby 2000, Mathew 2003, Sakai 2004, Sheftell 2003, Stark 2002, Steiner 2003)	Recurrence of migraine (Reappearance of moderate-to-severe pain before 24 hours elapsed since response at 2 hours or at 4h)	**RR (95% CI): 0.72 (0.59 to 0.87)** **SS in favour of eletriptan (less with eletriptan)** p = 0.26 for heterogeneity
		N = 4 n = 2362	Adverse events	**RR (95% CI): 1.01 (0.73 to 1.38)**

		(Garcia-Ramos 2003, Goadsby 2000, Mathew 2003, Steiner 2003)		**NS** p = 0.001 for heterogeneity

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Diener 2002		Placebo (N = 106) eletriptan 40 mg (N = 210) eletriptan 80 mg (N = 214) cafergot (N = 203)		Placebo vs eletriptan 40 mg vs eletriptan 80 mg Vs Cafergot tablets	Jadad quality score: 5
Garcia-Ramos 2003		Placebo (N = 92) eletriptan 40 mg (N = 192) naratriptan 2.5 mg in capsules (N = 199)		Placebo vs eletriptan 40 mg vs naratriptan 2.5 mg tablets	Jadad quality score: 4
Goadsby 2000		Placebo (N = 142) sumatriptan 100 mg in capsules (N = 129) eletriptan 20 mg (N = 144) eletriptan 40 mg (N = 136)		Placebo vs sumatriptan 100 mg vs eletriptan	Jadad quality score: 5

		eletriptan 80 mg (N = 141)		vs eletriptan vs eletriptan tablets	
Mathew 2003		Placebo (N = 419) eletriptan 40 mg (N = 822) sumatriptan 100 mg in capsules (N = 831)		Placebo Vs eletriptan 40 mg Vs sumatriptan 100 mg Tablets	Jadad quality score: 4
Sakai 2004		Placebo (N = 84) eletriptan 40 mg (N = 80) eletriptan 80 mg (N = 77) eletriptan 20 mg (N = 80)		Placebo Vs eletriptan 40 mg Vs eletriptan 80 mg Vs eletriptan 20 mg Tablets	Jadad quality score: 3
Sandrini 2002		Placebo (N = 84) sumatriptan 50 mg in capsules (N = 181) sumatriptan 100 mg in capsules (N = 170) eletriptan 40 mg (N = 176) eletriptan 80 mg (N = 184)		Placebo Vs sumatriptan 50 mg Vs sumatriptan 100 mg Vs Eletriptan 40 mg Vs eletriptan 80 mg Tablets	Jadad quality score: 3

Sheftell 2003		Placebo (N = 292) eletriptan 40 mg (N = 296) eletriptan 80 mg (N = 312) eletriptan 20 mg (N = 290)		Placebo Vs eletriptan 40 mg Vs eletriptan 80 mg Vs eletriptan 20 mg Tablets	Jadad quality score: 5
Stark 2002		Placebo (N = 304) eletriptan 40 mg (N = 453) eletriptan 80 mg (N = 462)		Placebo Vs eletriptan 40 mg Vs eletriptan 80 mg Tablets	Jadad quality score: 5
Steiner 2003		Placebo (N = 144) eletriptan 40 mg (N = 392) eletriptan 80 mg (N = 396) zolmitriptan 2.5 mg (N = 405)		Placebo Vs eletriptan 40 mg Vs eletriptan 80 mg Vs zolmitriptan 2.5 mg	Jadad quality score: 5

Remarks:
While most of the studies included data for comparison with other dosages of eletriptan, authors only reported data for the comparison eletriptan 40 mg vs placebo.

12.6.3 Frovatriptan versus placebo for acute treatment of migraine attack in adults

Meta-analysis: Poolsup 2005 (69), Efficacy and tolerability of frovatriptan in acute migraine treatment: systematic review of randomized controlled trials

Definition of migraine: In all included studies: migraine defined according to the IHS criteria

Inclusion criteria: For a study to be included in our systematic review it had to be (i) a double-blind, randomized, placebo-controlled trial that evaluated frovatriptan 2.5 mg in moderate or severe migraine attacks and (ii) reporting the efficacy data in terms of pain-free, headache response, headache recurrence, or relief of migraine-associated symptoms. There were no language restrictions.

Search strategy: MEDLINE, EMBASE, EMB review and the Cochrane Library. The bibliographic databases were searched from their respective inception to February 2005.

Assessment of quality of included trials: yes

Other methodological remarks:
The data from each study were analysed on an intention-to-treat basis.
In the pooling of RR and RD as well as the estimation of 95% confidence interval, the inverse variance weighted method was used. A random effects model was used where the results were heterogeneous on the basis of the Q-statistic for heterogeneity at the 0Æ1 level of significance

Ref	Comparison	N/n	Outcomes	Result
Poolsup 2005 Design: SR+MA Search date:	Frovatriptan 2.5 mg Vs Placebo	N = 5 n = 2866 (Goldstein 2002, Rapoport	Pain free at 2 h	Frovatriptan: 209/1804 Placebo: 34/1062 **RR: 3.70 (95% CI: 2.59 to 5.29)** NNT (95% CI): 12 (10 to 15) **SS in favour of frovatriptan**

February 2005		2002, Ryan 2002 (study 1, 2 and 3))		Q-statistic for heterogeneity = 0.81
		N = 5 n = 2866 (Goldstein 2002, Rapoport 2002, Ryan 2002 (study 1, 2 and 3))	Pain free at 4 h	Frovatriptan: 526/1804 Placebo: 252/1062 **RR: 2.67 (95% CI: 2.21 to 3.22)** NNT (95% CI): 6 (5 to 7) **SS in favour of frovatriptan** Q-statistic for heterogeneity = 3.51
		N = 5 n = 2866 (Goldstein 2002, Rapoport 2002, Ryan 2002 (study 1, 2 and 3))	Headache response at 2 h (PO) (Headache severity changed from moderate or severe (grade 2, 3) to mild or no headache (grade 0, 1), according to International Headache Society (IHS) criteria.)	Frovatriptan: 719/1804 Placebo: 116/1062 **RR: 1.66 (95% CI: 1.47 to 1.88)** NNT (95% CI): 7 (6 to 9) **SS in favour of frovatriptan** Q-statistic for heterogeneity = 0.55
		N = 5 n = 2866 (Goldstein 2002, Rapoport 2002, Ryan	Headache response at 4 h (Headache severity changed from moderate or severe (grade 2, 3) to mild or no headache (grade 0, 1), according to International Headache Society (IHS) criteria.)	Frovatriptan: 1097/1804 Placebo: 352/1062 **RR: 1.83 (95% CI: 1.66 to 2.00)** NNT (95% CI): 4 (4 to 5) **SS in favour of frovatriptan**

		2002 (study 1, 2 and 3))		Q-statistic for heterogeneity = 2.39
		N = 5 n = 1449 (Goldstein 2002, Rapoport 2002, Ryan 2002 (study 1, 2 and 3))	Headache recurrence after 4 h (Headache relieved at 4 h, but subsequently recurred within 24 h of initial dose.)	Frovatriptan: 192/1092 Placebo: 83/352 **RR: 0.74 (95% CI: 0.59 to 0.93)** NNT (95% CI): 17 (9 to 100) **SS in favour of frovatriptan (less with frovatriptan)** Q-statistic for heterogeneity = 3.74
		N = 5 n = 2866 (Goldstein 2002, Rapoport 2002, Ryan 2002 (study 1, 2 and 3))	Migraine associated nausea at 2h	Frovatriptan: 774/1804 Placebo: 523/1062 **RR: 0.86 (95% CI: 0.80 to 0.94)** NNT (95% CI): 15 (10 to 34) **SS in favour of frovatriptan (less with frovatriptan)** Q-statistic for heterogeneity = 3.88
		N = 5 n = 2866 (Goldstein 2002, Rapoport 2002, Ryan 2002 (study 1, 2 and 3))	Migraine associated photophobia at 2h	Frovatriptan: 971/1804 Placebo: 693/1062 **RR: 0.83 (95% CI: 0.78 to 0.88**) NNT (95% CI): 10 (7 to 13) **SS in favour of frovatriptan (less with frovatriptan)** Q-statistic for heterogeneity = 0.59
		N = 5 n = 2866 (Goldstein 2002,	Migraine associated phonophobia at 2h	Frovatriptan: 863/1804 Placebo: 598/1062 **RR: 0.86 (95% CI: 0.80 to 0.93)** NNT (95% CI): 13 (10 to 25)

		Rapoport 2002, Ryan 2002 (study 1, 2 and 3))		**SS in favour of frovatriptan (less with frovatriptan)** Q-statistic for heterogeneity = 0.90
		N = 2 n = 672 (Goldstein 2002, Rapoport 2002)	Adverse events	RR: 1.31 (95% CI: 1.07 to 1.62) NNH (95% CI): 10 (6 to 50) **SS in favour of placebo (more with frovatriptan)**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Goldstein 2002 BD, PC-RCT	635	Age 18–65 years • Had at least a 1-year history of moderate or severe migraine attacks that conformed to the IHS criteria • Onset of migraine before the age of 50 years • Experienced one to six attacks per month for at least 2 months immediately prior to enrolment Exclusion: Basilar or hemiplegic migraine • 15 or more headache days per month • Coexisting headaches of other causes that could not be reliably distinguished from migraine at onset • Clinically significant cerebrovascular, cardiac, hepatic, or renal disease • Pregnancy or lactation		frovatriptan 0.5 mg vs Frovatriptan 1 mg Vs Frovatriptan 2.5 mg Vs Frovatriptan 5 mg Vs Placebo 1 dose at the onset of moderate or severe migraine attack	Jadad quality score: 3

		Frovatriptan 2.5 mg = 131 Placebo = 123			
Rapoport 2002 BD, PC-RCT	1453	Age 18–65 years • Had a history of moderate or severe migraine for at least 1 year, with the onset before the age of 50 years • Experienced one to six attacks per month for at least 2 months immediately prior to enrolment Exclusion: Basilar or hemiplegic migraine • 15 or more headache days per month • Migraine with headaches of other aetiology that could not be reliably distinguished from migraine at onset • Clinically significant cerebrovascular, cardiac, hepatic, or renal disease Pregnancy or lactation Frovatriptan 2.5 mg = 219 Placebo = 199		frovatriptan 0.5 mg vs Frovatriptan 1 mg Vs Frovatriptan 2.5 mg Vs Frovatriptan 5 mg Vs Frovatriptan 10 mg Vs Frovatriptan 20 mg Vs Frovatriptan 40 mg Vs Placebo 1 dose at the onset of moderate or severe migraine attack	Jadad quality score: 3
Ryan 2002 (Study1, Study2, and Study3) BD, PC-RCT		Age 18–65 years • Had at least a 1-year history of migraine defined according to the IHS criteria • Experienced one to eight moderate or severe migraine (with or without aura) attacks per month over at least the previous 2 months		Frovatriptan 2.5 mg Vs Placebo	N/A

	<u>Study 1:</u> 322 <u>Study 2:</u> 1148 <u>Study 3:</u> 724	Excluion: Significant renal, hepatic, cardiovascular, or cerebrovascular disease • Vertebrobasilar or hemiplegic migraine • Pregnancy or lactation • More than 15 headache days per month <u>Study 1:</u> Frovatriptan = 214 Placebo = 108 <u>Study 2:</u> Frovatriptan = 760 Placebo = 388 <u>Study3:</u> Frovatriptan = 480 Placebo = 244		<u>Study 1:</u> Single dose to treat migraine attacks, up to 3 migraine attacks treated <u>Study 2:</u> Up to two doses of per attack, the second dose contingent upon headache recurrence, up to three migraine attacks treated <u>Study3:</u> Up to two doses of per attack, the second dose contingent upon headache recurrence, up to three migraine attacks treated, only attack 1 placebo controlled	

Remarks:

- Two studies were excluded from this MA: one investigated the cardiovascular effects of frovatriptan in patients at high risk of coronary artery disease. The other compared the early use of frovatriptan for mild migraine attack against dosing after the headache progressed to moderate or severe intensity. Two studies evaluated efficacy of frovatriptan in patient having moderate or severe migraine attack (Rapoport 2002, Goldstein 2002). The information was not reported for the studies included in Ryan 2002.

- It was noted that one of the included studies (Ryan 20002) summarized the results from three trials and, therefore, was treated as three separate studies in the MA. Unluckily, the described details of these three studies were brief, and it was not possible to appraise methodological quality of these studies

Author's conclusions:

"In conclusion, the available evidence suggests that frovatriptan may be a useful alternative to other effective agents for moderate to severe migraine attacks. It is consistently effective in rendering patients pain-free, reducing the intensity of headache and the risk of recurrence, improving symptoms associated with migraine and, is associated with more adverse events than placebo."

12.6.4 Naratriptan versus placebo for acute treatment of migraine attack in adults

Meta-analysis: Ashcroft 2004 (73), Naratriptan for the treatment of acute migraine: meta-analysis of randomised controlled trials

Definition of migraine: diagnosed according to the International Headache Society criteria.

Inclusion criteria: Only randomised controlled trials (RCTs) of naratriptan taken for symptomatic relief of acute attacks of migraine were considered. Multiple-attack and multiple-dose trials were included provided that single dose information was available separately.
Trials were only included if patients in one arm of the trial received a single dose of naratriptan for a single migraine attack. The analysis included only drugs and dosages that are commercially available.

Population: Included patients were adults (18–65 years of age) with migraine with or without aura

Search strategy: Reports of RCTs were identified through a systematic electronic search of Medline, Embase and the Cochrane Controlled Trials Register. Medline was searched from 1966 onwards to October 2002 using an optimally sensitive search strategy for identifying RCTs. Text words that were applied to the search included naratriptan, Naramig and Amerge. This was supplemented by searching the reference lists of all retrieved RCTs and contacting the manufacturer of naratriptan. Trial eligibility was determined independently by the two authors. Abstracts were considered; attempts were made to obtain relevant information not included in the published reports by either contacting the principal author of the trial or the manufacturer.

Assessment of quality of included trials: yes

Other methodological remarks:
Single dose of naratriptan for a single migraine attack.
The method of DerSimonian and Laird was used to calculate the pooled estimates and their corresponding 95% CIs.

Ref	Comparison	N/n	Outcomes	Result
Ashcroft 2004 Design: SR+MA Search date: October 2002	Naratriptan 2.5 mg Vs Placebo	N = 6 n = 2358 (Klassen 1997, Mathew 1997, Bates 1998, Bomhof 1999, Schoenen 1999, Havanka 2000)	Pain free at 2 h	**RR (95% CI): 2.52 (1.78–3.57**) **SS in favour of naratriptan**
		N = 6 n = 2358 (Klassen 1997, Mathew 1997, Bates 1998, Bomhof 1999,	Headache relief at 2 h	**RR (95% CI): 1.81 (1.55 to 2.11)** **SS in favour of naratriptan**

		Schoenen 1999, Havanka 2000)		
		N = 6 n = 2358 (Klassen 1997, Mathew 1997, Bates 1998, Bomhof 1999, Schoenen 1999, Havanka 2000)	Pain free at 4 h	Naratriptan: 528/1302 Placebo: 162/1056 **RR (95% CI): 2.58 (1.99 to 3.35)** **SS in favour of naratriptan** I^2: 45%
		N = 6 n = 2358 (Klassen 1997, Mathew 1997, Bates 1998, Bomhof 1999, Schoenen 1999, Havanka 2000)	Headache relief at 4 h	Naratriptan: 827/1302 Placebo: 326/1056 **RR (95% CI): 2.11 (1.75 to 2.54)** **SS in favour of naratriptan** I^2: 54%
		N = 6 n = 2358 (Klassen 1997, Mathew	Sustained pain relief up to 24h	Naratriptan: 578/1302 Placebo: 196/1056 **RR (95% CI): 2.43 (2.11 to 2.80)** **SS in favour of naratriptan**

		1997, Bates 1998, Bomhof 1999, Schoenen 1999, Havanka 2000)		I^2: 0%
		N.D.	Adverse events	Naratriptan: 315/1150 Placebo: 259/899 **RR (95% CI): 1.03 (0.89–1.18)** **NS**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Klassen 1997 DB-PG-RCT	613			Naratriptan 0.1 mg Vs Naratriptan 0.25 mg Vs Naratritptan 1 mg Vs Naratriptan 2.5 mg Vs Placebo Single migraine attack treated	Jadad quality score: 5
Mathew 1997 DB-CO-RCT	682			Naratriptan 0.25 mg Vs Naratritptan 1 mg Vs	Jadad quality score: 5

				Naratriptan 2.5 mg Vs Placebo Up to four migraine attacks treated	
Bates 1998 DB-PG-RCT	1222			Naratriptan 0.1 mg Vs Naratriptan 0.25 mg Vs Naratritptan 1 mg Vs Naratriptan 2.5 mg Vs Sumatriptan 100 mg Placebo Up to three migraine attacks treated	Jadad quality score: 5
Bomhof 1999 DB-PG-RCT	522			Naratriptan 2.5 mg Vs Rizatriptan 10 mg Vs Placebo Single migraine attack treated	Jadad quality score: 4
Schoenen 1999 DB-PG-RCT	181			Naratriptan 2.5 mg Vs Zolmitriptan 2.5 mg Vs Placebo	Jadad quality score: 5

				Up to three migraine attacks treated	
Havanka 2000 DB-PG-RCT	643			Naratriptan 1 mg Vs Naratriptan 2.5 mg Vs Naratriptan 5 mg Vs Naratriptan 7.5 mg Vs Naratriptan 10mg Vs Sumatriptan 100 mg Vs Placebo Single migraine attack treated	Jadad quality score: 5

Remarks:

- Given that migraine trials often include patients who are randomised to treatment but who do not have a migraine attack during the study period, the denominator was the number of patients randomised who had a migraine attack of moderate or severe intensity.
- The SR also identified data for comparison of naratriptan 1mg to placebo, or comparisons between different naratriptan doses. These data have not been reported in the present reported (comparison between doses exclude and other doses not available/recommended in BE).
- For most of the comparisons reported in this SR, data on specific adverse events were provided including chest pain/symptoms and tightness. As it was not explicitly described if these symptom refers to cardiovascular events, no data were reported in the present document.

Author's conclusions:

"Pooled data from RCTs have shown that naratriptan is an effective and well-tolerated treatment for acute attacks of migraine. Naratriptan 2.5 mg is more effective than the 1 mg dose, with an increase in adverse effects."

12.6.5 Rizatriptan versus placebo for acute treatment of migraine attack in adults

Meta-analysis: Ferrari 2001(80), Meta-analysis of rizatriptan efficacy in randomized controlled clinical trial.

Definition of migraine: according to the IHS criteria

Inclusion criteria: All phase III efficacy safety studies on rizatrptan10 mg in adults conducted by Merck and co. and completed by end 1998. Seven randomized placebo-controlled, double-blinded, phase III clinical trial were analysed.

Population: output patients who had at least 6-month history of migraine, at least 18 years, typically experiencing 1-8 migraine attacks per month.
Excluded: patients with coronary artery disease.

Search strategy: N.D.

Assessment of quality of included trials: no

Other methodological remarks:
Statistical analysis based on attack 1 data only (can be regarded as parallel group).
Included all patients who took medication.
Logistic regression model for pairwise comparisons.

Ref	Comparison	N/n	Outcomes	Result
Ferrari 2001 Design: MA	Rizatriptan 10 mg Vs	N = 7 n = 3305 (Teall 1998, Kramer 1998,	Pain free at 2 h	Rizatriptan: 41% (39 to 43) Placebo: 10% (8 to 12) P<0.001 **SS in favour of rizatriptan**

Search date: N.D.	Placebo	Tfelt-Hansen 1998, Merk and Co. 1999, Goldstein 1998, Ahrens 1999, study 52)		Studies were homogenous
		N = 7 n = 3305 (Teall 1998, Kramer 1998, Tfelt-Hansen 1998, Merk and Co. 1999, Goldstein 1998, Ahrens 1999, study 52)	Headache relief at 2 h (% of patients with a reduction of pain severity from moderate or severe at baseline to mild or none)	Rizatriptan: 71% (69 to 73) Placebo: 38% (35 to 40) P<0.001 **SS in favour of rizatriptan** Studies were homogenous
		N = 7 n = 3305 (Teall 1998, Kramer 1998, Tfelt-Hansen 1998, Merk and Co. 1999, Goldstein 1998, Ahrens	Pain free at 1 h	Rizatriptan: 12 % (11 to 13) Placebo: 3 % (2 to 4) P<0.001 **SS in favour of rizatriptan** Studies were homogenous

		1999, study 52)		
		N = 7 n = 3305 (Teall 1998, Kramer 1998, Tfelt-Hansen 1998, Merk and Co. 1999, Goldstein 1998, Ahrens 1999, study 52)	Headache relief at 1 h (% of patients with a reduction of pain severity from moderate or severe at baseline to mild or none)	Rizatriptan: 45% (43 to 47) Placebo: 25 % (23 to 28) P<0.001 **SS in favour of rizatriptan** Studies were homogenous
		N = 7 n = 3305 (Teall 1998, Kramer 1998, Tfelt-Hansen 1998, Merk and Co. 1999, Goldstein 1998, Ahrens 1999, study 52)	Sustained pain free up to 24h (% of patients who had pain free at 2 h and who did not have recurrence within 2-24 h without any additional medication)	Rizatriptan: 25% (23 to 27) Placebo: 7% (5 to 8) P<0.001 **SS in favour of rizatriptan** Studies were homogenous

		N = 7 n = 3305 (Teall 1998, Kramer 1998, Tfelt-Hansen 1998, Merk and Co. 1999, Goldstein 1998, Ahrens 1999, study 52)	Sustained pain relief up to 24h (% of patients who had pain relief at 2 h and who did not have recurrence within 2-24 hwithout any additional medication)	Rizatriptan: 37% (35 to 39) Placebo: 18% (16 to 20) P<0.001 **SS in favour of rizatriptan** Studies were homogenous
		N = nd n = 3168	Relief of disability at 2 h (% of patients with no functional disability (grade 0 on the 4 grade scale in the group of patient who had disability grade 1,2 or 3)	Rizatriptan: 44% (42 to 47) Placebo: 19% (17 to 21) P<0.001 **SS in favour of rizatriptan** Studies were homogenous
		N = nd n = 1915	Relief nausea at 2 h	Rizatriptan: 66% (63 to 68) Placebo: 45% (41 to 49) P<0.001 **SS in favour of rizatriptan** Studies were homogenous

		N = nd n = 1708	Relief of photophobia at 2h	Rizatriptan: 52% (50 to 55) Placebo: 24 % (21 to 26) P<0.001 **SS in favour of rizatriptan** Studies were homogenous
		N = nd n = 2442	Relief of phonophobia at 2h	Rizatriptan: 56% (54 to 59) Placebo: 30 % (27 to 33) P<0.001 **SS in favour of rizatriptan** Studies were homogenous
		N = 7 n = 3305 (Teall 1998, Kramer 1998, Tfelt-Hansen 1998, Merk and Co. 1999, Goldstein 1998, Ahrens 1999, study 52)	Adverse events	Rizatriptan: 43% Placebo: 30% **No analysis provided**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
All studies: RCT Study 22: Teall 1998 PG	4814	Outpatients who had at least 6-month history of migraine, at least 18 years, typically experiencing 1-8 migraine attacks per month. Excluded: patients with coronary artery disease. Analgesics and antiemetics prohibited 6h before to 2h after the dosing. Patients were prohibited to take ergotamine or other 5-HT1B/D agonists from 24 h before and after dosing Rizatriptan 10mg: 49% < 40y, 87% F, 89 % Caucasian, 11% other, 64%moderate baseline pain, 36% severe baseline pain, 1% missing data on basal pain or mild Placebo: 45% < 40y, 86% F, 91% Caucasian, 9% other, 62% moderate baseline pain, 37% severe baseline pain, 1% missing data on basal pain or mild All studies together Rizatriptan 10mg: n = 2068 Rizatriptan 5mg: n = 1486		Medication taken when moderate or severe pain intensity. Rescue medication after 2h if still suffering from moderate or severe headache: opiates paracetamol, NSAIDs and antiemetics. Study 22: Rizatriptan 10mg Vs Rizatriptan 5mg	

		Placebo: n = 1260 No study details provided		Vs Placebo Tablet formulation	
<u>Study 25:</u> Kramer 1998 CO				<u>Study 25:</u> Rizatriptan 10mg Vs Placebo Tablet formulation	
<u>Study 30:</u> Tfelt-Hansen 1998 PG				<u>Study 30:</u> Rizatriptan 10mg Vs Rizatriptan 5mg Vs Sumatriptan 100mg Vs Placebo Tablet formulation	
<u>Study 39:</u> Merk and Co. 1999 PG				<u>Study 39:</u> Rizatriptan 10mg Vs Rizatriptan 5mg Vs Placebo	

				Wafer formulation	
<u>Study 46:</u> Goldstein 1998 CO				<u>Study 46:</u> Rizatriptan 10mg Vs Rizatriptan 5mg Vs Sumatriptan 50 mg Vs Placebo Tablet formulation	
<u>Study 49</u> Ahrens 1999 PG				<u>Study 49:</u> Rizatriptan 10mg Vs Rizatriptan 5mg Vs Placebo Wafer formulation	
<u>Study 52</u> Unpublished CO				<u>Study 52</u> Rizatriptan 10mg Vs Rizatriptan 5mg Vs	

				Sumatriptan 50 mg Vs Placebo Tablet formulation	

Remarks:

- All studies are funded by Merk and Co.
- In all studies patients were instructed to take medication when they developed moderate or severe migraine headache.
- Study procedure was the same for all studies Details were not provided for individual studies. Also detail of which study contributed to pooled data were only given for outcomes pain free at 2 h and pain relief at 2 h, no details were provided for the other outcomes nevertheless we extrapolated that the same studies contributed to the different data each time that the same number of participants was reported.
- Tablets or wafer formulations were used in the studies.
- The analysis included adverse event occurring after a single dose of rizatriptan.
- Relief of nausea, photophobia, phonophobia and disability was also reported after 1 h. For the clarity of the presented document we have not reported these secondary outcome that are all not significant. Different outcomes were also reported for 0.5 and 1.5 time point. For consistency with other comparisons and clarity of the present report we have not reported all these outcome. At 0.5 h the only significant outcome was pain relief (18 % for rizatriptan 10 mg vs 15 % for placebo, p= 0.027).

Author's conclusions:

Rizatriptan 10 mg is an effective treatment for migraine with onset of action from 30 min in some patients.

12.6.6 Oral sumatriptan versus placebo for acute treatment of migraine attack of moderate or severe baseline pain intensity or mild baseline pain intensity in adults

Meta-analysis: Derry 2012(87), Sumatriptan (oral route of administration) for acute migraine attacks in adults (Review)

Definition of migraine: We used the definition of migraine specified by the International Headache Society (IHS 1988; IHS 2004), although we accepted diagnostic criteria equivalent to those of IHS 1988 where a specific reference was not provided.

Inclusion criteria: We included randomised, double-blind, placebo- and/or active controlled studies using oral sumatriptan to treat a migraine headache episode. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data for at least one of the outcomes specified below. We accepted studies reporting treatment of consecutive headache episodes if outcomes for the first, or each, episode were reported separately. Cross-over studies were accepted if there was adequate washout (N 48 hours) between treatments.

Population : Studies enrolled adults (at least 18 years of age) with migraine. There were no restrictions on migraine frequency, duration, or type (with or without aura). Participants taking stable prophylactic therapy to reduce migraine frequency were accepted. All included studies used one or more of these standard scales (reported in remarks) and reported outcomes as defined above.
We considered only data obtained directly from the patient.

Exclusion: We excluded studies designed to demonstrate prophylactic efficacy in reducing the number or frequency of migraine headaches.

Search strategy: We searched the following databases: •the Cochrane Central Register of Controlled Trials (CENTRAL) (2011, Issue 10); • MEDLINE (via OVID) (to 13 October 2011); • EMBASE (via OVID) (to 13 October 2011); • Oxford Pain Relief Database (Jadad 1996a).
We searched reference lists of retrieved studies and review articles for additional studies. We also searched online databases of clinical trials (www.gsk-clinicalstudyregister.com and www.clinicaltrials.gov). We made a written request for information about both published and unpublished data from the manufacturer of sumatriptan (GlaxoSmithKline), and asked specifically for further details on a number of studies published only on their clinical trial database. We did not search grey literature and short abstracts.

Assessment of quality of included trials: yes

Other methodological remarks:
We accepted randomisation at the individual patient level only.
The most likely source of missing data was in cross-over studies.
Where this might be problematic (e.g. where data were missing for > 10% of participants), we used only first-period data where available.
We calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants.
We calculated relative risk of benefit or harm with 95% confidence intervals (CIs) using a fixed effect model. We calculated NNT, NNTp, and NNH with 95% CIs using the pooled number of events by the method of Cook and Sackett.

Ref	Comparison	N/n	Outcomes	Result
Derry 2012 Design: SR+MA Search date: October 2011	Sumatriptan 50 mg Vs Placebo moderate or severe baseline pain intensity	N = 13 n = 6447 (160-104, Cutler 1995, Dahlof 2009, Diener 2004a, Diener 2004b, Goldstein 1998, Ishkanian 2007, Lipton 2000, Sandrini 2002, Savani 1999, Sheftell 2005a, Sheftell 2005b, Smith 2005)	Pain free at 2 h (PO)	Sumatriptan: 28% (1080/3922) Placebo: 11% (282/2525) **RR (95% CI): 2.7 (2.4 to 3.1)** NNT (95%CI): 6.1 (5.5 to 6.9) **SS in favour of sumatriptan** I^2: 53%
		N = 19 n = 8102 (160-104, Bussone 2000, Cutler 1995, Dahlof 2009, Diener	Pain relief at 2 h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	Sumatriptan: 57% (2822/4955) Placebo: 32% (1007/3147) **RR (95% CI): 1.8 (1.7 to 1.9)** NNT (95%CI): 4.0 (3.7 to 4.4) **SS in favour of sumatriptan** I^2: 52%

		2004a, Diener 2004b, Goldstein 1998, Goldstein 2005, shkanian 2007, Kudrow 2005, Lines 2001, Lipton 2000, Pfaffenrath 1998, Sandrini 2002, Sargent 1995, Savani 1999, Sheftell 2005a, Sheftell 2005b, Smith 2005)		
		N = 4 n = 2526 (Sandrini 2002, Sheftell 2005a, Sheftell 2005b, Smith 2005)	Sustained pain-free over 24 h (PO) (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	Sumatriptan: 17% (226/1309) Placebo: 7% (82/1217) **RR (95% CI): 2.6 (2.1 to 3.4)** NNT (95%CI): 9.5 (7.7 to 12) **SS in favour of sumatriptan** I^2: 0%

		N = 4 n = 2526 (Sandrini 2002, Sheftell 2005a, Sheftell 2005b; Smith 2005).	Sustained pain relief over 24 h (PO) (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.)	Sumatriptan: 35% (454/1309) Placebo: 18% (220/1217) **RR (95% CI): 1.9 (1.7 to 2.2)** NNT (95%CI): 6.0 (5.0 to 7.6) **SS in favour of sumatriptan** I^2: 0%
		N = 5 n = 1735 (Dahlof 2009, Diener 2004a, Diener 2004b, Sandrini 2002, Smith 2005)	Pain free at 1 h	Sumatriptan: 5% (45/902) Placebo: 2% (16/833) **RR (95% CI): 2.6 (1.5 to 4.6)** NNT (95%CI): 33 (21 to 73) **SS in favour of sumatriptan** I^2: 0%
		N = 9 n = 2766 (160-104, Diener 2004a, Diener 2004b, Goldstein 2005, Pfaffenrath 1998, Sandrini 2002, Sargent 1995, Savani 1999, Smith 2005)	Pain relief at 1 h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	Sumatriptan: 454/1655 Placebo: 157/1111 **RR (95% CI): 1.8 (1.52 to 2.13)** **SS in favour of sumatriptan** I^2: 18%

		N = 7 n = 1063 (160-104, Culter 1955, Diener 2004b, Ishkanian 2007, Kudrow 2005, Sandrini 2002, Sargent 1995)	Relief of nausea at 2 h	Sumatriptan: 268/596 Placebo: 123/377 **RR (95% CI): 1.38 (1.16 to 1.65)** **SS in favour of sumatriptan** I^2: 45%
		N = 6 n = 1144 (160-104, Culter 1955, Diener 2004b, Kudrow 2005, Sandrini 2002,Sargent 1995)	Relief of photophobia at 2 h	Sumatriptan: 284/638 Placebo: 160/506 **RR (95% CI): 1.42 (1.22 to 1.65)** **SS in favour of sumatriptan** I^2: 0%
		N = 4 n = 852 (160-104, Diener 2004b, Kudrow 2005, Sandrini 2002)	Relief of phonophobia at 2 h	Sumatriptan: 244/490 Placebo: 134/362 **RR (95% CI): 1.37 (1.16 to 1.6)** **SS in favour of sumatriptan** I^2: 0%

		N = 4 n = 607 (160-104, Cutler 1995, Sandrini 2002, Sargent 1995)	Improvement of functional disability	Sumatriptan: 49% (186/378) Placebo: 31% (72/229) **RR (95% CI): 1.5 (1.2 to 1.8)** NNT (95% CI): 5.6 (3.9 to 10) **SS in favour of sumatriptan** I^2: 46%
		N = 4 n = 2079 (Diener 2004a, Ishkanian 2007, Lipton 2000, Smith 2005)	Use of rescue medication up to 24 h	Sumatriptan: 20% (266/1339) Placebo: 42% (309/740) **RR (95% CI): 0.77 (0.68 to 0.87)** NNT to prevent (95% CI): 4.6 (3.8 to 5.6) **SS in favour of sumatriptan** I^2: 40%
		N = 5 n = 2098 (Dahlof 2009, Diener 2004b, Goldstein 1998, Goldstein 2005, Kolodny 2004)	Use of rescue medication up to 4 h	Sumatriptan: 23% (296/1278) Placebo: 45% (366/820) **RR (95% CI): 0.56 (0.49 to 0.63)** NNT to prevent (95% CI): 4.7 (3.9 to 5.8) **SS in favour of sumatriptan** I^2: 50%
		N = 10 n = 3728	Adverse events over 24 h	Sumatriptan: 32% (667/2114) Placebo: 24% (389/1614) **RR (95% CI): 1.3 (1.2 to 1.4)** NNH (95% CI): 13 (9.7 to 22)

		(Cutler 1995, Diener 2004a, Diener 2004b, Goldstein 1998, Ishkanian 2007, Kolodny 2004, Kudrow 2005, Pfaffenrath 1998, Savani 1999, Smith 2005)		**SS in favour of placebo** I : 31%

* Characteristics of included studies: see below

Ref	Comparison	N/n	Outcomes	Result
Derry 2012 Design: SR+MA Search date: October 2011	Sumatriptan 50 mg Vs Placebo mild baseline pain intensity	N = 7 n = 1514 (Carpay 2004, Jelinski 2006, Nett 2003, Pini 1999, Tfelt-Hansen 2006, Winner 2003a, Winner 2003b)	Pain free at 2h (PO)	Sumatriptan: 46% (357/783) Placebo: 23% (168/731) **RR (95% CI): 2.0 (1.7 to 2.4)** NNT (95% CI): 4.4 (3.8 to 5.7) **SS in favour of sumatriptan** I^2: 7%

		N = 4 n = 866 (Carpay 2004, Jelinski 2006, Nett 2003, Tfelt-Hansen 2006)	Sustained pain-free over 24 h (PO) (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	Sumatriptan: 28% (124/436) Placebo: 10% (44/430) **RR (95% CI): 2.8 (2.1 to 3.9)** NNT (95% CI): 5.5 (4.3 to 7.6) **SS in favour of sumatriptan** I^2: 0%
		N = 5 n = 1246 (Carpay 2004, Jelinski 2006, Nett 2003, Winner 2003a, Winner 2003b)	Pain free at 1 h	Sumatriptan: 26% (161/624) Placebo: 14% (87/622) **RR (95% CI): 1.9 (1.5 to 2.4)** NNT (95% CI): 8.5 (6.2 to 13) **SS in favour of sumatriptan** I^2: 0%
		N = 2 n = 280 (Carpay 2004, Winner 2003)	Relief of nausea at 2h	Sumatriptan: 78/145 Placebo: 10/135 **RR (95% CI): 6.88 (3.78 to 12.51)** **SS in favour of sumatriptan** I^2: 82%
		N = 2 n = 483 (Carpay 2004, Winner 2003)	Relief of photophobia at 2h	Sumatriptan: 135/237 Placebo: 44/246 **RR (95% CI): 2.95 (2.2 to 3.97)** **SS in favour of sumatriptan**

				I^2: 80%
		N = 2 n = 413 (Carpay 2004, Winner 2003)	Relief of phonophobia at 2h	Sumatriptan: 105/202 Placebo: 37/211 **RR (95% CI): 2.99 (2.15 to 4.16)** **SS in favour of sumatriptan** I^2: 85%
		N = 2 n = 384 (Jelinski 2006, Pini 1999)	Use of rescue medication up to 24 h	Sumatriptan: 30% (66/221) Placebo: 58% (94/163) **RR (95% CI): 0.54 (0.42 to 0.68)** NNTp (95% CI): 3.6 (2.7 to 5.5) **SS in favour of sumatriptan** I^2: 0%
		N = 6 n = 1242 (Jelinski 2006; Nett 2003; Pini 1999; Tfelt-Hansen 2006; Winner 2003a, Winner2003b)	Adverse events over 24 h	Sumatriptan: 16% (104/642) Placebo: 7% (43/600) **RR (95% CI): 2.3 (1.6 to 3.2)** NNH (95% CI): 11 (8.0 to 18) **SS in favour of placebo** I^2: 18%

Ref	Comparison	N/n	Outcomes	Result

Derry 2012 Design: SR+MA Search date: October 2011	Sumatriptan 100 mg Vs Placebo moderate or severe baseline pain intensity	N = 16 n = 6571 (Cutler 1995, Dodick 2002, Dowson 2002, Ensink 1991, Geraud 2000, Goadsby 2000, Kaniecki 2006, Mathew 2003, Myllyla 1998, Nappi 1994, Sandrini 2002, Sheftell 2005a, Sheftell 2005b, Tfelt-Hansen 1995, Tfelt-Hansen 1998, Visser 1996)	Pain free at 2 h (PO)	Sumatriptan: 32% (1291/4017) Placebo: 11% (272/2554) **RR (95% CI): 3.2 (2.8 to 3.6)** NNT (95% CI): 4.7 (4.3 to 5.1) **SS in favour of sumatriptan** I^2: 37%
		N = 21 n = 7811 (Cutler 1995, Dahlof 1991, Dowson 2002, Ensink	Pain relief at 2 h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	Sumatriptan: 61% (2877/4751) Placebo: 32% (967/3060) **RR (95% CI): 1.9 (1.8 to 2.0)** NNT (95% CI): 3.5 (3.2 to 3.7) **SS in favour of sumatriptan**

		1991, Geraud 2000, Goadsby 1991, Goadsby 2000, Havanka 2000, Kaniecki 2006, Mathew 2003, Myllyla 1998, Nappi 1994, Patten 1991, Pfaffenrath 1998, Sandrini 2002, Sargent 1995, Sheftell 2005a, Sheftell 2005b, Tfelt-Hansen 1995, Tfelt-Hansen 1998, Visser 1996)		I^2: 67%
		N = 6 n = 2891 (Dodick 2002, Dowson 2002, Kaniecki	Sustained pain-free over 24h (PO) (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	Sumatriptan: 24% (374/1590) Placebo: 8% (106/1301) **RR (95% CI): 2.8 (2.4 to 3.5)** NNT (95%CI): 6.5 (5.6 to 7.8) **SS in favour of sumatriptan**

		2006, Sandrini 2002, Sheftell 2005a, Sheftell 2005b)		I^2: 31%
		N = 6 n = 4116 (Geraud 2000, Kaniecki 2006, Mathew 2003, Sandrini 2002, Sheftell 2005a, Sheftell 2005b)	Sustained pain relief over 24 h (PO) (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.)	Sumatriptan: 36% (922/2538) Placebo: 17% (270/1578) **RR (95% CI): 2.1 (1.9 to 2.4)** NNT (95% CI): 5.2 (4.6 to 6.0) **SS in favour of sumatriptan** I^2: 0%
		N = 6 n = 3176 (Dowson 2002, Geraud 2000, Goadsby 2000, Mathew 2003, Sandrini	Pain free at 1h	Sumatriptan: 7% (158/2216) Placebo: 2% (15/960) **RR (95% CI): 4.0 (2.3 to 6.8)** NNT (95% CI): 18 (15 to 24) **SS in favour of sumatriptan** I^2: 38%

		2002, Tfelt-Hansen 1998)		
		N = 10 n = 3983 (Dowson 2002, Geraud 2000, Goadsby 2000, Havanka 2000, Mathew 2003, Pfaffenrath 1998, Sandrini 2002, Sargent 1995, Tfelt-Hansen 1998, Visser 1996)	Pain relief at 1 h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none)	Sumatriptan: 795/2709 Placebo: 317/1041 **RR (95% CI): 1.52 (1.37 to 1.69)** **SS in favour of sumatriptan** I^2: 11%
		N = 14 n = 2996 (Cutler 1995, DKSMSG 1999, Dowson 2002, Geraud 2000, Goadsby	Relief of nausea at 2 h	Sumatriptan: 880/1955 Placebo: 187/1274 **RR (95% CI): 1.88 (1.62 to 2.18)** **SS in favour of sumatriptan** I^2: 31%

		2000, Havanka 2000, Mathew 2003, Myllyla 1998, Nappi 1994, Pfaffenrath 1998, Sandrini 2002, Sargent 1995, Tfelt-Hansen 1995, Tfelt-Hansen 1998)		
		N = 9 n = 2494 (Cutler 1995, DKSMSG 1999, Dowson 2002, Geraud 2000, Mathew 2003, Myllyla 1998, Sandrini 2002, Sargent 1995, Tfelt-Hansen 1998)	Relief of photophobia at 2 h	Sumatriptan: 834/1703 Placebo: 201/791 **RR (95% CI): 1.85 (1.63 to 2.11)** **SS in favour of sumatriptan** I^2: 0%

		N = 7 n = 2128 (Bussone 2000, Dowson 2002, Geraud 2000, Mathew 2003, Myllyla 1998, Sandrini 2002, Tfelt-Hansen 1998)	Relief of phonophobia at 2 h	Sumatriptan: 736/1492 Placebo: 164/626 **RR (95% CI): 1.83 (1.59 to 2.11)** **SS in favour of sumatriptan** I^2: 33%
		N = 6 n = 1827 (Cutler 1995, Goadsby 2000, Havanka 2000, Mathew 2003, Sandrini 2002, Sargent 1995)	Improvement of functional disability	Sumatriptan: 58% (651/1113) Placebo: 31% (220/714) **RR (95% CI): 1.9 (1.7 to 2.1)** NNT (95% CI): 3.6 (3.1 to 4.3) **SS in favour of sumatriptan** I^2: 0%
		N = 6 n = 2810 (Dodick 2002, Geraud 2000,	Use of rescue medication up to 24 h	Sumatriptan: 33% (621/1877) Placebo: 58% (543/933) **RR (95% CI): 0.57 (0.52 to 0.62)** NNTp (95% CI): 4.0 (3.5 to 4.7)

		Goadsby 2000, Havanka 2000, Mathew 2003, Tfelt-Hansen 1995)		**SS in favour of sumatriptan** I^2: 79%
		N = 3 n = 1027 (Dowson 2002, Goadsby 1991, Tfelt-Hansen 1998)	Use of rescue medication up to 4 h	Sumatriptan: 27% (179/675) Placebo: 54% (189/352) **RR (95% CI): 0.55 (0.47 to 0.65)** NNTp (95% CI): 3.7 (3.0 to 4.8) **SS in favour of sumatriptan** I^2: 15%
		N = 12 n = 3257 (Cutler 1995, DKSMSG 1999, Dowson 2002, Ensink 1991, Geraud 2000, Goadsby 2000, Havanka 2000, Nappi 1994, Pfaffenrath 1998, Tfelt-	Adverse events over 24 h	Sumatriptan: 43% (931/2171) Placebo: 23% (255/1086) **RR (95% CI): 1.7 (1.5 to 1.9)** NNH (95%CI): 5.2 (4.4 to 6.2) **SS in favour of placebo** I^2: 75%

		Hansen 1995, Tfelt-Hansen 1998, Visser 1996)		
		N = 1 n = 261 (DKSMSG 1999)	Palpitation/tachycardia	Sumatriptan: 7/130 Placebo: 2/131 **RR (95% CI): 3.53 (0.75 to 16.66)** **NS**

Ref	Comparison	N/n	Outcomes	Result
Derry 2012 Design: SR+MA Search date: October 2011	Sumatriptan 100 mg Vs Placebo mild baseline pain intensity	N = 5 n = 1240 (Carpay 2004, Jelinski 2006, Nett 2003, Winner 2003a, Winner 2003b)	Pain free at 2 h (PO)	Sumatriptan: 58% (358/618) Placebo: 24% (151/622) **RR (95% CI): 2.4 (2.1 to 2.8)** NNT (95%CI): 3.0 (2.6 to 3.5) **SS in favour of sumatriptan** I^2: 64%
		N = 3 n = 771 (Carpay 2004, Jelinski 2006, Nett 2003)	Sustained pain-free over 24 h (PO) (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	Sumatriptan: 33% (127/389) Placebo: 10% (39/382) **RR (95% CI): 3.2 (2.3 to 4.5)** NNT (95%CI): 4.5 (3.6 to 5.9) **SS in favour of sumatriptan** I^2: 40%

		N = 5 n = 1240 (Carpay 2004, Jelinski 2006, Nett 2003, Winner 2003a, Winner 2003b)	Pain free at 1 h	Sumatriptan: 31% (189/618) Placebo: 14% (87/622) **RR (95% CI): 2.2 (1.8 to 2.8)** NNT (95%CI): 6.0 (4.7 to 8.3) **SS in favour of sumatriptan** I^2: 0%
		N = 3 n = 265 (Carpay 2004, Winner 2003a, Winner 2003b)	Relief of nausea at 2 h	Sumatriptan: 58/130 Placebo: 10/135 **RR (95% CI): 5.89 (3.18 to 10.91)** **SS in favour of sumatriptan** I^2: 77%
		N = 3 n = 475 (Carpay 2004, Winner 2003a, Winner 2003b)	Relief of photophobia at 2 h	Sumatriptan: 131/229 Placebo: 44/246 **RR (95% CI): 3.23 (2.41 to 4.33)** **SS in favour of sumatriptan** I^2: 78%

		N = 3 n = 400 (Carpay 2004, Winner 2003a, Winner 2003b)	Relief of phonophobia at 2 h	Sumatriptan: 120/189 Placebo: 37/211 **RR (95% CI): 3.7 (2.69 to 5.08)** **SS in favour of sumatriptan** I^2: 63%
		N = 4 n = 941 (Jelinski 2006, Nett 2003, Winner 2003a, Winner 2003b)	Adverse events over 24 h	Sumatriptan: 19% (89/471) Placebo: 7% (32/470) **RR (95% CI): 2.8 (1.9 to 4.1)** NNT (95%CI): 8.3 (6.1 to 13) **SS in favour of placebo** I^2: 0%
		N = 1 n = 238 (Jelinski 2006)	Palpitation/tachycardia	No events **Not estimable**

Ref + design	n	Population	Duration	Comparison	Methodology
Studies included for the comparisons with sumatriptan 50 mg for moderate to severe baseline pain intensity migraine attack or mild pain intensity migraine attack					
160-104 DB, double-dummy, PC, PG-RCT	818 (treated first attack)	Aged 18 years or over and suffering at least 1 acute attack of migraine, with or without aura (IHS 1988),every 6 weeks.	Assessment up to 4 h	Sumatriptan 25 mg Vs Sumatriptan 50 mg Vs Eletriptan 40 mg	RANDOMIZATION: **Low risk** Computer-generated pseudo-random code using the method of random permuted blocks

		Exclusions: participants excluded if ever taken sumatriptan before (any formulation) or oral eletriptan No prescription analgesic or antiemetic within 6 hours prior to study treatment No sumatriptan, ergotamine, or ergotamine-like agent within previous 48 hours Sumatriptan 25 mg, n = 180 Sumatriptan 50 mg, n = 181 Eletriptan 40 mg, n = 184 Eletriptan 80 mg, n = 180 Placebo, n = 93 M 150 F 668 (82%) Mean age 35 years Without aura 86%		Vs Eletriptan 80 mg Vs Placebo Single dose to treat each of up to 3 separate attacks Medication administered when migraine headache pain was of moderate or severe intensity Second dose (either same as first dose of study medication or a double-blind placebo) available after 2 hours for inadequate response, or for recurrence of headache within 24 hours of initial dosing Alternative rescue medication available 2 hours after second dose if appropriate	ALLOCATION CONCEALMENT: **Low risk** Next consecutive number corresponding to study drug in blister card BLINDING: performance bias and detection bias, all outcomes**: Low risk** Double-dummy Pharmaceutical industry support: Pfizer
Bussone 2000 DB, CO-RCT	233	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate) with an average of 1 to 6 attacks per month	Assessment up to 4 h	Sumatriptan 50 mg vs Placebo	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported

		Ergotamine and migraine prophylaxis discontinued before taking study medication Sumatriptan 50 mg, n = 156 Placebo, n = 56 M 49 F 184 (79%) Mean age 37 years Proportion with/without aura not reported		Single dose to treat each of up to 12 consecutive attacks Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication available after 4 h for inadequate relief Second dose of study medication available for recurrence between 4 and 24h At least 24 h between separate attacks, otherwise defined as recurrence	BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** Not reported Pharmaceutical industry support: Glaxo Wellcome
Carpay 2004 DB, PC, PG-RCT	481	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate), typically preceded by a mild-pain phase, and with an average of 1 to 6 attacks per month Exclusion: participants excluded if they had more than 6 migraines per month during either of the 2 months before	Assessment up to 24 h	Sumatriptan (fast disintegrating) 50 mg Vs Sumatriptan (fast disintegrating) 100 mg Vs Placebo Single dose to treat single attack	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** Not reported Pharmaceutical industry support: GlaxoSmithKline

		Screening Migraine prophylactic medication containing ergotamine, ergotamine-derivatives, or methysergide, and use of monoamine oxidase inhibitors was discontinued 2 weeks before the study. n = 444 analysed for efficacy Sumatriptan 50 mg, n = 141 Sumatriptan 100 mg, n = 148 Placebo, n = 155 M 74 F 358 (83%) Mean age 41 years Without aura 71%		Medication administered within 1 h of the onset of mild pain while pain was still mild Second dose of study medication available to treat recurrence in individuals experiencing pain-free results at 2 h Rescue medication (excluding ergot-containing medication or triptans) available after 2 h for inadequate relief or recurrence (in individuals not wanting a second dose of study medication)	
Cutler 1995 DB, PC, PG-RCT	259	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate) with an average of 1 to 6 attacks per month Migraine prophylaxis not allowed during 2-week period preceding treatment. No opioid-containing agents or ergotamine within 24 h, or simple analgesics within 6 h of taking study medication.	Assessment up to 4 h	Sumatriptan 25 mg Vs Sumatriptan 50 mg Vs Sumatriptan 100 mg Vs Placebo Single dose to treat single attack. Medication administered when migraine headache	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** Not reported Pharmaceutical industry support: Glaxo Research Institute

		Sumatriptan 25 mg, n = 66 Sumatriptan 50 mg, n = 62 Sumatriptan 100 mg, n = 66 Placebo, n = 65 M 22 F 237 (92%) Mean age 39 years Proportion with/without aura not reported		pain was of moderate or severe intensity Rescue medication (acetaminophen) was available after 2 h if pain had not improved relative to predose levels After 4 h, rescue medication other than acetaminophen was allowed if pain had still not improved	
Dahlof 2009 DB, PC, PG-RCT	667	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate) with an average of 1 to 6 attacks per month. Exclusion: Participants excluded if they treated non-migrainous headaches with analgesia for more than 10 days per month over the 6 months before screening No ergotamine, ergot-derivatives, or triptans within 24 h, or any analgesics within 6 h of taking study medication n = 541 analysed for efficacy	Assessment up to 24 h	Sumatriptan 50 mg Vs Tonabersat 20 mg Vs Tonabersat 40 mg Vs Placebo Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication available after 2 h	RANDOMIZATION: **Low risk** Computer-generated randomisation list ALLOCATION CONCEALMENT: **Low risk** Remote allocation, sealed envelopes BLINDING: performance bias and detection bias, all outcomes**:** **Unclear risk** Not reported

		Sumatriptan 50 mg, n = 136 Tonabersat 20 mg, n = 134 Tonabersat 40 mg, n = 137 Placebo, n = 134 M 85 F 456 (84%) Mean age 40 years Without aura 74%			
Diener 2004a DB, double-dummy, PC, PG-RCT	435	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity N moderate) with an average of 1 to 6 attacks per month. At the time of treatment participants had to be without aura with each of the following associated symptoms was present: nausea, photophobia, and phonophobia. Participants must have been free from any previous migraine for at least 24 h. n = 433 analysed for efficacy Sumatriptan 50 mg, n = 135 Effervescent acetylsalicylic acid 1000 mg, n = 147 (146 for efficacy) Placebo, n = 153 (152 for efficacy) M 66 F 367 (85%)	Assessment up to 24 h	Sumatriptan 50 mg Vs Effervescent acetylsalicylic acid 1000 mg Vs Placebo Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity Participants were encouraged to wait until 2 h after dosing before taking rescue medication if they experienced inadequate symptomatic relief, although it was	RANDOMIZATION: **Low risk** Computer-generated randomisation list ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Low risk** Double-dummy technique Pharmaceutical industry support: Bayer AG

		Mean age 43 years Without aura 79%		available at any time during the study	
Diener 2004b DB, double-dummy, PC, CO-RCT	313	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate) with an average of 1 to 6 attacks per month. Exclusion: Participants were excluded if they experienced any other type of headache, including tension-type headache n = 312 analysed for efficacy Sumatriptan 50 mg, n = 226 Ibuprofen 400 mg, n = 212 Effervescent acetylsalicylic acid 1000 mg, n = 222 Placebo, n = 222 M 59 F 253 (81%) Mean age 38 years Without aura 79%	Assessment up to 2 h	Sumatriptan 50 mg Vs Ibuprofen 400 mg Vs Effervescent acetylsalicylic acid 1000 mg Vs Placebo Single dose to treat each of 3 successive attacks Medication administered when migraine headache pain was of moderate or severe intensity Participants were encouraged to wait until 2 h after dosing before taking rescue medication if they experienced inadequate symptomatic relief, although it was available at any time during the study Minimum of 48 h between consecutive study treatments	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Low ris**k Double-dummy technique Pharmaceutical industry support: Bayer AG

Goldstein 1998 DB, PC, CO-RCT	1329	Aged 18 to 91, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity N moderate) with an average of 1 to 8 attacks per month. No monoamine oxidase inhibitors, propranolol, or lithium within 2 weeks; no sumatriptan, ergot derivatives, or opiates within 24 h; and no other form of analgesia or antiemetic within 6 h of taking study medication Standard migraine prophylaxis was permitted with the exception of NSAIDs and propranolol n = 1205 analysed for efficacy Sumatriptan 25 mg, n = 563 Sumatriptan 50 mg, n = 566 Rizatriptan 5 mg, n = 557 Rizatriptan 10 mg, n = 567 Placebo, n = 141 M 162, F 1167 (88%) Mean age 40 years Without aura 89%	Assessment up to 4 h	Sumatriptan 25 mg Vs Sumatriptan 50 mg Vs Rizatriptan 5 mg Vs Rizatriptan 10 mg Vs Placebo Single dose to treat each of 2 successive attacks Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication available after 2 h for inadequate headache response Each treated attack was separated by a minimum of 5 days	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** Not reported Pharmaceutical industry support: Merck Research Laboratories (supplies of sumatriptan provided by Glaxo Wellcome)
Goldstein 2005 DB, PC, PG-RCT	171	Meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine	Assessment up to 4 h	Sumatriptan 50 mg, Vs	**Does not meet our inclusion criteria (n<40 pers study group)**

		(untreated severity N moderate) with an average of 1 to 8 attacks per month. Exclusion: Participants were excluded if their migraines were accompanied by vomiting more than 20% of the time or required bed rest for at least half of their attacks n = 123 with moderate or severe baseline pain intensity Sumatriptan 50 mg, n = 67 Acetaminophen 1000 mg + aspirin 1000 mg + caffeine 260 mg, n = 69 Placebo, n = 35 M 32 F 139 (81%) Mean age 38 years Without aura 14%		Acetaminophen 1000 mg + aspirin 1000 mg + caffeine 260 mg Vs Placebo Single dose to treat single attack Medication administered when the first symptoms usually recognised as the beginning of a migraine attack occurred Rescue medication permitted, but no further details reported	
Ishkanian 2007 DB, PC, PG-RCT	216	Aged 18 to 65, suffering at least 6 self-described or physician-diagnosed "sinus" headaches in the 6 months prior to screening which, upon careful review at screening, were determined to satisfy IHS diagnostic criteria for migraine (1988) with or without aura. Participants must have had no previous diagnosis of migraine and have had no previous use of	Assessment up to 4 h	Sumatriptan 50 mg Vs Placebo Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity	RANDOMIZATION: **Low risk** Computer-generated randomisation schedules ALLOCATION CONCEALMENT: **Low risk** Remote allocation, assignments sealed and remained intact BLINDING: performance bias and detection bias, all outcomes: **Low risk** Matching placebo

		migraine-specific medications, such as 5-HT1B/1D agonists, ergotamine, or ergot-like medications. Exclusion: Participants with evidence of other types of headache, such as chronic daily headache (more than 15 headache days per month), were excluded No monoamine oxidase inhibitors or sumatriptan within 2 weeks of trial screening. No analgesics, antiemetics, or other acute migraine medications, or sinus/nasal medications (e.g. antihistamines, nasal sprays and decongestants) within 24 h of taking study medication. n = 215 analysed for efficacy Sumatriptan 50 mg, n = 108 Placebo, n = 108 (107 for efficacy) M 64 F 151 (70%) Mean age 40 years Without aura 90%		Rescue medication available after 2 h	Pharmaceutical industry support: GlaxoSmithKline
Jelinski 2006	361	Aged 18 to 65, meeting IHS criteria for migraine (1988) with or without aura. Had 1 to 6 migraine attacks per	Assessment up to 4 h	Sumatriptan 50 mg Vs Sumatriptan 100 mg	RANDOMIZATION: **Low risk** Computer-generated randomisation schedules

DB, Double-dummy, PC, PG-RCT		month in the 2 months prior to screening, and typically experienced moderate to severe migraine pain preceded by a mild pain phase. No use of monoamine oxidase inhibitors during the study period No analgesics, antiemetics, or other acute migraine medications within 6 h of taking study medication. No ergotamine, ergot-type medications, or other 5HT1 agonists within 24 h of study medication use. Participants permitted to continue their use of prophylactic medications (excluding methysergide) during the study, provided the dose was stable for at least 1 month before study entry Sumatriptan 50 mg, n = 126 Sumatriptan 100 mg, n = 126 Placebo, n = 109 M 52 F 309 (86%) Mean age 40 years Without aura 67%		Vs Placebo Single dose to treat single attack Medication administered within 2 h of the first sign of migraine pain, while the pain was still considered to be mild Second dose of study medication available to treat recurrence 2 to 24 h after initial dosing Rescue medication (analgesics, antiemetics, or other acute migraine medications) were available after 2 h for inadequate symptom relief	ALLOCATION CONCEALMENT: **Low risk** Treatment group assignment was unknown to patients and investigators BLINDING: performance bias and detection bias, all outcomes: **Low risk** Double-dummy technique Pharmaceutical industry support: GlaxoSmithKline
Kolodny 2004 DB, PC, CO-RCT	1447	Aged 18 years or older, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month	Assessment up to 4 h	Sumatriptan 25 mg Vs Sumatriptan 50 mg Vs	RANDOMIZATION: **Low risk** Computer-generated randomisation schedules

		history of migraine (untreated severity N moderate) No monoamine oxidase inhibitors, methysergide, or propranolol during the study period Standard antimigraine prophylactic medications (with the exception of NSAIDs, daily analgesics, or propanolol) were permitted n = 1287 analysed for efficacy Sumatriptan 25 mg, n = 554 (290 1st attack only) Sumatriptan 50 mg, n = 550 (285 1st attack only) Rizatriptan 5 mg, n = 536 (288 1st attack only) Rizatriptan 10 mg, n = 547 (296 1st attack only) Placebo, n = 288 M 203 F 1244 (86%) Mean age 40 years		Rizatriptan 5 mg Vs Rizatriptan 10 mg Vs Placebo Single dose to treat each of 2 consecutive attacks Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication (analgesics or antiemetics) was permitted from 2 h onwards in case of treatment failure or headache recurrence	ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Low risk** Matched placebos Pharmaceutical industry support: Merck & Co.
Kudrow 2005 DB, double-dummy, PC, PG-RCT	574	Aged 18 to 65, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate) with an average of 2 to 8 attacks per month, at least 2 of which were of moderate or severe	Assessment up to 24 h	Sumatriptan 50 mg Vs Valdecoxib 20 mg Vs Valdecoxib 40 mg Vs Placebo	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Low risk** Double-dummy technique

		intensity. Participants were only eligible for entry if they had previously used sumatriptan Exclusion: Changes to (or initiation of) migraine prophylactic medication less than 2 weeks before study screening visit were prohibited. Chronic use (more than 3 days per week) of analgesics, COX-2 inhibitors, or non-specific NSAIDs not permitted No ergotamine-containing or ergot-type medication, 5-HT1D or 5-HT1B/1D medication, or COX-2 inhibitors within 48 h of receiving study medication Sumatriptan 50 mg, n = 144 Valdecoxib 20 mg, n = 137 Valdecoxib 40 mg, n = 152 Placebo, n = 141 M 48 F 526 (92%) Mean age 41 years Without aura 64%		Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity Second dose of study medication available if headache worsened, failed to improve or recurred within 24 h Rescue medication available 2 h after initial dosing (encouraged wait, not enforced)	Pharmaceutical industry support: Pfizer Inc.
Lines 2001 DB, PC, PG-RCT	792	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity N moderate) with an average of 1 to 8 attacks per month.	Assessment up to 4 h	Sumatriptan 50 mg Vs Rizatriptan 5 mg Vs Placebo	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported

		n =785 analysed for efficacy Sumatriptan 50 mg, n = 356 Rizatriptan 5 mg, n = 349 Placebo, n = 80 M 158 F 634 (80%) Mean age 40 years Proportion with/without aura not reported		Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity Rescue medications, consisting of standard analgesics or antiemetics, were allowed from 2 h onwards	BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** Not reported Pharmaceutical industry support: Merck & Co
Lipton 2000 DB, PC, CO-RCT	311	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity N moderate) with an average of 1 to 10 attacks per month. Participants with clinical diagnosis of migrainous headache and episodic tension-type headache were also included in the study, although only those with IHS-diagnosed migraine were used for efficacy analysis Participants were required to have an HIQ score of 250 or greater at screening No monoamine oxidase inhibitor use during the study period n = 249 with migraine diagnosis for efficacy	Assessment up to 24 h	Sumatriptan 50 mg Vs Placebo Single dose to treat each of up to 10 attacks Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication available after 4 h 24 h headache-free interval was required between treated headaches	RANDOMIZATION: **Low risk** Computer-generated randomisation ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Low risk** Identical appearing placebo Pharmaceutical industry support: Glaxo Wellcome

		Total number of treated attacks = 1110 Sumatriptan 50 mg, n = 870 Placebo, n = 240 M 35 F 214 (86%) Mean age 38 years Proportion with/without aura not reported			
Nett 2003 DB, PC, PG-RCT	369	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine with a minimum of 6 months of regularly occurring menstrually associated migraines (defined as occurring between day -2 to day 4 relative to the first day of flow). Participants had to have had menstrually associated migraine in at least 2 of their last 3 perimenstrual periods before screening that were typically associated with moderate to severe pain preceded by a,mild pain phase Exclusion: Participants were excluded if they had tension-type headache for more than 15 days per month or more than 6 migraine attacks per month in either of the 2 months before screening	Assessment up to 2 h	Sumatriptan 50 mg, Vs Sumatriptan 100 mg, Vs Placebo Single dose to treat single menstrually associated migraine attack Medication administered within 1 h of the onset of pain, but only if the pain was mild at onset and only if the pain was still mild at the time of treatment Rescue medication or a second double-blind dose of study medication were available to treat either	RANDOMIZATION: **Low risk** Computer-generated randomisation ALLOCATION CONCEALMENT: **Low risk** Remote allocation BLINDING: performance bias and detection bias, all outcomes: **Low risk** All tablets were visually indistinguishable Pharmaceutical industry support: GlaxoSmithKline

		No monoamine oxidase inhibitors or ergotamine-containing or ergotamine-type migraine prophylactic medication during the study period. Other migraine prophylactic medications were permitted, provided they had been on a constant regimen for at least 1 month before screening and the regimen remained constant throughout the study. No analgesics, antiemetics, or non-serotonin-agonist acute migraine medications within 6 h of taking study medication n = 368 for efficacy, 349 for per-protocol efficacy Sumatriptan 50 mg, n = 124 (124 for efficacy, 116 for per-protocol efficacy) Sumatriptan 100 mg, n = 122 (122 for efficacy, 115 for per-protocol efficacy) Placebo, n = 123 (122 for efficacy, 118 for per-protocol efficacy) All F Mean age 36 years Without aura 75%		inadequate response after 2 h or recurrence between 2 and 24 h	

Pfaffenrath 1998 DB, PC, PG-RCT	1003	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate) with an average of 1 to 6 attacks per month. No use of lithium, monoamine oxidase inhibitors, serotonin reuptake inhibitors, or ergotamine-containing migraine prophylactic medications during the study period No analgesics or antiemetics within 6 h and no ergotamine-containing medications within 24 h of taking study medication n = 939 with moderate or severe baseline pain intensity Sumatriptan 25 mg, n = 303 (286 with moderate or severe baseline pain intensity) Sumatriptan 50 mg, n = 303 (285 with moderate or severe baseline pain intensity) Sumatriptan 100 mg, n = 298 (277 with moderate or severe baseline pain intensity) Placebo, n = 99 (91 with moderate or severe baseline pain intensity) M 157	Assessment up to 4 h	Sumatriptan 25 mg Vs Sumatriptan 50 mg Vs Sumatriptan 100 mg vs Placebo Single dose to treat each of 3 separate attacks Second randomised dose of study medication available to treat headache recurrence from 2 to 24 h after initial dosing Rescue medication (excluding ergotamine-containing preparations or sumatriptan) was permitted if headache relief was inadequate 4 h after initial dosing	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes **Low risk** Matching placebo Pharmaceutical industry support: Glaxo Wellcome

		F 846 (84%) Mean age 40 years Without aura 66%			
Pini 1999 2 phase study <u>Phase 1:</u> Randomised, open-label treatment of a single attack with 1 of 3 standard over-the-counter migraine medications when migraine headache pain was of mild or moderate intensity. Participants who failed to respond in phase 1 then went on to phase 2. <u>Phase 2:</u> DB, PC, PG-RCT	Phase 2: 219	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity mild or moderate) with an average of 1 to 8 attacks per month No migraine prophylaxis containing ergotamine during the study period No sumatriptan or ergotamine-containing drugs within 24 h, or other analgesics or antiemetics within 6 h of taking study medication <u>Phase 2:</u> n= 167 analysed for efficacy Sumatriptan 50 mg, n = 137 (106 for efficacy) Placebo, n = 82 (61 for efficacy) M 44 F 175 (80%) Mean age 37 years Proportion with/without aura not reported	Assessment up to 4 h	<u>Phase2:</u> Sumatriptan 50 mg Vs Placebo Single dose to treat single attack. Medication was administered when migraine headache pain was of mild or moderate intensity Second dose of study medication was available to treat recurrence between 4 and 24 h Rescue medication was available for insufficient relief of symptoms 4 h after initial dosing	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes **Unclear risk** Not reported Pharmaceutical industry support: Glaxo Wellcome (medication used was Imigran)
Sandrini 2002 DB, double dummy, PC, PG-RCT	774	Aged 18 years or older, meeting IHS criteria for migraine (1988) with or without aura, and suffering at least 1 attack every 6 weeks.	Assessment up to 24 h	Sumatriptan 50 mg Vs Sumatriptan 100 mg Vs	RANDOMIZATION**: Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported

		Exclusion: Participants were excluded if they had previously taken oral eletriptan or any formulation of sumatriptan. No ergotamine or any ergotamine-like agent within 48 h before, or 24 h after, taking study medication. No proprietary analgesic or antiemetic within 6 h of taking study medication. Sumatriptan 50 mg, n = 181 Sumatriptan 100 mg, n = 170 Eletriptan 40 mg, n = 175 Eletriptan 80 mg, n = 164 Placebo, n = 84 M 93 F 681 (88%) Mean age 38 years Without aura 65%		Eletriptan 40 mg Vs Eletriptan 80 mg Vs Placebo Single dose to treat each of up to 3 successive attacks Medication administered within 6 h of onset of a migraine attack, when the headache pain was of moderate or severe intensity, and if any aura phase had ended Second, blinded and randomised dose of study medication was available if there was no response to treatment after 2 h, or if there was a recurrence of headache within 24 h Rescue medication was available 2 h after the second dose if there was still no improvement in headache	BLINDING: performance bias and detection bias, all outcomes **Low risk** Double-dummy technique Pharmaceutical industry support: Pfizer Ltd
Sargent 1995	187	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or	Assessment up to 4 h	Sumatriptan 25 mg Vs	RANDOMIZATION: **Unclear risk** Not reported

BD, PC, PG-RCT		without aura. At least 1-year history of migraine (untreated severity N moderate) and suffering an average of 1 to 6 attacks per month. Migraine prophylaxis was not allowed during the 2-week period preceding treatment No simple analgesics during 6 h preceding treatment, and no opioid-containing agents or ergotamine during the 24 h preceding treatment Sumatriptan 25 mg, n = 48 Sumatriptan 50 mg, n = 46 Sumatriptan 100 mg, n = 46 Placebo, n = 47 M 16 F 171 (91%) Mean age 40 years Without aura 80%		Sumatriptan 50 mg Vs Sumatriptan 100 mg Vs Placebo Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication (acetaminophen) available after 2 h if pain had not improved relative to predose levels. Rescue medication other than acetaminophen was allowed beginning 4 h after initial dosing.	ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** Not reported Pharmaceutical industry support: Glaxo Research Institute
Savani 1999 DB, PC, PG-RCT	485	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate) and suffering an average of 1 to 6 attacks per month Exclusion: Participants were excluded if they had ever taken sumatriptan previously or were currently using a	Assessment up to 4 h	Sumatriptan 50 mg Vs Placebo Single dose to treat each of up to 3 separate attacks Second dose of study medication available to	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** Not reported Pharmaceutical industry support: Glaxo Wellcome

		monoamine oxidase inhibitor, a serotonin reuptake inhibitor, or lithium No analgesics or antiemetics within 6 h, or ergotamine or ergotamine-containing medication within 24 h of taking study medication. Normal prophylactic medication for migraine was permitted (unchanged throughout the study, if possible) less than 1% of participants had mild pain at baseline Sumatriptan 50 mg, n = 331 Placebo, n = 154 M 68 F 417 (86%) Mean age 36 to 40 years Without aura 67% to 87%		treat recurrence from 4 to 24 h after initial dosing Rescue medication (excluding ergotamine-containing preparations or sumatriptan) was permitted if headache relief was inadequate 4 h after taking study medication	
Sheftell 2005a and Sheftell 2005b **(Study 1 and Study 2)** Two identically designed studies DB, PC, PG-RCT		Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity N moderate) and suffering an average of 1 to 6 attacks per month. Exclusion: Participants were excluded if they experienced headache on	Assessment up to 24 h	Sumatriptan (rapid-release) 50 mg Vs Sumatriptan (rapid-release) 100 mg) Vs Placebo	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Low risk** Remote allocation generated by the study sponsor and not available to the investigators BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** Not reported

		more than 15 days per month in any of the 3 months before screening. No migraine prophylactic medication containing ergotamine, an ergot derivative, or methysergide, or use of monoamine oxidase inhibitor within 2 weeks before screening		Medication administered when migraine headache pain was of moderate or severe intensity Second dose of study medication or non-prohibited acute migraine medication available after 2 h to treat recurrence Rescue medication available after 2 h if pain not reduced to mild or none within 2 h after initial dosing	Pharmaceutical industry support: GlaxoSmithKline
	<u>Study 1:</u> 1477	<u>Study 1:</u> n = 1366 analysed for efficacy Sumatriptan (rapid-release) 50 mg, n = 494 (448 for efficacy) Sumatriptan (rapid-release) 100 mg, n = 488 (462 for efficacy) Placebo, n = 495 (456 for efficacy) M 196, F 1170 (86%) Mean age 41 years Without aura 70%			
	<u>Study 2:</u> 1475	<u>Study2:</u> n = 1330 analysed for efficacy Sumatriptan (rapid-release) 50 mg, n = 496 (454 for efficacy) Sumatriptan (rapid-release) 100 mg, n = 485 (440 for efficacy) Placebo, n = 494 (436 for efficacy)			

		M 204 F 1126 (85%) Mean age 40 years Without aura 67%			
Smith 2005 DB, double-dummy, PC, PG-RCT	972	Aged 18 years or older, meeting IHS criteria for migraine (1988 and 2004) with or without aura. At least 1-year history of migraine (untreated severity N moderate) and suffering an average of 2 to 6 attacks per month. Participants had a history of tolerating oral treatment with a 5-HT agonist for migraine n = 965 analysed for efficacy Sumatriptan 50 mg, n = 229 (226 for efficacy) Sumatriptan 50 mg, + naproxen 500 mg, n = 251 (250 for efficacy) Naproxen 500 mg, n = 250 (248 for efficacy) Placebo, n = 241 M 92 F 880 (91%) Mean age 42 years Without aura 75%	Assessment up to 24 h	Sumatriptan 50 mg Vs Sumatriptan 50 mg, + naproxen 500 mg Vs Naproxen 500 mg Vs Placebo Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication available after 2 h	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes**: Low risk** Double-dummy technique Pharmaceutical industry support: Pozen Inc.
Tfelt-Hansen 2006	101	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or	Assessment up to 2 h	Sumatriptan 50 mg Vs	RANDOMIZATION: **Unclear risk** Not reported

DB, PC, PG-RCT		without aura. At least 1-year history of migraine, in which attacks became moderate or severe following an initial mild pain phase, and suffered a total of 6 to 12 attacks per year Exclusion: Participants were excluded if they had treated a migraine with a triptan within the last 6 months Sumatriptan 50 mg, n = 53 Placebo, n = 48 M 22 F 79 (78%) Mean age 38 years Without aura 80%		Placebo Single dose to treat single attack. Medication administered within 1 h after the start of an attack, but only if the attack was still in the mild headache phase Second dose available to treat recurrence between 2 and 24 h Rescue medication available after 2 h if pain relief was incomplete. However, triptans or ergotamine could not be used as rescue medication within 24 of taking study medication.	ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes**:** **Unclear risk** Not reported Pharmaceutical industry support: GlaxoSmithKline
Winner 2003a and Winner 2003b **(Study 1 and Study 2)** Two identical studies		Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine with an average of 1 to 6 attacks per month. All participants were required to experience moderate or severe migraine pain preceded by a mild pain phase.	Assessment up to 24 h	Sumatriptan 50 mg Vs Sumatriptan 100 mg Vs Placebo Medication administered at the first sign of pain, while the pain was mild	RANDOMIZATION: **Low risk** Computer-generated randomisation scheduleALLOCATION CONCEALMENT: **Low risk** Treatment assignment sealed and remained intact throughout the study

DB, double-dummy, PC, PG-RCT		No use of monoamine oxidase inhibitors for a minimum of 2 weeks before screening or throughout the course of the study. Otherwise allowed to continue migraine prophylactic medications. No analgesics, antiemetics, or other migraine medication within the 6 h before taking study medication, and no ergotamine, ergot-type medications, or other serotonin1B/1D agonists within 24 h of study medication use		Second dose of study medication available to treat recurrence between 2 and 24 h after initial dosing Rescue medication (analgesics, antiemetics, or other acute migraine medications) available 4 h after initial dosing	BLINDING: performance bias and detection bias, all outcomes**: Low risk** Double-dummy technique Pharmaceutical industry support: GlaxoSmithKline
	<u>Study1:</u> 362	<u>Study1:</u> n = 354 analysed for efficacy 3% did not have mild pain at baseline Sumatriptan 50 mg, n = 122 Sumatriptan 100 mg, n = 115 Placebo, n = 117 M 43 F 311 (88%) Mean age 41 years Without aura 73%			
	<u>Study2:</u> 354	<u>Study 2:</u> n = 337 analysed for efficacy 4 % did not have mild pain at baseline Sumatriptan 50 mg, n = 111			

		Sumatriptan 100 mg, n = 107 Placebo, n = 119 M59 F 298 (88%) Mean age 43 years Without aura 79%			

Ref + design	n	Population	Duration	Comparison	Methodology
Studies included for the comparisons with sumatriptan 100 mg for moderate to severe baseline pain intensity migraine attack or mild pain intensity migraine attack					
Carpay 2004 DB, PC, PG-RCT	481	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate), typically preceded by a mild-pain phase, and with an average of 1 to 6 attacks per month Exclusion: participants excluded if they had more than 6 migraines per month during either of the 2 months before Screening Migraine prophylactic medication containing ergotamine, ergotamine-derivatives, or methysergide, and use of monoamine oxidase inhibitors was discontinued 2 weeks before the study. n = 444 analysed for efficacy	Assessment up to 24 h	Sumatriptan (fast disintegrating) 50 mg Vs Sumatriptan (fast disintegrating) 100 mg Vs Placebo Single dose to treat single attack Medication administered within 1 h of the onset of mild pain while pain was still mild Second dose of study medication available to treat recurrence in individuals experiencing pain-free results at 2 h	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** Not reported Pharmaceutical industry support: GlaxoSmithKline

		Sumatriptan 50 mg, n = 141 Sumatriptan 100 mg, n = 148 Placebo, n = 155 M 74 F 358 (83%) Mean age 41 years Without aura 71%		Rescue medication (excluding ergot-containing medication or triptans) available after 2 h for inadequate relief or recurrence (in individuals not wanting a second dose of study medication)	
Cutler 1995 DB, PC, PG-RCT	259	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate) with an average of 1 to 6 attacks per month Migraine prophylaxis not allowed during 2-week period preceding treatment. No opioid-containing agents or ergotamine within 24 h, or simple analgesics within 6 h of taking study medication. Sumatriptan 25 mg, n = 66 Sumatriptan 50 mg, n = 62 Sumatriptan 100 mg, n = 66 Placebo, n = 65 M 22 F 237 (92%) Mean age 39 years Proportion with/without aura not reported	Assessment up to 4 h	Sumatriptan 25 mg Vs Sumatriptan 50 mg Vs Sumatriptan 100 mg Vs Placebo Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication (acetaminophen) was available after 2 h if pain had not improved relative to predose levels	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** Not reported Pharmaceutical industry support: Glaxo Research Institute

				After 4 h, rescue medication other than acetaminophen was allowed if pain had still not improved	
Dahlof 1991 DB, PC, PG-RCT	1130	Aged 18 to 60 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate) with an average of 1 to 6 attacks per month. Use of migraine prophylactic therapy was stopped at least 2 weeks before receipt of study medication n = 984 with moderate or severe baseline pain intensity Sumatriptan 100 mg, n = 305 (275 with moderate or severe baseline pain intensity) Sumatriptan 200 mg, n = 283 (255 with moderate or severe baseline pain intensity) Sumatriptan 300 mg, n = 299 (271 with moderate or severe baseline pain intensity) Placebo, n = 205 (182 with moderate or severe baseline pain intensity) M 187 F 943 (83%)	Assessment up to 2 h	Sumatriptan 100 mg Vs Sumatriptan 200 mg, Vs Sumatriptan 300 mg Vs Placebo Single dose to treat each of 3 consecutive attacks. Medication was administered at the earliest sign of an attack Rescue medication (provided it did not contain ergotamine) was available after 2 h for inadequate symptom relief Minimum of 48 h between treated attacks	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** Not reported Pharmaceutical industry support: Glaxo Research Institute

		Mean age 40 years Without aura 33%			
DKSMSG 1999 DB, double-dummy, within patient CO-RCT	156	Aged 18 years or over, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate) with an average of 2 to 6 attacks per month. 144 received at least 1 treatment 115 completed treatment for all 4 attacks Sumatriptan 100 mg, n = 130 Diclofenac-potassium 50 mg, n = 131 Diclofenac-potassium 100 mg, n = 122 Placebo, n = 131 M 37 F 119 (76%) Mean age 33 years Proportion with/without aura not reported	Assessment up to 8 h	Sumatriptan 100 mg Vs Diclofenac-potassium 50 mg Vs Diclofenac-potassium 100 mg Vs Placebo Single dose to treat each of 4 consecutive attacks Medication administered at the first sign of migraine pain Paracetamol available as rescue medication after 2 h for inadequate symptom relief Each treated attack separated by at least a 48-h period free of acute headache medication and migraine symptoms	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes**: Low risk** Double-dummy technique Pharmaceutical industry support: Novartis Pharma
Dodick 2002 DB, PC, PG-RCT	475	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N	Assessment up to 24 h	Sumatriptan 100 mg Vs Almotriptan 12.5 mg Vs	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported

		moderate) with an average of 1 to 6 attacks per month, each separated by at least a 24-h headache-free period. Exclusion: Participants were excluded if they had a history of migraine with prolonged aura or if they experienced more than 6 headaches per month. No migraine medications (e.g. analgesics, NSAIDS, 5-HT1B/1D receptor agonists, or dopamine agonists) for 2 days prior to intake of study medication. No antipsychotic or antidepressant medication within the 3 months preceding study enrolment, or any investigational drug within 1 month of study enrolment Sumatriptan 100 mg, n = 193 Almotriptan 12.5 mg, n = 183 Placebo, n = 99 M 69 F 406 (85%) Mean age 43 years Without aura 79%		Placebo Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity Second dose of study medication available to treat recurrence within 24 h Rescue medication (excluding ergot alkaloids and 5-HT1B/1D agonists) was available if moderate-to-severe migraine pain persisted 2 h after initial dosing Of the 3 studies reported, only protocol CL13 is relevant	BLINDING: performance bias and detection bias, all outcomes**:** **Unclear risk** Not reported
Dowson 2002 DB, PC, PG-RCT	668	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history	Assessment up to 24 h	Sumatriptan 100 mg Vs Almotriptan 12.5 mg	RANDOMIZATION: **Unclear risk** Not reported

		of migraine (untreated severity N moderate) with an average of 1 to 6 attacks per month, each separated by at least a 24-h headache-free period. Exclusion: Participants were excluded if they had a history of migraine with prolonged aura or if they needed symptomatic medication for migraine in the 2 days before taking study medication. No investigational drug within 1 month of study treatment. No monoamine oxidase inhibitors, lithium,selective serotonin reuptake inhibitors, ergots or derivatives, or methysergide in the 2 weeks prior to study medication Sumatriptan 100 mg, n = 194 Almotriptan 12.5 mg, n = 184 Almotriptan 25 mg, n = 191 Placebo, n = 99 M 101 F 567 (85%) Mean age 42 years Without aura 78%		Vs Almotriptan 25 mg Vs Placebo Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity Second dose of study medication available to treat recurrence within 24 h Rescue medication (excluding ergot-derivatives) available if migraine pain did not disappear or become mild within 2 h of treatment	ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes**:** **Unclear risk** Not reported Pharmaceutical industry support: Almirall SA
Ensink 1991; DB, PC, PG-RCT	233	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history	Assessment up to 24 h	Sumatriptan 100 mg Vs Placebo	RANDOMIZATION: **Unclear risk** Not reported

		of migraine (untreated severity N moderate) with an average of 1 to 6 attacks per month. No prophylactic medication within 2 weeks of the start of the study n = 232 analysed for efficacy Sumatriptan 100 mg, n = 148 (131 with moderate or severe baseline pain intensity) Placebo, n = 84 (78 with moderate or severe baseline pain intensity) M 34 F 198 (85%) Mean age 41 years Without aura 67%		Single dose to treat single Attack Medication administered as soon as possible after onset of headache Second dose of study medication available after 2 h if headache persisted. Alternative rescue medication available 2 h after the second dose of study medication if their headache had not resolved. Third dose of study medication available to treat headache recurrence within 24 h	ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes**: Unclear risk** Not reported Pharmaceutical industry support: Glaxo Group Research Ltd.
Geraud 2000; DB, Double-dummy, PC, PG-RCT	1058	Aged 18 to 65, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate) with an average of 1 to 6 attacks per month.	Assessment up to 24 h	Sumatriptan 100 mg Vs Zolmitriptan 5 mg Vs Placebo Single dose to treat single attack	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes**: Low risk** Double-dummy technique

		Exclusion: Participants were excluded if they had taken sumatriptan or zolmitriptan previously Participants were permitted to use medications such as f-blockers, calcium channel blockers (excluding flunarizine), clonidine, and valproic acid for migraine prophylaxis. However, they were excluded if they had received regular treatment during the month preceding the study with psychoactive drugs or drugs with a clinically important action at a 5-HT receptor Sumatriptan 100 mg, n = 504 Zolmitriptan 5 mg, n = 498 Placebo, n = 56 M 174 F 884 (84%) Mean age 38 years Without aura 73%		Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication was available after 2 h if migraine symptoms persisted. However ergot derivatives were not permitted until 12 h after study medication, and sumatriptan could not be used as a rescue medication.	Pharmaceutical industry support: Glaxo Wellcome
Goadsby 1991; DB, PC, CO-RCT	61	Aged 18 to 60, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate) with an average of 1 to 6 attacks per month.	Assessment up to 2 h	Sumatriptan 100 mg Vs Placebo Single dose to treat each of 4 successive attacks	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes**: Low risk** Matching placebo

		Current prophylaxis was continued during the trial n = 41 analysed for efficacy Number of attacks in efficacy population Sumatriptan 100 mg, n = 94 (89 of moderate or severe intensity) Placebo, n = 94 (93 of moderate or severe intensity) Proportion of male/female participants not reported Mean age 39 years Proportion with/without aura not reported		Medication was administered as soon as participants were confident that they were having a migraine headache Rescue medication available after 2 h	Pharmaceutical industry support: Glaxo Group Research Ltd.
Goadsby 2000 DB, double dummy, PC, PG-RCT	692	Aged 18 or over, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate) with frequency of at least one attack every 6 weeks. Exclusion: Participants were excluded if they had more than 6 attacks per month No sumatriptan or any ergotamine-like compound within 48 h of taking study medication Sumatriptan 100 mg, n = 129	Assessment up to 2 h	Sumatriptan 100 mg Vs Eletriptan 20 mg Vs Eletriptan 40 mg Vs Eletriptan 80 mg Vs Placebo Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or	RANDOMIZATION: **Low risk** Computer-generated pseudorandom code using method of random permuted Blocks ALLOCATION CONCEALMENT: **Low risk** Study medication supplied pre-packed, dispensed as next consecutive number BLINDING: performance bias and detection bias, all outcomes**: Low risk** Double-dummy technique Pharmaceutical industry support: Pfizer Inc

		Eletriptan 20 mg, n = 144 Eletriptan 40 mg, n = 136 Eletriptan 80 mg, n = 141 Placebo, n = 142 M 124 F 568 (82%) Mean age 40 years Without aura 68%		severe intensity, and only if the aura phase had ended. Second blinded dose of study medication was available to treat recurrence within 24 h Rescue medication (analgesics, NSAIDs, or antiemetics) available as needed beginning 2 h after initial dosing	
Havanka 2000; DB, PC, PG-RCT	643	Aged 18 to 55, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate) with an average of 1 to 6 attacks per month. No use of monoamine oxidase inhibitors, serotonin reuptake inhibitors, lithium, of flunarizine during the study period No sumatriptan or ergot-containing medications within 24 h before or after study drug administration, and no antiemetics or analgesics within 6 h of study drug administration	Assessment up to 4 h	Sumatriptan 100 mg Vs Naratriptan 1 mg Vs Naratriptan 2.5 mg Vs Naratriptan 5 mg Vs Naratriptan 7.5 mg Vs Naratriptan 10 mg Vs Placebo Single dose to treat single attack. Medication administered when migraine headache	RANDOMIZATION: **Low risk** Computer-generated randomisation numbers ALLOCATION CONCEALMENT: **Low risk** Numbers assigned in consecutive order, starting with the lowest available BLINDING: performance bias and detection bias, all outcomes**:** **Unclear risk** Not reported Pharmaceutical industry support: Glaxo Wellcome

		Migraine prophylactic medication stopped at least 2 weeks before administration of study medication n = 642 analysed for efficacy Sumatriptan 100 mg, n = 98 Naratriptan 1 mg, n = 85 Naratriptan 2.5 mg, n = 87 Naratriptan 5 mg, n = 93 Naratriptan 7.5 mg, n = 93 Naratriptan 10 mg, n = 96 (95 with moderate or severe baseline pain intensity) Placebo, n = 91 M 77 F 566 (88%) Mean age not reported Without aura 75%		pain was of moderate or severe intensity Rescue medication available 4 h after dosing for persistent headache	
Jelinski 2006 DB, Double-dummy, PC, PG-RCT	361	Aged 18 to 65, meeting IHS criteria for migraine (1988) with or without aura. Had 1 to 6 migraine attacks per month in the 2 months prior to screening, and typically experienced moderate to severe migraine pain preceded by a mild pain phase. No use of monoamine oxidase inhibitors during the study period No analgesics, antiemetics, or other acute migraine medications within 6 h of taking study medication.	Assessment up to 4 h	Sumatriptan 50 mg Vs Sumatriptan 100 mg Vs Placebo Single dose to treat single attack Medication administered within 2 h of the first sign of migraine pain, while the pain was still considered	RANDOMIZATION: **Low risk** Computer-generated randomisation schedules ALLOCATION CONCEALMENT: **Low risk** Treatment group assignment was unknown to patients and investigators BLINDING: performance bias and detection bias, all outcomes: **Low risk** Double-dummy technique Pharmaceutical industry support: GlaxoSmithKline

		No ergotamine, ergot-type medications, or other 5HT1 agonists within 24 h of study medication use. Participants permitted to continue their use of prophylactic medications (excluding methysergide) during the study, provided the dose was stable for at least 1 month before study entry Sumatriptan 50 mg, n = 126 Sumatriptan 100 mg, n = 126 Placebo, n = 109 M 52 F 309 (86%) Mean age 40 years Without aura 67%		to be mild Second dose of study medication available to treat recurrence 2 to 24 h after initial dosing Rescue medication (analgesics, antiemetics, or other acute migraine medications) were available after 2 h for inadequate symptom relief	
Kaniecki 2006 DB, PC, PG-RCT	258	Aged 18 to 65, self-reporting tension/stress-type headache, who were given a diagnosis of migraine with or without aura according to IHS criteria (1988) at a screening visit. At least 1-year history of headache (untreated severity N moderate) with an average of 1 to 6 attacks per month Exclusion: Participants excluded if they had ever used a triptan, ergotamine, or an ergot derivative, or had persistent head or neck pain	Assessment up to 24 h	Sumatriptan 100 mg Vs Placebo Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity Second dose of study medication available after	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** Not reported Pharmaceutical industry support: GlaxoSmithKline

		outside of migraine attacks (more than 15 days per month during the 2 months before screening) No monoamine oxidase inhibitors within 2 weeks of study entry Sumatriptan 100 mg, n = 131 Placebo, n = 127 M 69 F 184 (73%) Mean age 37 years Proportion with/without aura not reported		2 h to treat recurrence or for pain if participant had at least a partial response to the first dose Alternative rescue medication (excluding ergotamine-containing medications and monoamine oxidase inhibitors) available after 2 h for persistent pain	
Mathew 2003 DB, Double-dummy, PC, PG-RCT	2113	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura and a monthly frequency of 1 to 6 attacks. No use of potent CYP3A4 inhibitors or monoamine oxidase inhibitors within 2 weeks prior to study entry. No analgesic or antiemetic within 6 h, or triptan, ergotamine-containing or ergot-type medication within 48 h of taking study medication n = 2072 analysed for efficacy Sumatriptan 100 mg, n = 831 Eletriptan 40 mg, n = 822 Placebo, n = 419	Assessment up to 24 h	Sumatriptan 100 mg Vs Eletriptan 40 mg Vs Placebo Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity Second dose of study medication available to treat recurrence after 2 h	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Low risk** Double-dummy technique Pharmaceutical industry support: Pfizer Ltd

		M 277 F 1795 (87%) Mean age 42 years Without aura 65%		Rescue medication available after 2 h for inadequate headache relief, although participants not permitted to take any other triptan, ergotamine, or ergotamine-like substance for 24 h after initial dosing	
Myllyla 1998 DB, Double-dummy, PC, PG-RCT	154	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate) with an average of 1 to 4 attacks per month n = 156 analysed for efficacy Sumatriptan 100 mg (+ optional dose of placebo after 1 h), n = 46 (42 for efficacy) Tolfenamic acid 200 mg (+ optional 2nd dose after 1 h), n = 47 (43 for efficacy) Placebo (+ optional dose of placebo after 1 h), n = 46 (41 for efficacy) M 15 F 126 (89%) Mean age 39 years Without aura 72%	Assessment up to 2 h	Sumatriptan 100 mg Vs Tolfenamic acid 200 mg Vs Placebo Up to 2 doses to treat each of 2 successive attacks. Medication administered at the first symptoms of a migraine attack Second dose of study medication if headache not improved after 1 h Alternative rescue medication (paracetamol, acetylsalicylic acid, naproxen, ketoprofen, prochlorperazine, or	RANDOMIZATION: **Low risk** Computer-generated randomisation code ALLOCATION CONCEALMENT: **Low risk** Complete randomisation blocks assigned to centres, participants entered in ascending sequential order of patient number BLINDING: performance bias and detection bias, all outcomes: **Low risk** Double-dummy technique Pharmaceutical industry support: A/S GEA Farmaceutisk Fabrik (medication used was Imigran)

				diazepam) available after 2 h if headache relief still insufficient At least 48 h required between the treatment of 2 successive attacks	
Nappi 1994 DB, PC, PG-RCT	250	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity > moderate). Exclusion: Participants were excluded if they were taking migraine prophylaxis n = 244 analysed for efficacy Sumatriptan 100 mg, n = 158 (148 with moderate or severe baseline pain intensity) Placebo, n = 86 (81 with moderate or severe baseline pain intensity) M 56 F 188 (77%) Mean age 38 years Without aura 87%		Sumatriptan 100 mg Vs Placebo Single dose to treat single attack Medication administered at the first sign of migraine Second dose of study medication available if symptom relief was inadequate at 2 h Alternative rescue medication (not ergotamine) was available if the response after 4 h was still inadequate Headache recurrence after either the first or second dose could be treated by a third dose of	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** Not reported Pharmaceutical industry support: Glaxo Group Research Ltd.

				study medication, providing it was more than 2 h after the most recent dose and less than 24 h after the first dose	
Nett 2003 DB, PC, PG-RCT	369	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine with a minimum of 6 months of regularly occurring menstrually associated migraines (defined as occurring between day -2 to day 4 relative to the first day of flow). Participants had to have had menstrually associated migraine in at least 2 of their last 3 perimenstrual periods before screening that were typically associated with moderate to severe pain preceded by a,mild pain phase Exclusion: Participants were excluded if they had tension-type headache for more than 15 days per month or more than 6 migraine attacks per month in either of the 2 months before screening No monoamine oxidase inhibitors or ergotamine-containing or ergotamine-type migraine prophylactic medication during the	Assessment up to 2 h	Sumatriptan 50 mg, Vs Sumatriptan 100 mg, Vs Placebo Single dose to treat single menstrually associated migraine attack Medication administered within 1 h of the onset of pain, but only if the pain was mild at onset and only if the pain was still mild at the time of treatment Rescue medication or a second double-blind dose of study medication were available to treat either inadequate response after 2 h or recurrence between 2 and 24 h	RANDOMIZATION: **Low risk** Computer-generated randomisation ALLOCATION CONCEALMENT: **Low ris**k Remote allocation BLINDING: performance bias and detection bias, all outcomes: **Low risk** All tablets were visually indistinguishable Pharmaceutical industry support: GlaxoSmithKline

		study period. Other migraine prophylactic medications were permitted, provided they had been on a constant regimen for at least 1 month before screening and the regimen remained constant throughout the study. No analgesics, antiemetics, or non-serotonin-agonist acute migraine medications within 6 h of taking study medication n = 368 for efficacy, 349 for per-protocol efficacy Sumatriptan 50 mg, n = 124 (124 for efficacy, 116 for per-protocol efficacy) Sumatriptan 100 mg, n = 122 (122 for efficacy, 115 for per-protocol efficacy) Placebo, n = 123 (122 for efficacy, 118 for per-protocol efficacy) All F Mean age 36 years Without aura 75%			
Patten 1991 DB, PC, PG-RCT	624	Aged 18 to 60 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate) with an average of 1 to 6 attacks per month.	Assessment up to 2 h	Sumatriptan (disp.) 100 mg Vs Sumatriptan (disp.) 200 mg Vs	RANDOMIZATION**: Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported

		All use of prophylactic migraine therapy was stopped at least 2 weeks before starting on the study medication 538 with moderate or severe baseline pain intensity Sumatriptan (dispersible) 100 mg, n = 142 Sumatriptan (dispersible) 200 mg, n = 140 Sumatriptan (dispersible) 300 mg, n = 155 Placebo, n = 101		Sumatriptan (disp.) 300 mg Vs Placebo Single dose to treat each of up to 3 successive attacks. Medication administered at the earliest sign of a migraine attack, provided at least 48 h had elapsed since the previous study treatment Rescue medication (excluding ergotamine-containing medication) was available after 2 h if symptoms were not adequately relieved	BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** Not reported Pharmaceutical industry support: Glaxo Group Research Ltd.
Pfaffenrath 1998 DB, PC, PG-RCT	1003	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate) with an average of 1 to 6 attacks per month. No use of lithium, monoamine oxidase inhibitors, serotonin reuptake inhibitors, or ergotamine-	Assessment up to 4 h	Sumatriptan 25 mg Vs Sumatriptan 50 mg Vs Sumatriptan 100 mg vs Placebo Single dose to treat each of 3 separate attacks	RANDOMIZATION**: Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes **Low risk** Matching placebo Pharmaceutical industry support: Glaxo Wellcome

		containing migraine prophylactic medications during the study period. No analgesics or antiemetics within 6 h and no ergotamine-containing medications within 24 h of taking study medication. n = 939 with moderate or severe baseline pain intensity Sumatriptan 25 mg, n = 303 (286 with moderate or severe baseline pain intensity) Sumatriptan 50 mg, n = 303 (285 with moderate or severe baseline pain intensity) Sumatriptan 100 mg, n = 298 (277 with moderate or severe baseline pain intensity) Placebo, n = 99 (91 with moderate or severe baseline pain intensity) M 157 F 846 (84%) Mean age 40 years Without aura 66%		Second randomised dose of study medication available to treat headache recurrence from 2 to 24 h after initial dosing Rescue medication (excluding ergotamine-containing preparations or sumatriptan) was permitted if headache relief was inadequate 4 h after initial dosing	
Pini 1995 DB, PC, PG-RCT	238	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity N moderate) n = 222 analysed for efficacy	Assessment up to 48 h	Sumatriptan 100 mg Vs Placebo Single dose to treat single attack	RANDOMIZATION**: Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** Not reported

		Sumatriptan 100 mg, n = 151 Placebo, n = 87 M 52 F 186 (78%) Mean age 37 years Without aura 61%		Medication administered at the earliest sign of migraine attack Rescue medication (ergotamine-free) was available after 4 h if the headache was not controlled	Pharmaceutical industry support: Glaxo
Sandrini 2002 DB, double dummy, PC, PG-RCT	774	Aged 18 years or older, meeting IHS criteria for migraine (1988) with or without aura, and suffering at least 1 attack every 6 weeks. Exclusion: Participants were excluded if they had previously taken oral eletriptan or any formulation of sumatriptan. No ergotamine or any ergotamine-like agent within 48 h before, or 24 h after, taking study medication. No proprietary analgesic or antiemetic within 6 h of taking study medication. Sumatriptan 50 mg, n = 181 Sumatriptan 100 mg, n = 170 Eletriptan 40 mg, n = 175 Eletriptan 80 mg, n = 164 Placebo, n = 84 M 93	Assessment up to 24 h	Sumatriptan 50 mg Vs Sumatriptan 100 mg Vs Eletriptan 40 mg Vs Eletriptan 80 mg Vs Placebo Single dose to treat each of up to 3 successive attacks Medication administered within 6 h of onset of a migraine attack, when the headache pain was of moderate or severe intensity, and if any aura phase had ended Second, blinded and randomised dose of study	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes **Low risk** Double-dummy technique Pharmaceutical industry support: Pfizer Ltd

		F 681 (88%) Mean age 38 years Without aura 65%		medication was available if there was no response to treatment after 2 h, or if there was a recurrence of headache within 24 h Rescue medication was available 2 h after the second dose if there was still no improvement in headache	
Sargent 1995 BD, PC, PG-RCT	187	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate) and suffering an average of 1 to 6 attacks per month. Migraine prophylaxis was not allowed during the 2-week period preceding treatment. No simple analgesics during 6 h preceding treatment, and no opioid-containing agents or ergotamine during the 24 h preceding treatment. Sumatriptan 25 mg, n = 48 Sumatriptan 50 mg, n = 46 Sumatriptan 100 mg, n = 46 Placebo, n = 47 M 16	Assessment up to 4 h	Sumatriptan 25 mg Vs Sumatriptan 50 mg Vs Sumatriptan 100 mg Vs Placebo Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication (acetaminophen) available after 2 h if pain had not improved relative to predose levels. Rescue medication other than	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** Not reported Pharmaceutical industry support: Glaxo Research Institute

		F 171 (91%) Mean age 40 years Without aura 80%		acetaminophen was allowed beginning 4 h after initial dosing.	
Sheftell 2005a and Sheftell 2005b **(Study 1 and Study 2)** Two identically designed studies DB, PC, PG-RCT	<u>Study 1:</u> 1477	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity N moderate) and suffering an average of 1 to 6 attacks per month. Exclusion: Participants were excluded if they experienced headache on more than 15 days per month in any of the 3 months before screening. No migraine prophylactic medication containing ergotamine, an ergot derivative, or methysergide, or use of monoamine oxidase inhibitor within 2 weeks before screening <u>Study 1:</u> n = 1366 analysed for efficacy Sumatriptan (rapid-release) 50 mg, n = 494 (448 for efficacy) Sumatriptan (rapid-release) 100 mg, n = 488 (462 for efficacy) Placebo, n = 495 (456 for efficacy) M 196, F 1170 (86%)	Assessment up to 24 h	Sumatriptan (rapid-release) 50 mg Vs Sumatriptan (rapid-release) 100 mg) Vs Placebo Medication administered when migraine headache pain was of moderate or severe intensity Second dose of study medication or non-prohibited acute migraine medication available after 2 h to treat recurrence Rescue medication available after 2 h if pain not reduced to mild or none within 2 h after initial dosing	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Low risk** Remote allocation generated by the study sponsor and not available to the investigators BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** Not reported Pharmaceutical industry support: GlaxoSmithKline

	<u>Study 2:</u> 1475	Mean age 41 years Without aura 70% <u>Study2:</u> n = 1330 analysed for efficacy Sumatriptan (rapid-release) 50 mg, n = 496 (454 for efficacy) Sumatriptan (rapid-release) 100 mg, n = 485 (440 for efficacy) Placebo, n = 494 (436 for efficacy) M 204 F 1126 (85%) Mean age 40 years Without aura 67%			
Tfelt-Hansen 1995 DB, double dummy, PC, PG-RCT	389	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate) and suffering an average of 2 to 6 attacks per month n = 385 analysed for efficacy Sumatriptan 100 mg, n = 122 Lysine acetylsalicylate 1620 mg + metoclopramide 10 mg, n = 137 Placebo, n = 126 M 94 F 327 (78%) Mean age 39 years	Assessment up to 4 h	Sumatriptan 100 mg Vs Lysine acetylsalicylate 1620 mg + metoclopramide 10 mg Vs Placebo Single dose to treat each of 2 consecutive attacks Medication administered when migraine headache pain was of moderate or severe intensity	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Low risk** Double-dummy technique

		Without aura 85%		Rescue medication (except for ergot alkaloids or morphinomimetic drugs) was allowed if the headache was inadequately controlled after 2 h	
Tfelt-Hansen 1998 DB, trible dummy, PC, PG-RCT	1099	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity N moderate) and suffering an average of 1 to 8 attacks per month Exclusion: Participants were excluded if they had ever been exposed to rizatriptan before No monoamine oxidase inhibitors, methysergide, or lithium within 2 weeks; sumatriptan, Midrin, or ergot derivatives within 48 h; any opiate within 24 h; or any other form of analgesia or antiemetic within 6 h of taking study medication Standard migraine prophylaxis was permitted with the exception of NSAIDs Sumatriptan 100 mg, n = 388 Rizatriptan 5 mg, n = 164	Assessment up to 4 h	Sumatriptan 100 mg Vs Rizatriptan 5 mg Vs Rizatriptan 10 mg Vs Placebo Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication was available to treat non-response at 2 h, or recurrence within 24 of initial dosing. Sumatriptan, Midrin, and ergot derivatives were prohibited as rescue	RANDOMIZATION: **Low risk** Computer-generated schedule ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: ***Low risk*** Triple-dummy technique Pharmaceutical industry support: Merck & Co.

		Rizatriptan 10 mg, n = 387 Placebo, n = 160 M 201 F 898 (82%) Mean age 38 years Without aura 84%		medications until 24 after initial dosing.	
Visser 1996; DB, PC, PG-RCT	449	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity N moderate) and suffering 8 or fewer migraine attacks per month. No fluoxetine hydrochloride within 6 weeks, prophylactic antimigraine treatment within 2 weeks, ergot derivatives or sumatriptan within 48 h, opiate within 24 h, or any other form of analgesia within 6 h of taking study medication Sumatriptan 100 mg, n = 72 Rizatriptan 10 mg, n = 89 Rizatriptan 20 mg, n = 82 Rizatriptan 40 mg, n = 121 Placebo, n = 85 M 47 F 402 (90%) Mean age 40 years Proportion with/without aura not reported	Assessment up to 2 h	Sumatriptan 100 mg Vs Rizatriptan 10 mg Vs Rizatriptan 20 mg Vs Rizatriptan 40 mg Vs Placebo Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity Second, blinded dose of study medication available after 2 h for inadequate headache response Rescue medication (opiates, acetaminophen, or NSAIDs) available after	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: ***Low risk*** Matching capsules Study Pharmaceutical industry support: Merck Research Laboratories

				4 h, and sumatriptan or ergotamine-derivatives available after 24h.	
Winner 2003a and Winner 2003b **(Study 1 and Study 2)** Two identical studies DB, double-dummy, PC, PG-RCT	<u>Study1:</u> 362	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine with an average of 1 to 6 attacks per month. All participants were required to experience moderate or severe migraine pain preceded by a mild pain phase. No use of monoamine oxidase inhibitors for a minimum of 2 weeks before screening or throughout the course of the study. Otherwise allowed to continue migraine prophylactic medications. No analgesics, antiemetics, or other migraine medication within the 6 h before taking study medication, and no ergotamine, ergot-type medications, or other serotonin1B/1D agonists within 24 h of study medication use <u>Study1:</u> n = 354 analysed for efficacy 3% did not have mild pain at baseline Sumatriptan 50 mg, n = 122 Sumatriptan 100 mg, n = 115	Assessment up to 24 h	Sumatriptan 50 mg Vs Sumatriptan 100 mg Vs Placebo Medication administered at the first sign of pain, while the pain was mild Second dose of study medication available to treat recurrence between 2 and 24 h after initial dosing Rescue medication (analgesics, antiemetics, or other acute migraine medications) available 4 h after initial dosing	RANDOMIZATION: **Low risk** Computer-generated randomisation scheduleALLOCATION CONCEALMENT: **Low risk** Treatment assignment sealed and remained intact throughout the study BLINDING: performance bias and detection bias, all outcomes**: Low risk** Double-dummy technique Pharmaceutical industry support: GlaxoSmithKline

		Placebo, n = 117 M 43 F 311 (88%) Mean age 41 years Without aura 73% <u>Study 2:</u> n = 337 analysed for efficacy 4 % did not have mild pain at baseline Sumatriptan 50 mg, n = 111 Sumatriptan 100 mg, n = 107 Placebo, n = 119 M59 F 298 (88%) Mean age 43 years Without aura 79%			
	<u>Study2:</u> 354				

Remarks:

- Authors analysed studies using a single dose of sumatriptan in established pain of at least moderate intensity **separately** from studies in which medication was taken before pain became well established or in which a second dose of medication was permitted.
- All participants experiencing outcomes of headache relief must, by definition, have had moderate to severe pain at baseline. Fourteen of the studies providing data on relief of associated symptoms included a small number (< 10%) of participants with mild baseline pain intensity. It is possible that these participants had fewer or less severe associated symptoms, but the number was considered small enough that even if this were so, there would not be a major effect on the overall result; these studies were therefore included in any pooled analyses to which they were relevant.
- Only one study (Carpay 2004) assessing participants with mild baseline pain intensity reported relief of functional disability as defined in this way, and therefore no separate pooled analyses could be performed.
- In some studies dispersible oral tablets of sumatriptan have been used and data have been pooled with classical oral tablets.

- Pain intensity or pain relief had to be measured by the patient (not the investigator or carer). Pain measures accepted for the primary outcomes were:

• pain intensity: four-point categorical scale, with wording equivalent to none, mild, moderate, and severe; or 100 mm visual analogue scale (VAS);

• pain relief: five-point categorical scale, with wording equivalent to none, a little, some, a lot, complete; or 100 mm VAS.

- Participants were generally excluded for: pregnancy or breastfeeding; inadequate contraception; confirmed or suspected cardiovascular or cerebrovascular disease (particularly history of ischemic heart disease); uncontrolled hypertension (diastolic N 95 mmHg or systolic N 160 mmHg); current or past drug abuse; psychiatric illness; epilepsy; hepatic disease; Raynaud's syndrome; and/or ophthalmoplegic, basilar, or hemiplegic migraine.
- The incidence of vomiting was very low in all studies and where reported did not permit analysis.
- The duration over which adverse events data were collected was not always specific, and where it was, there were differences across studies. Most studies probably collected data during the 24 hours pos-dose, In some studies a second, and sometimes third, dose of study medication was taken, and in all but one study rescue medication was allowed if there was an inadequate response after a given period of time. It is likely that in all cases adverse event data continued to be collected after such additional medication. Furthermore, a number of studies treated more than one attack. In most of the studies, it is unclear how multiple attacks were combined.
- For most of the comparisons reported in this SR, data on specific adverse events were provided including chest pain/symptoms. As it was not explicitly described if this symptom refers to cardiovascular events no data were reported in the present document.
- 160-104 is a clinical trial report provided by the manufacturer.
- Only three of the included studies did not report involvement of any pharmaceutical company.

Author's conclusions:

"Oral sumatriptan is effective as an abortive treatment for migraine attacks, relieving pain, nausea, photophobia, phonophobia, and functional disability, but is associated with increased adverse events."

"Treating early, while headache was still in the mild pain phase was significantly more effective than treating established moderate or severe headache pain.

"Sumatriptan 100 mg was significantly more effective than sumatriptan 50 mg in participants with moderate or severe baseline pain intensity and in in participants with mild baseline pain intensity."

"Sumatriptan 100 mg caused significantly more adverse events than sumatriptan 50 mg."

12.6.7 Sumatriptan s.c. versus placebo for acute treatment of migraine attack of moderate to severe basaline pain intensity in adults

Meta-analysis: Derry 2012sc(121), Sumatriptan (subcutaneous route of administration) for acute migraine attacks in adults.

Definition of migraine: We used the definition of migraine specified by the International Headache Society (IHS 1988; IHS 2004).

Inclusion criteria: We included randomised, double-blind, placebo-controlled or active-controlled studies, or both, using subcutaneous sumatriptan to treat a migraine headache episode. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data for at least one of the outcomes specified below. We accepted studies reporting treatment of consecutive headache episodes if outcomes for the first, or each, episode were reported separately. We accepted cross-over studies if there was adequate (at least 48 hours) washout between treatments.

Population: Studies included adults (at least 18 years of age) with migraine. There were no restrictions on migraine frequency, duration, or type (with or without aura). We accepted studies including participants taking stable prophylactic therapy to reduce the frequency of migraine attacks.

We excluded studies designed to demonstrate prophylactic efficacy in reducing the number or frequency of migraine attacks.

Search strategy: We searched the following databases: • the Cochrane Central Register of Controlled Trials (CENTRAL)
(2011, Issue 10); • MEDLINE (via OVID) (to 13 October 2011); • EMBASE (via OVID) (to 13 October 2011); • Oxford Pain Relief Database (Jadad 1996a).
We searched reference lists of retrieved studies and review articles for additional studies. We also searched online clinical trials databases (www.gsk-clinicalstudyregister.com and www.clinicaltrials.gov). We made a written request for information about both published and unpublished data from the manufacturer of sumatriptan (GlaxoSmithKline), but no additional studies were identified. We did not search grey literature and abstracts.

Assessment of quality of included trials: yes

Other methodological remarks:
We accepted randomisation at the individual patient level only.
The most likely source of missing data was in cross-over studies. Where this might be problematic (e.g. where data were missing for > 10% of participants), we used only first-period data, where available.
We calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants.
We calculated relative risk of benefit or harm with 95% confidence intervals (CIs) using a fixed effect model. We calculated NNT, NNTp, and NNH with 95% CIs, where possible, using the pooled number of events by the method of Cook and Sackett.

Ref	Comparison	N/n	Outcomes	Result
Derry 2012 s.c. Design: SR+MA Search date: September	Sumatriptan 6 mg s.c. Vs Placebo	N = 13 n = 2522 (Dahlof 1998; Diener 1999; Diener 2001; Facchinetti 1995; Mathew 1992; Mushet 1996 Study 1 and Study 2; S2BM03; Sang 2004; SUM40286; SUM40287; Winner 2006 Study 1 and Study 2).	Pain free at 2h (PO)	Sumatriptan s.c.: 59% (799/1351) Placebo: 15% (174/1171) **RR (95% CI): 3.9 (3.3 to 4.5)** NNT (95% CI): 2.3 (2.1 to 2.4) **SS in favour of sumatriptan s.c.** I^2: 62%
		N = 14 n = 2738 (Dahlof 1998; Diener 1999; Diener 2001; Facchinetti 1995; Jensen 1995; Mathew	Pain relief at 2 h (PO) (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	Sumatriptan s.c.: 79% (1152/1459) Placebo: 31% (395/1279) **RR (95% CI): 2.5 (2.3 to 2.7)** NNT (95% CI): 2.1 (2.0 to 2.2) **SS in favour of sumatriptan s.c.** I^2: 75%

		1992; Mushet 1996 Study 1 and Study 2; S2BM03; Sang 2004; SUM40286; SUM40287; Winner 2006 Study 1 and Study 2)		
		N = 16 n = 3592 (Bousser 1993; Cady 1991 Study 1 and Study 2; Cady 1993; Facchinetti 1995; Ferrari 1991; Henry 1993; Jensen 1995; Mathew 1992; Mushet 1996 Study 1 and Study 2; Pfaffenrath 1991; S2BM03;	Pain free at 1 h (PO)	Sumatriptan s.c.: 41% (905/2198) Placebo: 7% (99/1394) **RR (95% CI): 5.6 (4.6 to 6.8)** NNT (95% CI): 2.9 (2.7 to 3.2) **SS in favour of sumatriptan s.c.** I^2: 35%

		Sang 2004; SUM40286; SUM40287)		
		N = 24 n = 5177 (Bates 1994; Bousser 1993; Cady 1991 Study 1 and Study 2; Cady 1993; Dahlof 1998; Diener 1999; Diener 2001; Facchinetti 1995; Ferrari 1991; Gross 1994; Henry 1993; Jensen 1995; Mathew 1992; Mushet 1996 Study 1 and Study 2; Pfaffenrath 1991; S2BM03; Sang 2004; Schulman 2000; SUM40286; SUM40287;	Pain relief at 1 h (PO) (Pain reduced from moderate or severe to none or mild without the use of rescue medication)	Sumatriptan s.c.: 71% (2229/3139) Placebo: 26% (532/2038) **RR (95% CI): 2.7 (2.5 to 2.9)** NNT (95% CI): 2.2 (2.1 to 2.4) **SS in favour of sumatriptan s.c.** I^2: 68%

		Winner 2006 Study 1 and Study 2).		
		N = 5 n = 1336 (Cady 1993; SUM40286; SUM40287; Winner 2006 Study 1 and Study 2).	Sustained pain free over 24h (PO) (Headache relief at 2 hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication)	Sumatriptan s.c.: 31% (222/713) Placebo: 15% (91/623) **RR (95% CI): 2.2 (1.8 to 2.8)** NNT (95% CI): 6.1 (4.8 to 8.2) **SS in favour of sumatriptan s.c.** I^2: 0%
		N = 8 n = 1461 (Cady 1991 Study 1 and Study 2; Cady 1993; Henry 1993; Mathew 1992; Mushet 1996 Study 1 and Study 2; Pfaffenrath 1991)	Relief of nausea at 1 h	**RR (95% CI): 1.9 (1.7 to 2.2)** NNT (95% CI): 3.1 (2.7 to 3.7) **SS in favour of sumatriptan s.c.** I^2: not provided
		N = 5 n = 667	Relief of nausea at 2 h	Sumatriptan s.c.: 76% (276/364) Placebo: 34% (103/303) **RR (95% CI): 2.2 (1.9 to 2.6)** NNT (95% CI): 2.4 (2.1 to 2.9)

		(Dahlof 1998; Diener 1999; Facchinetti 1995; Winner 2006 Study 1 and Study 2).		**SS in favour of sumatriptan s.c.** I^2: 80%
		N = 6 n = 1460 (Cady 1991 Study 1 and Study 2; Cady 1993; Mathew 1992; Mushet 1996 Study 1 and Study 2)	Relief of photophobia at 1 h	**RR (95% CI): 3.0 (2.5 to 3.7)** NNT (95% CI): 2.7 (2.4 to 3.1) **SS in favour of sumatriptan s.c.** I^2: not provided
		N = 3 n = 631 (Diener 1999; Winner 2006 Study 1 and Study 2)	Relief of photophobia at 2 h	Sumatriptan s.c.: 71% (245/343) Placebo: 36% (105/288) **RR (95% CI): 1.9 (1.6 to 2.2)** NNT (95% CI): 2.9 (2.4 to 3.6) **SS in favour of sumatriptan s.c.** I^2: 0%
		N = 3 n = 300	Relief of phonophobia at 1 h	Sumatriptan s.c.: Placebo: **RR (95% CI): 2.6 (1.8 to 3.7)** NNT (95% CI): 2.4 (1.9 to 3.3)

		(Cady 1993; Mushet 1996 Study 1 and Study 2)		**SS in favour of sumatriptan s.c.** I^2: not provided
		N = 3 n = 572 (Diener 1999; Winner 2006 Study 1 and Study 2)	Relief of phonophobia at 2 h	Sumatriptan s.c.: 72% (223/310) Placebo: 39% (101/262) **RR (95% CI): 1.8 (1.5 to 2.2)** NNT (95% CI): 3.0 (2.4 to 3.9) **SS in favour of sumatriptan s.c.** I^2: not provided
		N = 4 n = 1328 (Cady 1991 Study 1 and Study 2; Cady 1993; Diener 2001)	Partial relief of functional disability at 1 h (Moderate or severe functional disability to mild or none)	Sumatriptan s.c.: 72% (649/899) Placebo: 22% (96/429) **RR (95% CI): 3.2 (2.7 to 3.8)** NNT (95% CI): 2.0 (1.8 to 2.2) **SS in favour of sumatriptan s.c.** I^2: 49%
		N = 3 n = 750 (S2BM03; Winner 2006 Study 1 and Study 2)	Relief of functional disability at 2 h (Any functional disability at baseline to none)	Sumatriptan s.c.: 56% (213/377) Placebo: 17% (62/373) **RR (95% CI): 3.4 (2.7 to 4.4)** NNT (95% CI): 2.5 (2.2 to 3.3) **SS in favour of sumatriptan s.c.** I^2: 92%

		N= 5 n = 987 (Cady 1998, Dalhof 1998, Diener 1999, Diener 2001, Schulman 2000)	Use of rescue medication (up to 24h)	Sumatriptan s.c.: 168/621 Placebo: 176/366 **RR (95% CI): 0.52 (0.45 to 0.60)** **SS in favour of sumatriptan s.c.** I^2: 77%
		N = 9 n = 1342 (Akpunonu 1995; Bates 1994; Facchinetti 1995; Gross 1994; Jensen 1995; Mathew 1992; Pfaffenrath 1991; Russell 1994; Sang 2004).	Adverse events	Sumatriptan s.c.: 44% (341/767) Placebo: 24% (137/575) **RR (95% CI): 2.1 (1.8 to 2.5)** NNH (95% CI): 4.9 (3.9 to 6.4) **SS in favour of placebo** I^2: 49%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Akpunonu 1995 DB, PC, PG-RCT	136	Aged 18 years or older, meeting IHS criteria for migraine (1988) with aura. At least 1-year history of migraine. Participants with a frequency of tension headache of at least 15 days per month were excluded No concurrent use of monoamine oxidase inhibitors, lithium, or selective 5-HT reuptake inhibitors No use of ergotamine within 24 h of study drug administration Sumatriptan 6 mg, n = 88 Placebo, n = 48 100% with aura	N.D.	Sumatriptan s.c. Vs Placebo Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication (excluding ergot derivatives) available after 90 minutes if headache relief not achieved Each participant provided with an open-label 100 mg sumatriptan tablet to treat recurrence over the 24 h period after discharge	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear ris**k Not described BLINDING: **Unclear risk** Not described
Bates 1994 DB, PC, PG-RCT	177	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with aura. At least 6-month history of migraine (untreated severity > moderate) and at least 50% of attacks with aura.	Assessment up to 24 h	Sumatriptan s.c. Vs Placebo Single dose to treat single attack.	**Does not meet our inclusion criteria (n<40/study group, for patient with moderate or severe baseline pain intensity)**

		Excluded participants with previous use of subcutaneous sumatriptan 171 for efficacy, 82 with moderate or severe baseline pain intensity Sumatriptan 6 mg, n = 90 (88 for efficacy, 47 with moderate or severe baseline pain intensity) Placebo, n = 87 (83 for efficacy, 35 with moderate or severe baseline pain intensity) M 46, F 125 (73%) Mean age 40 years All treated attacks with aura		Medication administered at onset of migraine aura	
Bousser 1993 DB, PC, CO-RCT	96	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity > moderate) with an average of 2 to 6 attacks per month, of which at least 2 were early-morning migraine attacks. No ergot-containing preparations were allowed within 24 h of taking study drugs Sumatriptan 6 mg, n = 49 (41 for 1st attack efficacy) Placebo, n = 47 (40 for 1st attack efficacy)	Assessment up to 24 h	Sumatriptan s.c. Vs Placebo 2 consecutive early-morning attacks treated when migraine headache pain was of moderate or severe intensity Single dose to treat each of 2 successive attacks with recommended second dose of study medication after 1 h for inadequate relief	RANDOMIZATION: **Low risk** Computer-generated randomisation code ALLOCATION CONCEALMENT: **Unclear ris**k Not described BLINDING: **Low risk** Study drug and placebo provided in identical syringes

		M 17, F 79 (82%) Mean age 41 years		Rescue medication available 2 h after initial dosing, provided it did not contain ergotamine	
Cady 1991 Study 1 and Study 2 2 separate identical trials DB, PC, PG-RCT All outcomes reported as pooled results from the 2 studies (Study 1 and Study 2)	Study 1: 574 Study 2: 530	Aged 18 years or over, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity > moderate). Participants excluded if previously treated with sumatriptan. Long-term prophylactic medications for migraine allowed. No opioids or ergotamine within 24 h, or simple analgesics within 6 h of taking study medication. Study 1: Sumatriptan 6 mg, n = 384 Placebo, n = 190 M 73, F 501 (87%) Mean age 40 years Study2: Sumatriptan 6 mg, n = 350 Placebo, n = 180	Assessment up to 2 h	Sumatriptan s.c. Vs Placebo Single dose to treat single attack, with the option of a second randomised dose of study medication or placebo if pain relief was inadequate at 1 h Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication available at the discretion of the investigator if migraine persisted 1 h after second dose of study medication	RANDOMIZATION: **Unclear ris**k Not described ALLOCATION CONCEALMENT: **Low ris**k Allocation based on chronological order that patients presented for treatment BLINDING: **Unclear ris**k Not described

		M 53, F 477 (90%) Mean age 39 years Proportion with/without aura not reported			
Cady 1993 DB, PC, CO-RCT	170	Aged 18 years or over, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity > moderate). No ergotamine or analgesics containing opioid derivatives within 24 h, or simple analgesics or antiemetics within 6 h of taking study medication Each treatment separated by a pain-free interval of at least 24 h 120 treated all 4 attacks Sumatriptan 6 mg, n = 166 (128 treating first attack with moderate or severe baseline pain intensity) Placebo, n = 144 (42 treating first attack with moderate or severe baseline pain intensity) M 15, F 155 (91%) Mean age 41 years	Assessment up to 1.5 h	Sumatriptan s.c. Vs Placebo Single dose to treat each of 4 consecutive attacks (3 with sumatriptan, 1 with placebo). Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication available after 1.5 h	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: **Low risk** Placebo injections designed to match the active dose

Cady 1998 DB, PC, PG-RCT	135	Aged 18 years or over, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity > moderate) with an average of 1 to 6 attacks per month. Participants had to have treated at last 1 disabling migraine in the workplace in the past 60 days, and had to be working 8-hour (minimum) shifts at their jobs No monoamine oxidase inhibitors within 2 weeks of screening. No ergotamine-containing medications or sumatriptan within 24 h, and no analgesics, antiemetics, or other acute migraine medications within 6 h of taking study medication. Participants were excluded if they had previously used sumatriptan (any formulation) 132 for efficacy Sumatriptan 6 mg, n = 67 Placebo, n = 68 (65 for efficacy) M 20, F 112 (85%) Mean age 40 years Without aura 69%	Assessment up to 2 h	Sumatriptan s.c. Vs Placebo Single dose to treat single attack. Medication administered when migraine headache of moderate or severe intensity occurred within the first 4 h of a minimum 8 h work shift Rescue medication (with the exception of ergotamine-containing medications or sumatriptan) available after 2 h for intolerable pain Second dose of study medication available to treat recurrence in the workplace, provided no use of rescue medication had occurred	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: **Low risk** Matching placebo

Dahlof 1998 DB, PC, PG-RCT	335	Aged 18 to 55 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity > moderate) with an average of 1 to 6 attacks per month. Participants were excluded if they had previously received subcutaneous sumatriptan Migraine prophylactic therapy stopped at least 2 weeks before the administration of study treatment No ergotamine-containing preparations within 24 h, or analgesics within 6 h of receiving study medication Sumatriptan 6 mg, n = 47 Naratriptan 0.5 mg, n = 60 Naratriptan 1 mg, n = 55 Naratriptan 2.5 mg, n = 42 Naratriptan 5 mg, n = 34 Naratriptan 10 mg, n = 34 Placebo, n = 63 M 47, F 288 (86%) Mean age 38 years Without aura 89%	Assessment up to 4 h	Sumatriptan 6mg s.c. Vs Naratriptan 0.5 mgs.c vs Naratriptan 1 mg s.c. vs Naratriptan 2.5 mg s.c. vs Naratriptan 5 mg s.c. vs Naratriptan 10 mg s.c. vs Placebo Single dose to treat single attack. Medication administered when migraine headache pain was of moderate to severe intensity Rescue medication (excluding ergotamine-containing therapy) was available after 4 h for inadequate relief of symptoms	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: **Unclear risk** Not reported
Diener 1999	278	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or	Assessment up to 2 h	Sumatriptan 6 mg s.c. vs	RANDOMIZATION: **Unclear risk** Not reported

DB, double-dummy, PC, PG-RCT		without aura. At least 1-year history of migraine (untreated severity > moderate) with an average of 2 to 6 attacks per month. No analgesics or migraine drugs within 24 h of study medication administration. No use of compound analgesics, sumatriptan, ergotamine tartrate, DHE, codeine, or barbiturates for more than 10 days per month prior to screening. 275 for efficacy Sumatriptan 6 mg, n = 114 Intravenous acetylsalicylic acid lysinate 1.8 g, n = 119 Placebo, n = 42 M 55, F 220 (80%) Mean age 41 years Without aura 67%		Intravenous acetylsalicylic acid lysinate 1.8 g vs Placebo Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication available after 2 h	ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: **Low risk** double dummy
Diener 2001 DB, PC, PG-RCT	924	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity > moderate) with an average of 1 to 6 attacks per month. Each treated attack associated with 1 of the following symptoms: nausea,	Assessment up to 2 h	Sumatriptan 6 mg s.c. Vs Alniditan 1.4 mg s.c. vs Alniditan 1.8 mg s.c. vs Placebo Single dose to treat single attack.	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: **Unclear risk** Not reported

		vomiting, photophobia, or phonophobia Participants were excluded if they used acute migraine medication (ergotamine, ergot-derivatives, sumatriptan, aspirin, or NSAIDs) for more than 10 days per month No long-term prophylactic migraine therapy with methysergide, tricyclic antidepressants, or monoamine oxidase inhibitors (although prophylactic therapy with flunarizine, pizotifen, or beta-blockers started before the trial was not a reason for exclusion) Sumatriptan 6 mg, n = 317 Alniditan 1.4 mg, n = 309 Alniditan 1.8 mg, n = 141 Placebo, n = 157 (156 for efficacy) M 126, F 798 (86%) Mean age 41 years Without aura 86%		Medication administered when migraine headache pain was of moderate or severe intensity, after any aura symptoms had resolved Rescue medication (excluding sumatriptan and ergotamine-derivatives) was available after 2 h if needed	
Facchinetti 1995 DB, PC, PG-RCT	226	Female participants, aged 18 to 50 years, meeting IHS criteria for migraine (1988) without aura. At least 6-month history of migraine occurring -3 to +5 days relative to the first day of menstruation and a history of regular menstrual cycles.	Assessment up to 24 h	Sumatriptan 6 mg s.c. vs Placebo Single dose to treat each of 2 attacks	RANDOMIZATION: **Low risk** Computer-generated randomisation scheme ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING:

		169 for first dose efficacy assessment with moderate or severe baseline pain intensity Sumatriptan 6 mg, n = 115 (77 for first dose efficacy with moderate or severe baseline pain intensity) Placebo, n = 111 (92 for first dose efficacy with moderate or severe baseline pain intensity) F 226 Mean age 37 years 3% to 6% of subjects with aura (included in efficacy analyses)		Second dose of study medication available to treat recurrence within 24 h Rescue medication (excluding ergotamine-containing preparations or sumatriptan) available if relief was inadequate after 2 h	**Low risk** Matching placebo-filled syringes Study
Ferrari 1991 DB, PC, PG-RCT	639	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity > moderate) with a maximal frequency of 6 attacks per month. No prophylaxis for migraine within 2 weeks, ergot-containing preparations within 24 h, or simple analgesics/ NSAIDs within 6 h of taking study medication 636 for efficacy Sumatriptan 6 mg, n = 423 (422 for efficacy)	Assessment up to 24 h	Sumatriptan 6 mg s.c. Vs Sumatriptan 8 mg s.c. Vs Placebo Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity Second blinded and re-randomised dose of study medication available if,	RANDOMIZATION: **Low risk** Computer-generated randomisation scheme ALLOCATION CONCEALMENT: **Low risk** Patients were entered in ascending sequential order at each centre BLINDING: **Low risk** Placebo was supplied in matching ampoules containing isotonic saline solution

		Sumatriptan 8 mg, n = 110 (109 for efficacy) Placebo, n = 106 (105 for efficacy) M 118 F 521 (82%) Mean age 40 years Without aura 70%		after 1 h, the patient was not completely pain-free Rescue medication (excluding ergotamine and dihydroergotamine) available after 2 h if symptoms were not improved at this time	
Gross 1994 DB, PC, PG-RCT	86	Aged 18 to 65, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity > moderate) with an average of 1 to 6 attacks per month. Participants were excluded if they had previously used sumatriptan to treat more than 6 migraine attacks Sumatriptan 6 mg, n = 60 (48 with moderate or severe baseline pain intensity) Placebo, n = 26 (18 with moderate or severe baseline pain intensity) M 17, F 69 (82%) Mean age 44 years Without aura 70%	Assessment up to 2 h	Sumatriptan 6 mg s.c. vs Placebo Single dose to treat single attack. Second dose of study medication available for inadequate relief after 1 h or for recurrence between 1 and 24 h Alternative rescue medication (excluding ergotamine-containing medications) available 1 h after the second dose of study medication if migraine relief still inadequate	**Does not meet our inclusion criteria (n<40/study group)**

Henry 1993 DB, PC, PG-RCT	76	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura Participants were required to have been treating with oral dihydroergotamine correctly for migraine prophylaxis for at least 1 month, which could be maintained at the same dose schedule for the duration of the study Sumatriptan 6 mg, n = 37 Placebo, n = 39 M 10 F 66 (87%) Mean age 43 years	Assessment up to 4 h	Sumatriptan 6 mg s.c. vs Placebo Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity Second identical dose of study medication available after 1 h if participants had inadequate relief or for recurrence between 2 and 24h Alternative rescue medication (non-ergotamine) was available after 2 h for either inadequate relief or recurrence	**Does not meet our inclusion criteria (n<40/study group)**
Jensen 1995 2-phase study Phase 1: DB, PC, CO-RCT	118	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. History of 1 to 6 moderate or severe migraine attacks per month.	Assessment up to 2 h	Sumatriptan 6 mg s.c. vs Placebo Single dose	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: **Unclear risk** Not reported

Phaser 2: OL		Participants were excluded if they had previous experience with subcutaneous sumatriptan No ergotamine in the 24-h period before taking study medication or within 6 h afterwards 108 treated both attacks Sumatriptan 6 mg, n = 117 attacks Placebo, n = 109 attacks M 12, F 106 (90%) Mean age 43 years		to treat each of 2 successive migraine attacks. Medication administered when migraine headache pain was of moderate or severe intensity Second dose of study medication (identical to first dose) available to treat recurrence between 2 and 24h Rescue medication (except ergotamine) available if initial treatment not effective within 2 h	
Mathew 1992 DB, PC, PG-RCT	242	Aged 18 or older, meeting IHS criteria for migraine (1988) with or without aura No use of analgesic or ergot-containing medication within the previous 24 h (or 6 h for simple analgesics) Migraine prophylaxis was allowed Sumatriptan 1 mg, n = 30 Sumatriptan 2 mg, n = 30	Assessment up to 4 h	Sumatriptan 1 mg Vs Sumatriptan 2 mg Vs Sumatriptan 3 mg Vs Sumatriptan 4 mg Vs Sumatriptan 6 mg Vs Sumatriptan 8 mg Vs Placebo	**Does not meet our inclusion criteria (n<40/study group)**

		Sumatriptan 3 mg, n = 30 Sumatriptan 4 mg, n = 30 Sumatriptan 6 mg, n = 30 Sumatriptan 8 mg, n = 30 Placebo, n = 62 M 32, F 210 (87%) Mean age 38 years Without aura 80 %		Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication (excluding ergot-containing drugs) were available at the discretion of the investigator beginning 1 h after dosing. Scores were adjusted for use of rescue medications by carrying the last observation (before rescue) forward. Headache relief could not be achieved if rescue medication was used.	
Mushet 1996 Study 1 and Study 2 with identical procedure DB, PC, PG-RCT		Aged 18 to 65, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine with an average of 1 to 6 attacks per month during the 2 months before screening. Participants were excluded if they had ever used subcutaneous sumatriptan, although use of oral	Assessment up to 2 h	Sumatriptan 6 mg s.c. vs Placebo Single dose to treat single attack. Rescue medication available after 2 h for	**Does not meet our inclusion criteria (n<40/study group)**

	<u>Study 1:</u> 80 <u>Study 2:</u> 78	sumatriptan was not a reason for exclusion Any chronic use of migraine prophylaxis, calcium channel blockers, tricyclic antidepressants, beta- blockers, and serotoninergics was required to remain unchanged for the duration of the study <u>Study 1</u> Sumatriptan 6 mg, n = 40 Placebo, n = 39 M 11, F 69 (86%) Mean age 40 years Without aura 68% <u>Study 2:</u> Sumatriptan 6 mg, n = 40 Placebo, n = 39 All participants had moderate or severe baseline pain intensity M 10, F 68 (87%) Mean age 39 years Without aura 62%		participants who had not yet experienced headache relief	
Pfaffenrath 1991 DB, PC, PG-RCT	235	Aged 18 to 65, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine with a maximum of 6 attacks per month.	Assessment up to 2 h	Sumatriptan 6 mg s.c. vs Placebo Single dose to treat single	RANDOMIZATION: **Low risk** Computer-generated randomisation scheme ALLOCATION CONCEALMENT:

		Participants receiving migraine prophylaxis were required to withdraw from prophylactic therapy at least 2 weeks prior to randomisation Ergotamine preparations were not to be used within 24 h of taking test medication 216 with moderate or severe baseline pain intensity Sumatriptan 6 mg, n = 155 (147 with moderate or severe baseline pain intensity) Placebo, n = 80 (69 with moderate or severe baseline pain intensity) M 43, F 192 (82%) Mean age 41 years Without aura 65%		attack. Medication administered when migraine headache pain was of moderate or severe intensity Second dose of study medication available after 1 h if participants had inadequate relief Alternative rescue medication (excluding ergotamine) was available if relief was still inadequate after 2 h	**Low risk** Patients were entered in ascending sequential order at each centre BLINDING: **Low risk** Placebo was supplied in matching syringes
Russell 1994 DB, PC, CO-RCT	230	Aged 18 to 65, with GP diagnosed migraine. At least 6-month history of migraine (untreated severity > moderate) with an average of 1 to 6 attacks per month. Participants were excluded if they had previously used sumatriptan or were currently using migraine prophylactic agents	Assessment up to 2 h	Sumatriptan 6 mg s.c. vs Placebo Single dose to treat each of 2 successive attacks	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: **Unclear risk** Not reported

		209 treated both attacks Sumatriptan 6 mg, n = 209 Placebo, n = 209 M 20, F 189 (90%) Mean age 44 years Without aura 65% Approximately 1% of participants had mild baseline pain intensity when study medication was administered		Second dose of study medication available after 2 h for participants not completely free from headache, or experiencing recurrence of headache within 24 h Rescue medication (non-ergotamine) was available 1 h after second injection if symptom relief remained inadequate	
S2BM03 DB, PC, CO-RCT	120	Aged 18 to 65, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity > moderate) with a frequency of 1 to 6 attacks per month. Participants required to have a history of attacks (> 50% of attacks) that progressed from mild to moderate or severe intensity in a 60 minutes from attack onset In addition participants had to have used sumatriptan regularly for at least 6 months before study entry and experience recurrence in >>50% of attacks treated with sumatriptan	Assessment up to 72 h	Sumatriptan 6 mg s.c. vs Placebo Each participant received 2 doses; 1 of either sumatriptan or placebo at the onset of migraine and the other at 4 h Five optional open-label doses of sumatriptan 6 mg were available from 6 to 72 h for the treatment of recurrent headache, although no more than 2 doses of sumatriptan were	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: **Unclear risk** Not reported

		At least a 48 h washout period (sumatriptan-free) required between the 2 treated attacks No ergotamine-containing prophylactic medication, or use of monoamine oxidase inhibitors, 5-hydroxtryptamine reuptake inhibitors, or lithium during the study period 90 treated both attacks and provided cross-over efficacy data Sumatriptan 6 mg, n = 106 (90 for cross-over efficacy analysis, of which 87 had moderate or severe baseline pain intensity) Placebo, n = 106 (90 for cross-over efficacy analysis, of which 81 had moderate or severe baseline pain intensity) M 13, F 77 (86%) Mean age 45 years		permitted in any 24 h period Rescue medication was permitted from 6 h after the first dose of study medication. No further open-label sumatriptan was permitted if rescue medication was used.	
Sang 2004 Triple-blind, PC, PG-RCT	44	Aged 18 years or older, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity > moderate) with an average of 1 to 15 attacks per month. Sumatriptan 6 mg, n = 15	Assessment up to 24 h	Sumatriptan 6 mg vs Intravenous LY293558 1.2 mg/kg vs Placebo Single dose to treat single attack.	**Does not meet our inclusion criteria (n<40/study group)**

		Intravenous LY293558 1.2 mg/kg, n = 13 Placebo, n = 16 (15 with moderate or severe baseline pain intensity) M 20, F 24 (55%) Mean age 40 years Without aura 89%		Medication administered when migraine headache pain was of moderate or severe intensity	
Schulman 2000 DB, PC, PG-RCT	119	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity O4> moderate) with an average of 1 to 6 attacks per month, and at least 1 debilitating migraine treated in the workplace within 2 months of study enrolment. Participants were required to be employed outside their homes, work a minimum of an 8 h shift, and be willing to self-treat a migraine at work with an injection Participants were excluded if they were currently receiving monoamine oxidase inhibitors or had previously taken sumatriptan. Participants were not to have taken any analgesics, antiemetics, or other acute migraine medications within 6 h before use of study medication	Assessment up to 2 h	Sumatriptan 6 mg s.c. vs Placebo Single dose to treat single attack. Medication administered to treat the next moderate or severe migraine that occurred in the workplace during the first 4 h of an 8 h workday Rescue medication (excluding ergotamine, ergot-containing medications or other sumatriptan preparations) available after 2 h if needed	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Low risk** Patients assigned a treatment number in chronological order as they were screened, each treatment number corresponded to a number on the label of unassigned trial medication BLINDING: **Low risk** Matching placebo; identical packaging and double-blind medication labels

		116 for efficacy Sumatriptan 6 mg, n = 76 (for efficacy) Placebo, n = 40 (for efficacy) M 14, F 105 (88%) Mean age 40 years Without aura 73%			
SUM40286 DB, PC, PG-RCT	299	of migraine with 1 to 6 attacks per month, and awakening with at least 1 moderate or severe migraine during the 3 months preceding screening. Participants were excluded if they experienced tension-type headache on 15 or more days per month in any of the 3 months before screening. Participants had to have successfully treated a migraine attack in the past with a 5-HT1 agonist, although participants must not have used a subcutaneous formulation of a 5-HT1 agonist previously 297 for efficacy Sumatriptan 6 mg, n = 146 (145 for efficacy) Placebo, n = 153 (152 for efficacy)	Assessment up to 2 h	Sumatriptan 6 mg s.c. vs Placebo Single dose to treat single attack. Medication administered within 1 h of awakening with moderate or severe migraine pain, provided the pain continued to be moderate or severe by the time of dosing Second dose of study medication, up to 100 mg of oral sumatriptan, or alternative rescue medication (usual migraine therapy) was available after 2 h if relief from initial dose was inadequate	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: **Unclear risk** Not reported

		M 50, F 247 (83%) Mean age 41 years			
SUM40287 DB, PC, PG-RCT	288	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine with 1 to 6 attacks per month, and awakening with at least 1 moderate or severe migraine during the 3 months preceding screening. Participants were excluded if they experienced tension-type headache on 15 or more days per month in any of the 3 months before screening. Participants had to have successfully treated a migraine attack in the past with a 5-HT1 agonist, although participants must not have used a subcutaneous formulation of a 5-HT1 agonist previously 287 for efficacy Sumatriptan 6 mg, n = 149 (148 for efficacy) Placebo, n = 139 M 38, F 249 (87%) Mean age 39 years	Assessment up to 2 h	Sumatriptan 6 mg s.c. vs Placebo Single dose to treat single attack. Medication administered within 1 h of awakening with moderate or severe migraine pain, provided the pain continued to be moderate or severe by the time of dosing. Second dose of study medication, up to 100 mg of oral sumatriptan, or alternative rescue medication (usual migraine therapy) was available after 2 h if relief from initial dose was inadequate.	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: **Unclear risk** Not reported

Winner 2006 Study 1 and Study 2 identically designed DB, PC, PG-RCT		Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine with 1 to 6 attacks per month, and had awakened with moderate or severe migraine pain at least once in the 3 months preceding screening. No migraine prophylactic medication containing ergotamine, an ergot derivative, or methysergide, and no use of a monoamine oxidase inhibitor within 2 weeks before the studies. Participants were eligible for the studies only if they had previously treated a migraine successfully with a 5-HT1B/1D agonist, but participants who had previously used subcutaneous sumatriptan were excluded No analgesics, antiemetics, or acute migraine medications from 6 h before through to 2 h after administration of study medication. No other 5-HT agonists within 24 h before or after use of study medication	Assessment up to 2 h	Sumatriptan 6 mg s.c. vs Placebo Single dose to treat single attack. Medication administered to treat a morning migraine (defined as a headache of moderate or severe intensity on awakening) within 1 hour of awakening Second dose of study medication or alternative rescue medication available after 2 h for participants with inadequate relief or for those experiencing recurrence within 24 h	RANDOMIZATION: **Low risk** Computer-generated randomisation schedule ALLOCATION CONCEALMENT: **Low risk** Remote allocation BLINDING: **Low risk** Matching inactive vehicle injection in identical prefilled single-dose syringe cartridges
	<u>Study 1:</u>	<u>Study1:</u>			

	299 <u>Study 2:</u> 288	297 for efficacy Sumatriptan 6 mg, n = 146 (145 for efficacy, 144 with moderate or severe baseline pain intensity) Placebo, n = 153 (152 for efficacy, 151 with moderate or severe baseline pain intensity) M 50, F 247 (83%) Mean age 41 years Without aura 61% <u>Study 2:</u> 287 for efficacy Sumatriptan 6 mg, n = 149 (148 for efficacy) Placebo, n = 139 M 38, F 249 (87%) Mean age 39 years Without aura 73%			

Remarks:

- Authors analysed studies using a single dose of sumatriptan in established pain of at least moderate intensity **separately** from studies in which medication was taken before pain was well established or in which a second dose of medication was permitted. The baseline headache intensity at which study medication was administered was largely consistent amongst the included studies, with the majority administering the study drug when migraine headache pain was of moderate or severe intensity. Two required participants to administer medication at the onset of aura (Bates 1994)

or migraine (S2BM03). Seven studies did not report the baseline headache intensity at which study medication was administered, but all of these studies were dominated by participants with moderate or severe migraine attacks at the time of dosing.

- The SR identifies and extra study S2BS78 that reported on a mixed population of participants treating either mild intensity headaches or moderate and severe intensity headaches, and failed to provide specific data for either population. Given the clinical heterogeneity between these two populations of participants, this study did not provide any data toward efficacy.
- The incidence of vomiting was very low in all studies and where reported did not permit analysis.
- Few of the included studies reported relief of functional disability and those that did were inconsistent in both the definition of relief used and the time point at which relief was measured. Data were not pooled for analysis.
- Not all studies reported baseline incidence of associated symptoms from which relief could be calculated. These studies were not pooled in the analysis. Five of the studies providing data on relief of associated symptoms (Cady 1993; Facchinetti 1995; Pfaffenrath 1991; Wendt 2006; Winner 2006 Study 1) included a small number (< 10%) of participants with mild baseline pain intensity.
- Regarding adverse events, the duration over which data were collected was not always specific, and where it was, there were differences between studies. There are also several inconsistency between studies, despite these inconsistencies, authors have included as much data as possible in the adverse event analyses in order to be more inclusive and conservative, but analyses of pooled data on adverse events should be interpreted cautiously.
- The SR also identifies studies comparing sumatriptan s.c. 4mg and 8mg vs placebo. We have not reported these data in the present document because these are not available doses in BE.
- Three studies (388 participants) provided data comparing sumatriptan 6 mg (with an optional second dose of sumatriptan 6mg if initial relief was inadequate after one hour) with placebo (with an optional second dose of placebo if initial relief was inadequate). This constitutes a different medication regiment which was not included in our methodology. These data are therefore not reported in this document.
- For most of the comparisons reported in this SR, data on specific adverse events were provided including chest pain/symptoms. As it was not explicitly described if this symptom refers to cardiovascular events no data were reported in the present document.
- Participants were generally excluded for: pregnancy or breastfeeding, inadequate contraception, confirmed or suspected cardiovascular or cerebrovascular disease (particularly history of ischaemic heart disease), uncontrolled hypertension (diastolic > 95 mmHg or systolic > 160 mmHg), current or past drug abuse, psychiatric illness, epilepsy, hepatic disease, Raynaud's syndrome, and/or opthalmoplegic, basilar or hemiplegic migraine.
- Pain intensity or pain relief had to be measured by the patient (not the investigator or carer). Authors considered only data obtained directly from the patient and accepted the following pain measures for the primary outcomes:
  • pain intensity: four-point categorical scale, with wording equivalent to none, mild, moderate, and severe; or 100 mm visual analogue scale (VAS);
  • pain relief: five-point categorical scale, with wording equivalent to none, a little, some, a lot, complete; or 100 mm VAS.

Author's conclusions:
"Subcutaneous sumatriptan is an effective treatment for the relief of headache pain, other symptoms associated with migraine, and functional disability, with single doses of 4 mg or more providing clinically useful levels of relief from as early as one hour after administration. Higher doses are effective in more individuals, but at the expense of greater numbers of adverse events. Most events were described as mild and of short duration. These data suggest that a 4 mg dose (where available) may be a sensible starting dose, with increase to 6 mg if the response is inadequate, and the higher dose is tolerated. There is no evidence that taking a second dose of sumatriptan 6 mg in the event of an inadequate response one hour after the initial dose has a significant impact on headache relief by two hours."
"There were no significant differences between relief at one hour and relief at two hours for any of the analysed associated symptoms."

12.6.8 Sumatriptan intranasal versus placebo for acute treatment of migraine attack in adults

Meta-analysis: Menshawy 2018, Intranasal sumatriptan for acute migraine attacks: a systematic review and meta-analysis

Definition of migraine: criteria defined by the International Headache Society (IHS)(second edition).

Inclusion criteria: We included all studies satisfying the following criteria: (1) Population: patients diagnosed with episodic migraine, with or without aura. (2) Intervention: sumatriptan NS (all doses, formulations, or delivery devices), (3) Comparator: placebo/active comparator nasal spray, (4) Outcomes: safety and efficacy parameters related to the treatment, and (5) Study design: randomized controlled trials (RCTs).

We excluded the following: (1) non-randomized trials, (2) in vitro and animal studies, and (3) studies whose data were unreliable for extraction and analysis (outcomes were not reported in a dichotomous format or those that did not describe numerical data for the control arm). Duplicates were removed and retrieved references were screened.

Search strategy: We searched PubMed, SCOPUS, Embase, and Cochrane CENTRAL through August 2016, using relevant keywords (Sumatriptan OR Sumatriptan succinate OR Succinate Sumatriptan OR Imitrex OR Imigran OR AVP-825 OR ONZETRA OR Xsail) AND (Migraine OR Migraine disorders OR Migraineur). All published articles were considered with no restrictions in terms of language. We searched the bibliography of included studies for additional relevant records.

Assessment of quality of included trials: yes

Other methodological remarks:
Data were pooled as risk ratios (RR) with 95% confidence intervals (CI), using the Mantel Haenszel (M-H) method. When a significant heterogeneity was present, the analysis was conducted under the random effects model; otherwise, the fixed effect model was used

Ref	Comparison	N/n	Outcomes	Result
Menshawy 2018 Design: SR+MA Search date: August 2016	Sumatriptan intranasal Vs Placebo		Pain free at 2h	**R = 1.70, 95% CI [1.31 to 2.21]** p < 0.0001 **SS in favour of intranasal sumatriptan** I^2: 53%
			Pain free at 1h	**RR = 1.56, 95% CI [1.10, 2.21]** p = 0.01 **SS in favour of intranasal sumatriptan** I^2: 35%
		N = 2 n = 310 (Cady 2014, Rao 2016)	Sustained pain-free over 24h	RR = 2.21, 95% CI [1.33, 3.68] p = 0.002 **SS in favour of intranasal sumatriptan** I^2: 0%

			Headache relief at 1h	RR = 1.47, 95%CI [1.24, 1.73] p < 0.00001 **SS in favour of intranasal sumatriptan** I^2: 59%
			Headache relief at 2 h	RR = 1.58, 95%CI [1.35, 1.84] p < 0.00001 **SS in favour of intranasal sumatriptan** I^2: 69%
			Meaningful relief	RR = 1.66, 95% CI [1.41, 1.95] p < 0.00001 **SS in favour of intranasal sumatriptan** I^2: 0%
			Disability-free patients at 1h	RR = 1.17, 95% CI [0.98, 1.41] p = 0.08 **NS** I^2: 69%
			Disability-free patients at 2 h	RR = 1.38, 95% CI [1.20, 1.60] p < 0.00001 **SS in favour of intranasal sumatriptan** I^2: 45%

			Use of rescue medication at 2h	RR = 0.75, 95%CI [0.60, 0.94] p = 0.01 **SS in favour of intranasal sumatriptan** I^2: 35%
			Adverse events	RR = 2.54, 95% CI [1.66, 378] p < 0.0001 **SS in favour of placebo** I^2: 64%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Rao 2016 **CO-RCT**	54	Patients were > 18 years of age, with migraine (according to the International Classification of Headache Disorders, 2nd edition) for at least 1 year, and experienced 2 to 10 migraine attacks per month		Ketorolac 31.5 mg NS Vs Sumatriptan 20 mg NS VS Placebo NS	RANDOMIZATION: Low risk ALLOCATION CONCEALMENT: Low risk BLINDING: Low risk INCOMPLETE OUTCOME DATA: Low risk REPORTING: Low risk OTHER: High risk: Funded by drug company.

Cady 2014 RCT	212	Males and females, 18 to 65 years of age, diagnosed with migraine with or without aura, according to the International Classification of Headache Disorders, 2nd Edition 108 vs 104		Sumatriptan 22 mg (bidirectional delivery system: AVP-825) Vs Placebo (bidirectional delivery system: AVP-825)	RANDOMIZATION: Low risk ALLOCATION CONCEALMENT: Low risk BLINDING: Low risk INCOMPLETE OUTCOME DATA: Low risk REPORTING: Low risk OTHER: High risk: Funded by drug company.
Djupesland 2010 PG-RCT	117	Migraineurs, 18 to 65 years of age, who had migraine with or without aura, according to the International Headache Society (IHS) criteria 39 vs 39 vs 39		Sumatriptan 10 mg (bidirectional delivery system: OptiNose) Vs Sumatriptan 20 mg (bidirectional delivery system: OptiNose) Vs Placebo (bidirectional delivery system: OptiNose)	RANDOMIZATION: Unclear risk: not described ALLOCATION CONCEALMENT: Low risk BLINDING: Low risk INCOMPLETE OUTCOME DATA: Low risk REPORTING: Low risk OTHER: Unclear risk
Wang 2007 PG-RCT	56	Migraineurs, 18 to 65 years of age, who had migraine with or without aura according to the IHS criteria 28 vs 28		Sumatriptan 20 mg NS Vs Placebo NS	RANDOMIZATION: Low risk ALLOCATION CONCEALMENT: Low risk BLINDING: Low risk

					INCOMPLETE OUTCOME DATA: Low risk REPORTING: Low risk OTHER: Unclear risk
Winner 2006 PG-RCT	731	Migraineurs, 12 to 17 years of age who had a history of migraine of at least 6 months duration (with or without aura) in accordance with the IHS criteria 250 vs 237 vs 244		Sumatriptan 5 mg NS Vs Sumatriptan 20 mg NS Vs Placebo NS	RANDOMIZATION: Low risk ALLOCATION CONCEALMENT: Unclear risk: not reported BLINDING: Low risk INCOMPLETE OUTCOME DATA: Low risk REPORTING: Low risk OTHER: Unclear risk
Ahonen 2004 CO-RCT	94	Migraineurs were between 8 and 17 years old, body weight of 20 to 35 kg, headache fulfilling the IHS criteria for migraine with or without aura		Sumatriptan NS Vs Placebo NS	RANDOMIZATION: Low risk ALLOCATION CONCEALMENT: Low risk BLINDING: Low risk INCOMPLETE OUTCOME DATA: Low risk REPORTING: Low risk OTHER: Unclear risk

S2B-340 PG-RCT	763	Patients were 18 to 65 years of age, meeting the IHS criteria for migraine (1988) with or without aura, with at least 1-year history of migraine and an average of 1 to 6 attacks 305 vs 302 vs 156		Sumatriptan 10 mg NS Vs Sumatriptan 20 mg NS Vs Placebo NS	RANDOMIZATION: Unclear risk: not reported ALLOCATION CONCEALMENT: Unclear risk: not reported BLINDING: Unclear risk: not reported INCOMPLETE OUTCOME DATA: Unclear risk: not reported REPORTING: Unclear risk: not reported
Peikert 1999 PG-RCT	584	Male and female migraineurs, aged between 18 and 65 years, with a migraine history of at least 1 year and on average over the last 12 months had experienced between 1 and 6 attacks per month, with or without aura, according to the IHS criteria 123 vs 122 vs 155 vs 120 vs 64		Sumatriptan 2.5 mg NS Vs Sumatriptan 5 mg NS Vs Sumatriptan 10 mg NS Vs Sumatriptan 20 mg NS Vs Placebo NS	RANDOMIZATION: Low risk ALLOCATION CONCEALMENT: Low risk BLINDING: Low risk INCOMPLETE OUTCOME DATA: Low risk REPORTING: Low risk OTHER: Unclear risk
Diamond 1998 PG-RCT	1086	Men or women (between 18 and 65 years of age) with a 1-year or longer history of migraine with or without aura, diagnosed according to the IHS criteria 299 vs 296 vs 292 vs 199		Sumatriptan 5 mg NS Vs Sumatriptan 10 mg NS VS Sumatriptan 20 mg NS Vs Placebo NS	RANDOMIZATION: Low risk ALLOCATION CONCEALMENT: Unclear risk: not reported BLINDING: Low risk INCOMPLETE OUTCOME DATA: Low risk REPORTING:

					Low risk OTHER: High risk: Funded by drug company
Ryan 1997 (study 1 and study 2) PG-RCT	845	Men or women (aged 18 and 65 years) with a 1-year history of migraine with or without aura diagnosed according to the IHS criteria in 2 studies: 202, 215, 106, 109 , 101, 112		Sumatriptan 10 mg NS VS Sumatriptan 20 mg NS Vs Placebo NS	RANDOMIZATION: Low risk ALLOCATION CONCEALMENT: Unclear risk: not reported BLINDING: Low risk INCOMPLETE OUTCOME DATA: Low risk REPORTING: Low risk OTHER: High risk: Funded by drug company
Salonen 1994 PG-RCT (two studies)	455	Patients were 18 to 65 years of age, meeting the IHS criteria for migraine (1988), with or without aura, and at least 1-year history of migraine and an average of 6 attacks per month in 2 studies 40, 42, 40, 41, 42, 40 34, 33, 36, 40, 35, 32		Sumatriptan 1 mg NS Vs Sumatriptan 5 mg NS Vs Sumatriptan 10 mg NS Vs Sumatriptan 20 mg NS Vs Sumatriptan 40 mg NS Vs Placebo NS	RANDOMIZATION: Low risk ALLOCATION CONCEALMENT: Low risk BLINDING: Low risk INCOMPLETE OUTCOME DATA: Low risk REPORTING: Low risk OTHER: Unclear risk
Salonen 1991 PG-RCT	74	Patients were 18 to 65 years of age, meeting the IHS criteria for migraine (1988), with or without aura,		Sumatriptan 40 mg NS Vs Placebo NS	RANDOMIZATION: Low risk ALLOCATION CONCEALMENT:

		without narcotic analgesics or ergotamine use within the previous 24 h, or any other analgesics within the 6 h before administration of study medication 37 vs 37			Unclear risk: not reported BLINDING: Low risk INCOMPLETE OUTCOME DATA: Low risk REPORTING: Low risk OTHER: Unclear risk

Remarks:

- No details were provided on the studies contributing to each individual outcome. It was therefore not possible to determine the number of patients included in the analysis.
- These results are from pooled studies using different sumatriptan dosages going from 1mg to 40mg. Different delivery system were also pooled.
- In all these studies most patients were females, and most of them had a migraine headache without aura of a moderate-to-severe degree.
- Winner et al. recruited adolescent migraineurs (with a mean age of 14 years) and Ahonen et al. recruited migraineurs within an age range of 8 to 17 years.

Author's conclusions:

"In conclusion, intranasal sumatriptan is effective for the treatment of acute migraine attacks. However, it was associated with a six-fold increase in the risk of taste disturbance, compared to the placebo.

Future RCTs are recommended to provide head-to-head comparison of different administration routes and drug formulations of sumatriptan."

12.6.9 Zolmitriptan versus placebo for acute treatment of migraine attack of moderate or severe pain intensity at baseline in adults

Meta-analysis: Bird 2014 (158), Zolmitriptan for acute migraine attacks in adults.
Definition of migraine: We used the definition of migraine specified by the International Headache Society (IHS 1988; IHS 2004), although we accepted diagnostic criteria equivalent to those of IHS 1988 where a specific reference was not provided.

Inclusion criteria: We included randomised, double-blind, placebo- and/or active controlled studies using oral sumatriptan to treat a migraine headache episode. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data for at least one of the outcomes specified below. We accepted studies reporting treatment of consecutive headache episodes if outcomes for the first, or each, episode were reported separately. Cross-over studies were accepted if there was adequate washout (N 48 hours) between treatments.

Population : Studies enrolled adults (at least 18 years of age) with migraine. There were no restrictions on migraine frequency, duration, or type (with or without aura). Participants taking stable prophylactic therapy to reduce migraine frequency were accepted. All included studies used one or more of these standard scales (reported in remarks) and reported outcomes as defined above.

Exclusion: We excluded studies designed to demonstrate prophylactic efficacy in reducing the number or frequency of migraine headaches.

Search strategy: We searched the following electronic databases: • the Cochrane Central Register of Controlled Trials (CENTRAL), *The Cochrane Library* (Issue 3 of 12, 2014). • MEDLINE (via Ovid) (1990 to 12 March 2014). • EMBASE (via Ovid) (1990 to 12 March 2014). • Oxford Pain Relief Database, searched on 22 May 2013.
Searches of MEDLINE and EMBASE started in 2009 because we were looking only for randomised controlled trials and these two databases are routinely searched and all controlled trials added to CENTRAL. This may not capture studies that have been published or indexed in the previous year, but searching back to 2009 provided a considerable overlap. We did not apply any language restrictions.
We searched for additional studies in reference lists of retrieved studies and review articles, and in three clinical trials databases (www.astrazenecaclinicaltrials.com, www.clinicaltrials.gov, and apps.who.int/trialsearch). AstraZeneca, the manufacturer of Zomig, provided a database search of publications relating to zolmitriptan in migraine; no mention of unpublished data was made. No studies, published or unpublished, were identified in the list they provided that were not identified by our searches.

Assessment of quality of included trials: yes

Other methodological remarks:
We accepted randomisation to the individual patient only.
For analysis of studies with more than one treatment arm contributing to any one analysis (for example two formulations of the same dose of zolmitriptan in the same study with a single placebo group), we would split the placebo group equally between the two treatment arms so as not to double-count placebo participants.

Where participants treated more than one attack we used first attack data preferentially. When that was not reported we have used data from combined attacks and have considered how this might fect the results. The most likely source of missing data was in cross-over studies; we planned to use only the first-period data where possible, but where that was not provided we treated the results as if they were parallel group results. For all outcomes we carried out analyses, as far as possible, on a modified intention-to-treat (ITT) basis. Where suHicient information was reported, we re-included missing data in the analyses we undertook. We planned to exclude data from outcomes where data from 10% or more of participants were missing with no acceptable reason provided or apparent. We calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants. Relative risk (RR) of benefit ('relative benefit') or harm ('relative risk') was calculated with 95% confidence intervals (CIs) using a fixed-effect model. We calculated NNT, NNTp, and NNH with 95% CIs, where possible, using the pooled number of events by the method of Cook and Sackett.

Ref	Comparison	N/n	Outcomes	Result
Bird 2014 Design: SR+MA Search date: March 2014	Zolmitriptan 2.5 mg (mainly **oral** formulations) Vs Placebo	N = 11 n = 5825 (attacks) (Charlesworth 2003, Dib 2002, Dowson 2002, Loder 2005, Pascual 2000, Rapoport 1997, Ryan 2000, Sakai 2002, Solomon 1997, Steiner 2003,	Pain free at 2h (PO)	Zolmitriptan: 30% (1030/3455) Placebo: 10% (243/2370) **RR (95% CI): 3.0 (2.6 to 3.5)** NNT (95% CI): 5.1 (4.7 to 5.7). **SS in favour of zolmitriptan** I^2: 33%

		Tuchman 2006)		
		N = 11 n = 4904 (attacks) (311CIL/0099 2000, Charlesworth 2003, Dib 2002, Dowson 2002, Loder 2005, Pascual 2000, Rapoport 1997, Ryan 2000, Sakai 2002, Spierings 2004, Tuchman 2006)	Pain relief at 2h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	Zolmitriptan: 60% (1758/2921) Placebo: 29% (584/1983) **RR (95% CI): 2.1 (1.9 to 2.2)** NNT (95% CI): 3.3 (3.0 to 3.6). **SS in favour of zolmitriptan** I^2: 45%
		N = 2 n = 984	Sustained pain-free over 24h (PO) (Pain-free within two hours, with no use of rescue medication or recurrence	Zolmitriptan: 19% (129/694) Placebo: 6% (16/290) **RR (95% CI): 3.5 (2.1 to 5.8)**

		(Pascual 2000, Steiner 2003)	of moderate to severe pain within 24 hours.)	NNT (95% CI): 7.7 (6.0 to 11) **SS in favour of** zolmitriptan I^2: 0%
		N = 4 n = 2059 (attacks) (Charlesworth 2003, Rapoport 1997, Sakai 2002, Steiner 2003)	Sustained pain relief over 24 h (PO) (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.)	Zolmitriptan: 39% (557/1436) Placebo: 14% (85/623) **RR (95% CI): 2.9 (2.4 to 3.6)** NNT (95% CI): 4.0 (3.5 to 4.7) **SS in favour of zolmitriptan** I^2: 0%
		N = 7 n = 2140 (Charlesworth 2003, Dowson 2002, Loder 2005, Pascual 2000, Rapoport 1997, Sakai 2002, Steiner 2003)	Relief of nausea at 2h	Zolmitriptan: 662/1250 Placebo: 322/890 **RR (95% CI): 1.53 (1.37 to 1.69)** **SS in favour of zolmitriptan** I^2: 42%
		N = 7 n = 2700 (Charlesworth 2003, Dowson 2002, Loder 2005, Pascual	Relief of photophobia at 2h	Zolmitriptan: 790/1558 Placebo: 300/1142 **RR (95% CI): 1.99 (1.78 to 2.23)** **SS in favour of zolmitriptan** I^2: 70%

		2000, Rapoport 1997, Sakai 2002, Steiner 2003)		
		N = 6 n = 2068 (Charlesworth 2003, Dowson 2002, Loder 2005, Pascual 2000, Sakai 2002, Steiner 2003)	Relief of phonophobia at 2h	Zolmitriptan: 607/1138 Placebo: 249/930 **RR (95% CI): 2.03 (1.8 to 2.3)** **SS in favour of zolmitriptan** I^2: 77%
		N = 12 n = 6055 (attacks) (Charlesworth 2003, Dib 2002, Dowson 2002, Klapper 2004, Loder 2005, Pascual 2000, Rapoport 1997, Ryan 2000, Sakai 2002, Solomon 1997, Steiner	Adverse events	Zolmitriptan: 32% (1167/3628) Placebo: 17% (422/2427) **RR (95% CI): 1.7 (1.6 to 1.9)** NNH (95% CI): 6.8 (5.9 to 7.9) **SS in favour of placebo (more with zolmitriptan)** I^2: 74%

		2003, Tuchman 2006)		
		N = 6 n = 2784 Dib 2002, Klapper 2004, Loder 2005, Rapoport 1997, Ryan 2000, Tuchman 2006)	Vasodilation/warm feeling	Zolmitriptan: 38/1566 Placebo: 13/1218 **RR (95% CI): 2.23 (1.18 to 4.22)** **SS in favour of placebo (more with zolmitriptan)** I^2: 0%

* Characteristics of included studies: see below

Ref	Comparison	N/n	Outcomes	Result
Bird 2014 Design: SR+MA Search date: March 2014	Zolmitriptan 5 mg (oral formulations) Vs Placebo	N = 8 n = 4277 (attacks) (Dahlof 1998, Geraud 2000, Ho 2008, Rapoport 1997, Ryan 2000, Sakai 2002,	Pain free at 2h (PO)	Zolmitriptan: 750/2445 Placebo: 181/1832 **RR (95% CI): 3.2 (2.7 to 3.7)** NNT (95% CI): 4.8 (4.3 to 5.4) **SS in favour of zolmitriptan** I^2: 42%

		Spierings 2004, Visser 1996)		
		N = 8 n = 4292 (Dahlof 1998, Geraud 2000, Ho 2008, Rapoport 1997, Ryan 2000, Sakai 2002, Spierings 2004, Visser 1996)	Pain relief at 2h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	Zolmitriptan: 1452/2450 Placebo: 560/1842 **RR (95% CI): 1.9 (1.8 to 2.1)** NNT (95% CI): 3.5 (3.2 to 3.9) **SS in favour of zolmitriptan** I^2: 53%
		N = 1 n = 693 (attacks) (Ho 2008)	Sustained pain-free over 24h (PO) (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	Zolmitriptan: 62/345 Placebo: 17/348 **RR (95% CI): 3.68 (2.2 to 6.16)** **SS in favour of zolmitriptan**

		N = 5 n = 2827 (attacks) (Geraud 2000, Ho 2008, Rapoport 1997, Sakai 2002, Spierings 2004)	Sustained pain relief over 24 h (PO) (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.)	Zolmitriptan: 627/1682 Placebo: 175/1145 **RR (95% CI): 2.4 (2.0 to 2.8)** NNT (95% CI): 4.6 (4.0 to 5.3) **SS in favour of zolmitriptan** I^2: 24%
		N = 6 n = 2310 (Dahlof 1998, Geraud 2000, Rapoport 1997, Ryan 2000, Sakai 2002, Visser 1996)	Pain relief at 1h (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	Zolmitriptan: 38% (558/1477) Placebo: 22% (183/833) **RR (95% CI): 1.8 (1.5 to 2.1)** NNT (95% CI): 6.3 (5.1 to 8.3) **SS in favour of zolmitriptan** I^2: 0%
		N = 6 n = 2056 (Charlesworth 2003, Geraud 2000, Ho 2008, Rapoport 1997, Sakai 2002, Spierings 2004)	Relief of nausea at 2h	Zolmitriptan: 609/1187 Placebo: 316/869 **RR (95% CI): 1.51 [1.36 to 1.68)** **SS in favour of zolmitriptan** I^2: 50%

		N = 6 n = 2690 (Charlesworth 2003, Geraud 2000, Ho 2008, Rapoport 1997, Sakai 2002, Spierings 2004)	Relief of photophobia at 2h	Zolmitriptan: 766/1555 Placebo: 271/1135 **RR (95% CI): 2.03 (1.81 to 2.29)** **SS in favour of zolmitriptan** I^2: 63%
		N = 6 n = 2512 (Charlesworth 2003, Geraud 2000, Ho 2008, Rapoport 1997, Sakai 2002, Spierings 2004)	Relief of phonophobia at 2h	Zolmitriptan: 730/1471 Placebo: 254/1041 **RR (95% CI): 2.04 (1.81 to 2.3)** **SS in favour of zolmitriptan** I^2: 67%
		N = 5 n = 2571 (Dahlof 1998, Geraud 2000, Sakai 2002, Ryan 2000, Spierings 2004)	Use of rescue medication	Zolmitriptan: 561/1539 Placebo: 596/1032 **RR (95% CI): 0.6 (0.55 to 0.65)** **SS in favour of zolmitriptan (less rescue medication with zolmitriptan)** I^2: 78%

		N = 7 n = 4230 (Dahlof 1998, Geraud 2000, Ho 2008, Rapoport 1997, Ryan 2000, Sakai 2002, Spierings 2004)	Adverse events	Zolmitriptan: 1083/2620 Placebo: 318/1610 **RR (95% CI): 2.0 (1.8 to 2.2)** NNH (95% CI): 4.6 (4.2 to 5.3) **SS in favour of placebo (more with zolmitriptan)** I^2: 17%
		N = 6 n = 3004 (Dahlof 1998, Geraud 2000, Ho 2008, Rapoport 1997, Ryan 2000, Spierings 2004)	Vasodilation/warm feeling	Zolmitriptan: 76/1738 Placebo: 15/1268 **RR (95% CI): 2.93 (1.65 to 5.2)** **SS in favour of placebo (more with zolmitriptan)** I^2: 5%

Ref	Comparison	N/n	Outcomes	Result

Bird 2014 Design: SR+MA Search date: March 2014	Zolmitriptan 5 mg (nasal formulation) Vs Placebo	N = 3 n = 5095 (attacks) (Charlesworth 2003, Dodick 2005, Gawel 2005)	Pain free at 2h (PO)	Zolmitriptan: 866/2579 Placebo: 300/2516 **RR (95% CI): 2.8 (2.5 to 3.2)** NNT (95% CI): 4.6 (4.2 to 5.2). **SS in favour of zolmitriptan** I^2: 65%
		N = 3 n = 3164 (Charlesworth 2003, Dodick 2005, Gawel 2005)	Pain relief at 2h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	Zolmitriptan: 1085/1596 Placebo: 518/1568 **RR (95% CI): 2.1 (1.9 to 2.2)** NNT (95% CI): 2.9 (2.6 to 3.2) **SS in favour of zolmitriptan** I^2: 87%
		N = 2 n = 4298 (attacks) (Dodick 2005, Gawel 2005)	Sustained pain-free over 24h (PO) (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	Zolmitriptan: 284/2171 Placebo: 56/2127 **RR (95% CI): 4.9 (3.7 to 6.5)** NNT (95% CI): 9.6 (8.3 to 11) **SS in favour of zolmitriptan** I^2: 85%
		N = 2 n = 4279 (attacks) (Charlesworth 2003, Dodick 2005)	Sustained pain relief over 24 h (PO) (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.)	Zolmitriptan: 818/2172 Placebo: 200/2107 **RR (95% CI): 4.0 (3.4 to 4.6)** NNT (95% CI): 3.6 (3.3 to 3.9) **SS in favour of zolmitriptan**

				I^2: 0%
		N = 2 n = 2684 (Charlesworth 2003, Dodick 2005).	Pain relief at 1h (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	Zolmitriptan: 56% (763/1362) Placebo: 32% (420/1322) **RR (95% CI): 1.8 (1.6 to 1.9)** NNT (95% CI): 4.2 (3.6 to 4.9) **SS in favour of zolmitriptan** I^2: 76%
		N = 3 n = 5191 (Charlesworth 2003, Dodick 2005, Gawel 2005)	Use of rescue medication	Zolmitriptan: 894/2633 Placebo: 1650/2558 **RR (95% CI): 0.53 (0.5,0.56)** **SS in favour of zolmitriptan (less rescue medication with zolmitriptan)** I^2: 78%
		N = 3 n = 4842 (Charlesworth 2003, Dodick 2005, Gawel 2005)	Adverse events	Zolmitriptan: 2101/2445 Placebo: 742/2397 **RR (95% CI): 2.4 (2.1 to 2.6)** NNH (95% CI): 4.2 (3.8 to 4.7) **SS in favour of placebo (more adverse events with zolmitriptan)** I^2: 0%

Ref + design	n	Population	Duration	Comparison	Methodology
Studies included for comparisons with oral zolmitriptan 2.5 mg					
311CIL/0099 2000 DB, PC, PG-RCT	440 (treated attack)	Aged 18-65 years, meeting IHS criteria for migraine with or without aura. Onset < 50 years and Q 1 attack/month before start of trial No methysergide or methylergonovine within 2 weeks Excluded participants with previous unacceptable experience with a triptan, or with ischaemic heart or other vascular disease, or severe hepatic or renal disease zolmitriptan 2.5 mg, n = 174 naratriptan 2.5 mg, n = 174 placebo, n = 92 M 71 F 369 (84%) Mean age not reported, presence of aura not reported Use of prophylactic medication not reported	Assessment up to 2h	zolmitriptan 2.5 mg Vs naratriptan 2.5 mg Vs placebo Part 1 only: single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity Second dose of trial medication available after 4 h if necessary	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes **Unclear risk** Not reported INCOMPLETE OUTCOME DATA: **Low risk** drop-outs described Baseline pain not equally distributed between groups - correction made
Charlesworth 2003 DB, double dummy, PC, PG-RCT	1383	Aged 18-65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1 year history of	Assessment up to 24h	zolmitriptan 0.5 mg nasal spray Vs zolmitriptan 1 mg nasal spray Vs	RANDOMIZATION: **Low risk** "computer-generated random numbers scheme” ALLOCATION CONCEALMENT: **Unclear risk** Not reported

		migraine with onset < 50 years and an average of 1 to 6 attacks/month for the previous 2 months No MAOI, methysergide or methylergonovine within 2 weeks and no analgesics within 6 h. Excluded participants with uncontrolled hypertension, vascular disease, cardiac arrhythmias n = 1372 with moderate/severe intensity zolmitriptan 0.5 mg nasal spray, n = 221 zolmitriptan 1 mg nasal spray, n = 236 zolmitriptan 2.5 mg nasal spray, n = 224 zolmitriptan 5 mg nasal spray, n = 235 zolmitriptan 2.5 mg oral, n = 230 placebo, n = 226 M 234 F 1138 (83%) Mean age 41 years Without aura ˜62%		zolmitriptan 2.5 mg nasal spray Vs zolmitriptan 5 mg nasal spray Vs zolmitriptan 2.5 mg oral Vs Placebo Single dose to treat each of 3 attacks Medication administered when migraine headache pain was of moderate or severe intensity Approved rescue medications were allowed after the 4 h post dose assessment	BLINDING: performance bias and detection bias, all outcomes **Low risk** "double dummy method" INCOMPLETE OUTCOME DATA: **Low risk** drop-outs described
Dib 2002 DB, PC, CO-RCT	235	Aged 18-65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1 year history	N.D.	zolmitriptan 2.5 mg Vs ketoprofen 75 mg	RANDOMIZATION: **Unclear risk** not described”

		of migraine with a frequency of 1 to 6 attacks/month for previous 3_months. Able to recognise early signs of attack No NSAID, triptan or prophylactic ergot (time not specified) Excluded participants who experienced regular vomiting zolmitriptan 2.5 mg, n = 208 ketoprofen 75 mg, n = 214 ketoprofen 150 mg, n = 211 placebo, n = 205 M 39 F 196 Mean age 38 years 6% to 11% with aura		Vs ketoprofen 150 mg Vs placebo, Four consecutive attacks treated with single dose of each test medication Medication administered when migraine headache pain was of moderate or severe intensity. Minimum of 48 h between attacks Rescue medication permitted after 2 h	ALLOCATION CONCEALMENT: **Low risk** remote allocation BLINDING: performance bias and detection bias, all outcomes: **Low risk** "each treatment was enclosed in opaque soM gelatin capsules" INCOMPLETE OUTCOME DATA: **Low risk** drop-outs described, missing data < 10%
Dowson 2002 DB, PC, PG-RCT	471	Aged 18- 65 years, meeting IHS criteria for migraine (1988) with or without aura. Patients required to have an age of migraine onset of <50 years and at least1 attack/month for the previous 3 months No MAOI, methysergide, methylergonovine within 2 weeks, no triptans or ergot within 24 h, no opiates within 12 h and no analgesics within 6 h		zolmitriptan 2.5 mg ODT Vs placebo Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity	RANDOMIZATION: **Unclear risk** not described” ALLOCATION CONCEALMENT: **Low risk** "sealed envelopes" BLINDING: performance bias and detection bias, all outcomes: **Low risk** "matched for taste, size and shape" INCOMPLETE OUTCOME DATA: **Low risk** drop-outs described

		Excluded participants who had uncontrolled hypertension or cardiovascular disease zolmitriptan 2.5 mg ODT, n = 231 placebo, n = 239 F 87% Mean age 42 years With aura 23 %		A 2nd dose of study medication or rescue medication was allowed after 2 h	
Klapper 2004 DB, PC, PG-RCT	280	Aged 18- 65 years, meeting IHS criteria for migraine (1988) with or without aura with an onset < 50 years. Participants were required to suffer from 1 attack/month for previous 3_ months and the migraines experienced had to be initially mild but progress to moderate/severe intensity. Participants also had to be able to distinguish from other types of headache and have moderate/severe disability (MIDAS) No MAOI, methysergide, methylergonovine (time not specified) Excluded participants with uncontrolled hypertension or cardiovascular disease	Assessment up to 12 h	zolmitriptan 2.5 mg Vs placebo Single dose to treat single attack, when pain mild and within 4 h of onset. 2nd dose or rescue medication allowed after 2 h for persistent or recurrent headache	RANDOMIZATION: **Unclear risk** not described" ALLOCATION CONCEALMENT: **Unclear risk** not described" BLINDING: performance bias and detection bias, all outcomes: **Low risk** "matched placebo" INCOMPLETE OUTCOME DATA: **Low risk** drop-outs described

		zolmitriptan 2.5 mg, n = 138 placebo, n = 142 M 39 F 241 Mean age 42 years Without aura 59%			
Loder 2005 DB, PC, PG-RCT	566	Aged 18- 65 years, meeting IHS criteria for migraine (1988) with or without aura Participants were required to have a history of migraine of at least 1 year, with an age of onset of < 50 years and at least 2 attacks/month for the previous 3 months No_ MAOI, propranolol or cimetidine within 2 weeks Excluded participants with a history or symptoms of IHD or other vascular disease, uncontrolled hypertension or renal or liver impairment n = 565 analysed for efficacy zolmitriptan 2.5 mg ODT, n = 282 placebo, n = 284 M 83 F 482 (85%) Mean age 41 years Without aura 72%	Assessment up to 24 h	zolmitriptan 2.5 mg ODT Vs placebo Single dose to treat single attack, as soon as possible (pain mild/moderate/severe) 2nd dose or rescue med permitted after 2 h	RANDOMIZATION: **Unclear risk** not described" ALLOCATION CONCEALMENT: **Unclear risk** not described" BLINDING: performance bias and detection bias, all outcomes: **Low risk** "matched placebo" INCOMPLETE OUTCOME DATA: **Low risk** drop-outs described

		˜35% treated when pain mild			
Pascual 2000 DB, PC RCT	766	Meeting IHS criteria for migraine (1988) with or without aura. Participants required to have a history of migraine for ar least six months and usually experience 1 to 8 attacks/month No MAOI or methysergide within 2 weeks, propranolol within 3 days, triptan, ergot or opiate within 24 h and any other analgesic or antiemetic within 6 h. Other stable prophylaxis permitted Excluded participants with cerebrovascular or cardiovascular disease n = 727 for efficacy zolmitriptan 2.5 mg, n = 304 (289 for efficacy) rizatriptan 10 mg, n = 308 (292 for efficacy) placebo, n = 154 (146 for efficacy) F 83% Mean age 39 years With aura 12%	Assessment up to 24 h	zolmitriptan 2.5 mg Vs rizatriptan 10 mg Vs Placebo Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication allowed after 2 h	RANDOMIZATION: **Unclear risk** not described” ALLOCATION CONCEALMENT: **Unclear risk** not described” BLINDING: performance bias and detection bias, all outcomes **Unclear risk** not described” INCOMPLETE OUTCOME DATA: **Low risk** drop-outs described, missing data 5%
Rapoport 1997 DB, PC, PG-RCT	1144	Aged 12- 65 years, meeting IHS criteria for migraine (1988) with or without aura Participants were	Assessment up to 24 h	zolmitriptan 1 mg Vs zolmitriptan 2.5 mg	RANDOMIZATION: **Unclear risk** not described”

		required to have a history of migraine for at least a year, with onset <50 years and 1 to 6 attacks/month for the previous 6 months No sumatriptan or ergot within 48 h and analgesics/NSAIDs within 6 h. Prophylaxis was allowed Excluded participants with hypertension or any medical or physical condition that might put the patient at risk with exposure to zolmitriptan n = 999 analysed for efficacy zolmitriptan 1 mg, n = 125 zolmitriptan 2.5 mg, n = 260 zolmitriptan 5 mg, n = 245 zolmitriptan 10 mg, n = 248 placebo, n = 121 M 123 F 876 (˜88%) Mean age 41 years (all groups included at least 1 individual aged 12 or 13)		vs zolmitriptan 5 mg vs zolmitriptan 10 mg vs placebo Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity 2nd dose or rescue medication permitted after 4 h (but no ergot or sumatriptan for 12 h)	ALLOCATION CONCEALMENT: **Low risk** sequentially numbered medication packets BLINDING: performance bias and detection bias, all outcomes: ***Low risk*** "matching oral placebo or zolmitriptan" INCOMPLETE OUTCOME DATA: **Unclear risk** PP analysis reported. "Results from the all-treated analysis did not differ ..."
Ryan 2000 DB, PC, PG-RCT	924	Aged 18- 65 years, meeting IHS criteria for migraine (1988) with or without aura Pariticpants were required to have a history of migraine for at least 1 year, with	Assessment up to 4 h	zolmitriptan 2.5 mg vs zolmitriptan 5 mg vs placebo	RANDOMIZATION: **Unclear risk** not described” ALLOCATION CONCEALMENT: **Unclear risk** not described”

		onset <50 years and 2 to 6 attacks/month in the previous 2 months and other chronic non-migraine medications permitted if stable for 2 months Excluded participants with hypertension or any medical or physical condition that might put the patient at risk with exposure to zolmitriptan 734 treated 3 attacks zolmitriptan 2.5 mg, n = 546 (487 for efficacy) zolmitriptan 5 mg, n = 542 (482 for efficacy) placebo, n = 282 + 285 (247 + 252 for efficacy) F 86% Mean age 40 years Without aura 60%		Single dose of each of three treatments for initial treatment of each of three attacks. Second (R, DB) dose at 4 h to treat recurrence if necessary, or at 8 h to prevent recurrence if rescue medication not used Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication permitted after 2 h, but asked to wait 4 h if possible	BLINDING: performance bias and detection bias, all outcomes: ***Low risk*** tablets were "identical in appearance" INCOMPLETE OUTCOME DATA: **Unclear risk** ITT population comprised participants treating 3 attacks
Sakai 2002 DB, PC, PG-RCT	229	Aged 18- 64 years, meeting IHS criteria for migraine (1988) with or without aura Participants required to have a history of migraine for at least 1 year, with onset < 50 years and 1 to 6 attacks/month in the previous 3 months	Assessment up to 4 h	zolmitriptan 1 mg vs zolmitriptan 2.5 mg vs zolmitriptan 5 mg vs placebo	RANDOMIZATION: **Unclear risk** not described" ALLOCATION CONCEALMENT: **Unclear risk** not described" BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** not described"

		No ergotamine within 48 h and no analgesics, steroids, antidepressants, antiemetics, anticonvulsants, sedatives within 8 h Excluded participants with cardiovascular disease, uncontrolled hypertension and those with severe renal or hepatic disease n = 202 in analysis zolmitriptan 1 mg, n = 52 (47) zolmitriptan 2.5 mg, n = 61 (54) zolmitriptan 5 mg, n = 57 (52) placebo, n = 59 (49) M 52 F 150 (74%) Mean age 38 years Without aura 64%		vs Single dose to treat single Attack Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication permitted after 4 h	INCOMPLETE OUTCOME DATA: **Unclear risk** some outcomes (PF2, HR1, SHR24) reported only for PP population
Solomon 1997 DB, PC, PG-RCT	270	Aged 12 -65 years, meeting IHS criteria for migraine (1988) with or without aura Participants were required to have a history of migraine for a minimum of 1 year, with onset <50 years and 1 to 6 attacks/month for the previous 6 months No_MAOI, no NSAID, analgesic, sedative, antiemetic within 6 h and	Assessment up to 24h	zolmitriptan 2.5 mg Vs placebo Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity	RANDOMIZATION: **Unclear risk** not described” ALLOCATION CONCEALMENT: **Low risk** "sequentially numbered medication packet"BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** not described” INCOMPLETE OUTCOME DATA: **Unclear risk** PP analysis reported

		no sumatriptan or ergotamines within 48 h Excluded participants with hypertension or any medical or physical condition that might put the patient at risk with exposure to zolmitriptan zolmitriptan 2.5 mg, n = 178 placebo, n = 92 M 39 F 231 (86%) Mean age 40 years Without aura ˜68%			for efficacy. "Results did not differ from those of the alltreated group for [HR2]"
Steiner 2003 DB, double-dummy, PC, PG-RCT	1337	Aged 18 - 65 years, meeting IHS criteria for migraine (1988) with or without aura (IHS 1988). Participants were required to experience attacks at least once every 6 weeks No MAOI or CYP3A4 inhibitors within 2 weeks, no analgesic or antiemetic for that attack and no triptan, ergotamine, dihydroergotamine within 48 h Excluded participants if their migraines were consistently resistant to all treatments or if they had any clinically significant medical illness/lab abnormalities, especially	Assessment up to 24h	zolmitriptan 2.5 mg vs eletriptan 40 mg vs eletriptan 80 mg vs placebo Single dose to treat single attack. 2nd dose available after 4 h for recurrence Medication administered when migraine headache pain was of moderate or severe intensity	RANDOMIZATION: **Low risk** "computer-generated list" ALLOCATION CONCEALMENT: **Low risk** remote allocation. Centre "allocated prenumbered treatments to consecutive patients by next-number on this list" BLINDING: performance bias and detection bias, all outcomes: **Low risk** double-dummy design: matched tablets for eletriptan, identical capsules for zolmitriptan INCOMPLETE OUTCOME DATA: **Low risk** drop-outs described

		those indicative of CHD, HF and hypertension n = 1312 analysed for efficacy zolmitriptan 2.5 mg, n = 405 eletriptan 40 mg, n = 392 eletriptan 80 mg, n = 396 placebo, n = 144 F 85% Mean age 40 years Without aura ˜73%		Rescue medication permitted after 2 h	
Tuchman 2006 Db, PC, PG-RCT	336	Aged 18 years and over, meeting IHS criteria for menstrual migraine (1988) with or without aura. Participants were required to have had at least 3 menstrual migraine headaches of moderate/severe intensity within the previous 3 months No MAOI within 2 weeks or SSRI if dose not stabilised. Study medication should not be used for attacks already treated with other acute medication (NSAIDs, paracetamol) Excluded participants with uncontrolled hypertension or cardiovascular disease n= 334 analysed for efficacy	Assessment up to 24h	zolmitriptan 2.5 mg vs placebo Single dose to treat each of up to 6 attacks with at least 24 h between treated attacks Medication administered when migraine headache pain was of moderate or severe intensity	RANDOMIZATION: **Unclear risk** not described ALLOCATION CONCEALMENT: **Unclear risk** not described BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** not described INCOMPLETE OUTCOME DATA: **Low risk** drop-outs described

		zolmitriptan 2.5 mg, n = 174 placebo, n = 160 All F Mean age 38 years Without aura ˜72%			
Visser 1996 Single centre, DB, PC, dose-finding, PG-RCT	84	Aged 18 - 55 years, meeting IHS criteria for migraine (1988) with or without aura Participants were required to have a history of migraine of at least 1 year, with an age of onset < 40 years with an average of 1 to 6 attacks/month No prophylactics within 1 month Excluded participants who experienced regular vomiting or had a personal or family history of CAD, peripheral vascular disease, hypertension or renal or liver disease zolmitriptan 1 mg, n = 22 zolmitriptan 5 mg, n = 21 zolmitriptan 25 mg, n = 21 placebo, n = 20 M 17, F 67 Mean age 43 years Without aura 63%	Assessment up to 24h	zolmitriptan 1 mg vs zolmitriptan 5 mg vs zolmitriptan 25 mg vs placebo Single dose to treat single attack. Optional 2nd dose available after 2 h Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication permitted after 3 h (for single dose patients)	**Study does not meet our inclusion criteria (n<40 /study group)**
Studies included for comparisons with oral zolmitriptan 5mg					

Dahlof 1998 DB, PC, PG-RCT	951	Aged 18-65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1 year history of migraine with onset < 40 years and an average of 1 to 6 attacks/month Prophylaxis allowed, excluding medications considered psychoactive or active at 5-HT receptor sites. No sumatriptan or ergot within 72 h or analgesics within 24 h Excluded participants with cardiovascular disease, uncontrolled hypertension and severe renal or hepatic disease n = 840 analysed for efficacy zolmitriptan 5 mg, n = 213 zolmitriptan 10 mg, n = 214 zolmitriptan 15 mg, n = 215 zolmitriptan 20 mg, n = 210 placebo, n = 99 M 139 F 701 (83%) Mean age 40 years Without aura 69%	Assessment up to 24h	zolmitriptan 5 mg Vs zolmitriptan 10 mg Vs zolmitriptan 15 mg Vs zolmitriptan 20 mg Vs Placebo Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity Rescue medications were allowed after 2 h. Ergot-derivatives or sumatriptan were not allowed as rescue medication within 12 hours of taking study medication	RANDOMIZATION: **Low risk** "computer-generated numerical sequence" ALLOCATION CONCEALMENT: **Low risk** "assigning the next medication pack in the .... sequence" BLINDING: performance bias and detection bias, all outcomes: **Low risk** "all tablets were identical in appearance" INCOMPLETE OUTCOME DATA: **Low risk** drop-outs described, missing data W 5%
Geraud 2000	1058	Aged 18- 65 years, meeting IHS criteria for migraine (1988) with or	Assessment up to 24 h	zolmitriptan 5 mg Vs	RANDOMIZATION: **Unclear risk** not described”

DB, double-dummy, PC, PG-RCT		without aura. Patients required to have a history of migraine for at least 1 year, with an onset at < 50 years and with 1 to 6 attacks/month in the previous 6 months. Triptan naïve participants only Prophyalxis with beta-blockers, calcium channel blockers (except flunarizine), clonidine and valproic acid was allowed. No psychoactive drugs or drugs with a clinically important action at 5-HT receptor were permitted in the previous 4 weeks Excluded participants with cardiovascular disease, uncontrolled hypertension and severe renal or hepatic disease zolmitriptan 5 mg, n = 498 sumatriptan 100 mg, n = 504 placebo, n = 56 M 174 F 884 (84%) Mean age 38 years Without aura ˜73%		sumatriptan 100 mg Vs placebo Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication permitted after 2 h if symptoms persisted (no ergot for 12 h, no sumatriptan)	ALLOCATION CONCEALMENT **Unclear risk** not described” BLINDING: performance bias and detection bias, all outcomes: **Low risk** "double dummy technique" INCOMPLETE OUTCOME DATA: **Low risk** drop-outs described, missing data 2%
Ho 2008 DB, PC, PG-RCT	1380	Aged over 18 years, meeting IHS criteria for migraine (2004) with or without aura Participants were required to have good general health	Assessment up to 24 h	zolmitriptan 5 mg Vs telcagepant 150 mg Vs	RANDOMIZATION: **Low risk** "computer-generated randomised schedule"

		and a history of migraine for at least 1 year, with 1 to 8 attacks (of moderate/severe intensity) per month Patients taking prophylaxis were allowed to enter the study provided that their prescribed daily dose had not changed during the 3 months before screening; ˜55% of included participants were using prophylaxis No potent CYP3A4 inhibitors or inducers, SNRIs, SSRIs, MAO inhibitors or propranolol within 1 month Excluded participants with cardiovascular disease or uncontrolled hypertension zolmitriptan 5 mg, n = 345 telcagepant 150 mg, n = 333 telcagepant 300 mg, n = 354 placebo, n = 348 F 85% Mean age 42 years		telcagepant 300 mg Vs placebo Single dose to treat single attack, when pain > moderate. 2nd dose (blinded) or rescue medication was permitted if there had been no response at 2 h or if headache returned within 48 h. Blinded 2nd dose for zolmitriptan and placebo participants was always placebo, for telcagepant either telcagepant or placebo	ALLOCATION CONCEALMENT: **Low risk** "interactive voice response for remote allocation, with numbered containers BLINDING: performance bias and detection bias, all outcomes: **Low risk** "matched placebo" INCOMPLETE OUTCOME DATA: **Low risk** drop-outs described, missing data < 10%
Rapoport 1997 DB, PC, PG-RCT	1144	Aged 12- 65 years, meeting IHS criteria for migraine (1988) with or without aura Participants were required to have a history of migraine for at least a year, with	Assessment up to 24 h	zolmitriptan 1 mg Vs zolmitriptan 2.5 mg vs zolmitriptan 5 mg	RANDOMIZATION: **Unclear risk** not described” ALLOCATION CONCEALMENT: **Low risk** sequentially numbered medication packetsBLINDING:

		onset <50 years and 1 to 6 attacks/month for the previous 6 months No sumatriptan or ergot within 48 h and analgesics/NSAIDs within 6 h. Prophylaxis was allowed Excluded participants with hypertension or any medical or physical condition that might put the patient at risk with exposure to zolmitriptan n = 999 analysed for efficacy zolmitriptan 1 mg, n = 125 zolmitriptan 2.5 mg, n = 260 zolmitriptan 5 mg, n = 245 zolmitriptan 10 mg, n = 248 placebo, n = 121 M 123 F 876 (˜88%) Mean age 41 years (all groups included at least 1 individual aged 12 or 13)		vs zolmitriptan 10 mg vs placebo Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity 2nd dose or rescue medication permitted after 4 h (but no ergot or sumatriptan for 12 h)	performance bias and detection bias, all outcomes: ***Low risk*** "matching oral placebo or zolmitriptan" INCOMPLETE OUTCOME DATA: **Unclear risk** PP analysis reported. "Results from the all-treated analysis did not differ ..."
Ryan 2000 DB, PC, PG-RCT	924	Aged 18- 65 years, meeting IHS criteria for migraine (1988) with or without aura Participants were required to have a history of migraine for at least 1 year, with onset <50 years and 2 to 6	Assessment up to 4 h	zolmitriptan 2.5 mg vs zolmitriptan 5 mg vs placebo	RANDOMIZATION: **Unclear risk** not described” ALLOCATION CONCEALMENT: **Unclear risk** not described” BLINDING: performance bias and detection bias, all outcomes: ***Low***

		attacks/month in the previous 2 months and other chronic non-migraine medications permitted if stable for 2 months Excluded participants with hypertension or any medical or physical condition that might put the patient at risk with exposure to zolmitriptan 734 treated 3 attacks zolmitriptan 2.5 mg, n = 546 (487 for efficacy) zolmitriptan 5 mg, n = 542 (482 for efficacy) placebo, n = 282 + 285 (247 + 252 for efficacy) F 86% Mean age 40 years Without aura 60%		Single dose of each of three treatments for initial treatment of each of three attacks. Second (R, DB) dose at 4 h to treat recurrence if necessary, or at 8 h to prevent recurrence if rescue medication not used Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication permitted after 2 h, but asked to wait 4 h if possible	***risk*** tablets were "identical in appearance" INCOMPLETE OUTCOME DATA: **Unclear risk** ITT population comprised participants treating 3 attacks
Sakai 2002 DB, PC, PG-RCT	229	Aged 18- 64 years, meeting IHS criteria for migraine (1988) with or without aura Participants required to have a history of migraine for at least 1 year, with onset < 50 years and 1 to 6 attacks/month in the previous 3 months	Assessment up to 4 h	zolmitriptan 1 mg vs zolmitriptan 2.5 mg vs zolmitriptan 5 mg vs placebo vs	RANDOMIZATION: **Unclear risk** not described" ALLOCATION CONCEALMENT: **Unclear risk** not described" BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** not described"

		No ergotamine within 48 h and no analgesics, steroids, antidepressants, antiemetics, anticonvulsants, sedatives within 8 h Excluded participants with cardiovascular disease, uncontrolled hypertension and those with severe renal or hepatic disease n = 202 in analysis zolmitriptan 1 mg, n = 52 (47) zolmitriptan 2.5 mg, n = 61 (54) zolmitriptan 5 mg, n = 57 (52) placebo, n = 59 (49) M 52 F 150 (74%) Mean age 38 years Without aura 64%		Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication permitted after 4 h	INCOMPLETE OUTCOME DATA: **Unclear risk** some outcomes (PF2, HR1, SHR24) reported only for PP population
Spierings 2004 DB, PC, PG-RCT	671	Aged 18 - 65 years, meeting IHS criteria for migraine (1988) with or without aura Participants were required to have a history of migraine of at least 1 year, with an age of onset of < 50 years and an average of 2 attacks/month No MAOI or initiation of SSRI within 2 weeks and no concomitant treatment with propranolol or cimetidine	Assessment up to 24h	zolmitriptan 5 mg ODT vs placebo Single dose to treat each of 2 attacks Medication administered when migraine headache pain was of moderate or severe intensity	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes **Low risk** "matching placebo" INCOMPLETE OUTCOME DATA: **Low risk** drop-outs described

		Excluded participants with a history or symptoms of IHD or other vascular disease or uncontrolled hypertension n = 670 analysed for efficacy zolmitriptan 5 mg ODT, n = 329 placebo, n = 341 M 90 F 580 Mean age 42 years Without aura 65%		2nd dose or rescue med after 2 h if necessary	
Visser 1996 Single centre, DB, PC, dose-finding, PG-RCT	84	Aged 18 - 55 years, meeting IHS criteria for migraine (1988) with or without aura Participants were required to have a history of migraine of at least 1 year, with an age of onset < 40 years with an average of 1 to 6 attacks/month No prophylactics within 1 month Excluded participants who experienced regular vomiting or had a personal or family history of CAD, peripheral vascular disease, hypertension or renal or liver disease zolmitriptan 1 mg, n = 22 zolmitriptan 5 mg, n = 21 zolmitriptan 25 mg, n = 21	Assessment up to 24h	zolmitriptan 1 mg vs zolmitriptan 5 mg vs zolmitriptan 25 mg vs placebo Single dose to treat single attack. Optional 2nd dose available after 2 h Medication administered when migraine headache pain was of moderate or severe intensity	**Study does not meet our inclusion criteria (n<40 /study group)**

		placebo, n = 20 M 17, F 67 Mean age 43 years Without aura 63%		Rescue medication permitted after 3 h (for single dose patients)	
Studies included in comparisons with nasal zolmitriptan 5mg					
Charlesworth 2003 DB, double dummy, PC, PG-RCT	1383	Aged 18-65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1 year history of migraine with onset < 50 years and an average of 1 to 6 attacks/month for the previous 2 months No MAOI, methysergide or methylergonovine within 2 weeks and no analgesics within 6 h. Excluded participants with uncontrolled hypertension, vascular disease, cardiac arrhythmias n = 1372 with moderate/severe intensity zolmitriptan 0.5 mg nasal spray, n = 221 zolmitriptan 1 mg nasal spray, n = 236 zolmitriptan 2.5 mg nasal spray, n = 224 zolmitriptan 5 mg nasal spray, n = 235	Assessment up to 2h	zolmitriptan 0.5 mg nasal spray Vs zolmitriptan 1 mg nasal spray Vs zolmitriptan 2.5 mg nasal spray Vs zolmitriptan 5 mg nasal spray Vs zolmitriptan 2.5 mg oral Vs Placebo Single dose to treat each of 3 attacks Medication administered when migraine headache pain was of moderate or severe intensity Approved rescue medications were allowed	RANDOMIZATION: **Low risk** "computer-generated random numbers scheme” ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes **Low risk** "double dummy method" INCOMPLETE OUTCOME DATA: **Low risk** drop-outs described

		zolmitriptan 2.5 mg oral, n = 230 placebo, n = 226 M 234 F 1138 (83%) Mean age 41 years Without aura ˜62%		after the 4 h post dose assessment	
Dodick 2005_ DB, PC, PG-RCT	1869	Aged 18- 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1 year history of migraine, with onset <50 years and 2 to 6 attacks/month. No prophylactics or non-stable dose of SSRI within 2 months. No MAOI within 2 weeks. No analgesics, ergots or triptans within 24 h. Furthermore, no naratriptan within 36 h and no frovatriptan within 5 days. Excluded participants who had hypertension or any medical or physical condition that might put the patient at risk with exposure to zolmitriptan. n = 1868 analysed for efficacy zolmitriptan 5 mg nasal spray, n = 935 (1745 attacks) placebo, n = 934 (1718 attacks) M 248	Assessment up to 4 h	zolmitriptan 5 mg nasal spray Vs placebo Single dose to treat up to 2 attacks Study medication to be taken within 15 minutes of pain becoming moderate or severe intensity. Headaches with moderate/severe intensity upon awakening were not to be treated Rescue medication permitted after 4 h	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Low risk** "matching placebo" INCOMPLETE OUTCOME DATA: **Low risk** drop-outs described

		F 1620 Mean age 41 years Without aura 56%			
Gawel 2005 DB, PC, PG-RCT	915	Aged 18-65 years, meeting IHS criteria for migraine (1988) with or without aura Participants had history of migraine for at least a year, with at least 1 attack/month for the previous 3 months No MAOI, methysergide, methylergonovine within 2 weeks and no triptans, ergot within 24 h, opiates, analgesics within 12 h Excluded participants with a history, symptoms or significant risk factors for CV disease, uncontrolled hypertension and severe hepatic impairment n = 913 analysed for efficacy zolmitriptan 5 mg nasal spray, n = 464 placebo, n = 451 M 114 F 798 (87%) Mean age 41 years Only 73 participants (8%) treated when pain mild		zolmitriptan 5 mg nasal spray Vs placebo Single dose to treat single attack, at any time after onset (pain mild/moderate/severe) 2nd dose or rescue medication (not triptan or ergot) permitted after 2 h	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Low risk** "placebo nasal spray device exactly matched zolmitriptan device in terms of appearance, weight, drug volume, and labelling" INCOMPLETE OUTCOME DATA: **Low risk** drop-outs described

Remarks:

- Authors analysed studies using a single dose of zolmitriptan in established pain of at least moderate intensity s**eparately** from studies in which the medication was taken before pain became well established, or in which a second dose of medication was required. In most studies the treated migraine attacks had to be of moderate or severe baseline intensity. Gawel 2005 treated any severity, but fewer than 10% were mild, and results were reported separately for attacks of moderate or severe baseline intensity. Loder 2005 treated 'as soon as possible', but reported some outcomes for attacks of moderate or severe baseline intensity. Finally, Klapper 2004 treated when pain intensity was mild.
- There were insufficient data to allow pooled analysis from studies in which participants treated attacks when pain was mild, or that included mixed baseline intensities.
- There were also insufficient data from studies that allowed second or third doses of medication for a single attack in order to allow analysis of these different dosing strategies.
- The SR also identified and reported data on studies comparing zolmitriptan 1mg or 10mf to placebo. As these are not available/recommended doses in BE, we have not report these comparisons in the present document.
- Solomon 1997 and Rapoport 1997 included participants aged 12 to 65 years. “we included these studies because we felt that the number of individuals younger than 18 years was small, and because all were > 12 years of age they were likely to require an adult dose.”
- All studies included both men and women, except the study concerning menstrual migraine (Tuchman 2006). The participants in Tuchman 2006 were required to have a diagnosis of menstrual migraine.
- For the comparisons with oral zolmitriptan 2.5 mg: different formulations of zolmitriptan have been pooled in the main analysis including oral tablets, oral disintegrating tablets and nasal formulation. Only Charlesworth 2003 used nasal spray but also included information on the use of zolmitriptan oral tablet. Dowson 2002 and Loder 2005 used oral disintegrating tablets.
- For the comparisons with oral zolmitriptan 5 mg : The single study that used an oral disintegrating tablet formulation is Spierings 2004. The outcomes for relief of associated symptoms included studies for oral formulations only, except Charlesworth 2003 which used oral tablet but also included information on the use of zolmitriptan nasal spray.
- Concerning adverse events: Visser 1996 did not report adverse events for the placebo group, so no comparison could be made. The duration over which data were collected was not always specified and, where it was, there were differences between studies. Most studies probably collected data during the 24 hours following treatment, some studies reported effect up to 10 days. A number of studies treated more than one attack. It was unclear how multiple attacks were combined.
- Pain intensity or pain relief had to be measured by the patient (not the investigator or carer). Pain measures accepted for the primary outcomes were:

• pain intensity: four-point categorical scale, with wording equivalent to none, mild, moderate, and severe; or 100 mm visual analogue scale (VAS);

- pain relief: five-point categorical scale, with wording equivalent to none, a little, some, a lot, complete; or 100 mm VAS.

Author's conclusions:
"Zolmitriptan is effective as an abortive treatment for migraine attacks for some people, but is associated with increased adverse events compared to placebo.
"Zolmitriptan is an effective treatment for some people for the relief of headache pain and other symptoms associated with migraine, with single doses of 2.5 mg or more providing clinically useful levels of relief."
"There was no significant difference in efficacy between 2.5 mg and 5 mg doses for any outcome in these studies."
"5 mg nasal spray formulation was better than oral tablets for headache relief at one and two hours, but not pain-free at two hours."
"Given that 2.5 mg and 5 mg produce the same effect, a 2.5 mg dose would be a sensible starting dose, with increase to 5 mg if there was inadequate response. The intranasal formulation provides more rapid relief of headache pain than oral tablets, but one in seven patients will experience taste disturbances.
"There was no statistically significant difference between the two formulations for participants experiencing any adverse events."

12.7 Triptans vs triptans

12.7.1 Almotriptan versus zolmitriptan for acute treatment of migraine attack in adults

Meta-analysis: Xu 2016(41), Network meta-analysis of migraine disorder treatment by NSAIDs and triptans

Definition of migraine:

Inclusion criteria: Articles were included if they: (1) were randomized clinical trials (RCTs); (2) were categorized as double blind; (3) included relevant clinical outcomes and treatments; (4) contained comparisons between different treatments.

Search strategy: We employed search strategies to explore the medical literature for relevant studies in PubMed and EMBASE systematically, and 2,967 records were identified using the following terms: “migraine disorders”, “tryptans”, “non-steroidal anti-inflammatory agents”, “ergot alkaloids”, “opioid analgesics”, “sumatriptan”, “zolmitriptan”, “almotriptan”, “rizatriptan”, “naratriptan”, “ibuprofen”, “eletriptan”, “diclofenac-potassium” and “aspirin” in PubMed. Reviewers also provided 3 additional references.

Assessment of quality of included trials: yes

Other methodological remarks:
We initially carried out a conventional pair-wise metaanalysis which directly compares each pair of treatments.
The corresponding odds ratios (ORs) and 95% confidence intervals (CIs) for each study were pooled in order to obtain the overall effect size. Furthermore, a NMA was performed for each endpoint with a Bayesian framework using R 3.2.3 software.

Ref	Comparison	N/n	Outcomes	Result
Xu 2016 Design: SR+MA Search date:	Almotriptan Vs Zolmitriptan	N = 1 n = 1062	Pain free at 2 h	OR (95% CI): 0.90 (0.73 to 1.11) NS
			Pain relief at 2h	OR (95% CI): 0.93 (0.77 to 1.12) NS
			Use of rescue medication	OR (95% CI): 0.99 (0.74 to 1.32) NS
			Migraine recurrence	OR (95% CI): 1.07 (0.8 to 1.42) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Goadsby 2007 DB, PC, PG-RCT	1062	Aged 18- 65 years, meeting IHS criteria for migraine (2004) with or without aura Participants required to have a history of migraine for at least 1 year, with an onset < 50 years and 2 to 6 attacks/month in the previous 2 months Excluded participants with cardiovascular disease, uncontrolled hypertension and moderate/severe renal or hepatic disease zolmitriptan 2.5 mg, n = 530 almotriptan 12.5 mg, n = 532 M 160, F 902 (85%) Mean age 40 years (range 18 to 72) 122 major protocol violations: 11 participants had mild baseline pain_	Assessment up to 24 h	zolmitriptan 2.5 mg vs almotriptan 12.5 mg Single dose to treat single attack but a second dose could be taken if symptoms were alleviated but recurred within 24 h Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication permitted (other than triptan or ergots) but time not specified	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Low risk** "both agents were encapsulated to ensure treatment blinding" INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs described (as reported in Bird 2014)

Remarks:
Authors initially carried out a conventional pair-wise meta-analysis which directly compares each pair of treatments. The corresponding odds ratios (ORs) and 95% confidence intervals (CIs) for each study were pooled in order to obtain the overall effect size. Furthermore, a NMA was performed for each endpoint. In the present document we only reported results from the pair-wise comparisons.

12.7.2 Eletriptan versus zolmitriptan for acute treatment of migraine attack in adults

Meta-analysis: Xu 2016(41), Network meta-analysis of migraine disorder treatment by NSAIDs and triptans

Definition of migraine:

Inclusion criteria: Articles were included if they: (1) were randomized clinical trials (RCTs); (2) were categorized as double blind; (3) included relevant clinical outcomes and treatments; (4) contained comparisons between different treatments.

Search strategy: We employed search strategies to explore the medical literature for relevant studies in PubMed and EMBASE systematically, and 2,967 records were identified using the following terms: “migraine disorders”, “tryptans”, “non-steroidal anti-inflammatory agents”, “ergot alkaloids”, “opioid analgesics”, “sumatriptan”, “zolmitriptan”, “almotriptan”, “rizatriptan”, “naratriptan”, “ibuprofen”, “eletriptan”, “diclofenac-potassium” and “aspirin” in PubMed. Reviewers also provided 3 additional references.

Assessment of quality of included trials: yes

Other methodological remarks:
We initially carried out a conventional pair-wise metaanalysis which directly compares each pair of treatments.
The corresponding odds ratios (ORs) and 95% confidence intervals (CIs) for each study were pooled in order to obtain the overall effect size. Furthermore, a NMA was performed for each endpoint with a Bayesian framework using R 3.2.3 software.

Ref	Comparison	N/n	Outcomes	Result
Xu 2016 Design: SR+MA Search date:	Eletriptan Vs Zolmitriptan	N = 1 n = 1312	Pain free at 1h	OR (95% CI): 1.59 (0.96 to 2.64) NS
			Pain relief at 1h	**OR (95% CI): 1.39 (1.06 to 1.81)** **SS in favour of eletriptan**

			Pain free at 2 h	**OR (95% CI): 1.93 (1.50 to 2.49)** **SS in favour of eletriptan**
			Pain relief at 2h	OR (95% CI): 1.13 (0.93 to 1.38) NS
			Nausea absence at 2h	OR (95% CI): 1.10 (0.91 to 1.34) NS
			Migraine recurrence	OR (95% CI): 0.92 (0.68 to 1.23) NS
			Adverse events	OR (95% CI): 1.08 (0.85 to 1.37) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Steiner 2003 DB, double-dummy, PC, PG-RCT	1337	Aged 18 - 65 years, meeting IHS criteria for migraine (1988) with or without aura (IHS 1988). Participants were required to experience attacks at least once every 6 weeks No MAOI or CYP3A4 inhibitors within 2 weeks, no analgesic or antiemetic for that attack and no triptan,	Assessment up to 24h	zolmitriptan 2.5 mg vs eletriptan 40 mg vs eletriptan 80 mg vs placebo	RANDOMIZATION: **Low risk** "computer-generated list" ALLOCATION CONCEALMENT: **Low risk** remote allocation. Centre "allocated prenumbered treatments to consecutive patients by next-number on this list"

		ergotamine, dihydroergotamine within 48 h Excluded participants if their migraines were consistently resistant to all treatments or if they had any clinically significant medical illness/lab abnormalities, especially those indicative of CHD, HF and hypertension n = 1312 analysed for efficacy zolmitriptan 2.5 mg, n = 405 eletriptan 40 mg, n = 392 eletriptan 80 mg, n = 396 placebo, n = 144 F 85% Mean age 40 years Without aura ˜73%		Single dose to treat single attack. 2nd dose available after 4 h for recurrence Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication permitted after 2 h	BLINDING: performance bias and detection bias, all outcomes: **Low risk** double-dummy design: matched tablets for eletriptan, identical capsules for zolmitriptan INCOMPLETE OUTCOME DATA: **Low risk** drop-outs described (As reported in Bird 2014)

Remarks:
Authors initially carried out a conventional pair-wise meta-analysis which directly compares each pair of treatments. The corresponding odds ratios (ORs) and 95% confidence intervals (CIs) for each study were pooled in order to obtain the overall effect size. Furthermore, a NMA was performed for each endpoint with a Bayesian framework using R 3.2.3 software. In the present document we only reported results from the pair-wise comparison

Author's conclusions:

“We can derive that rizatriptan and eletriptan tend to show effective performance with respect to outcomes including 1 h-pain-relief and rescue medication.”

12.7.3 Naratriptan versus rizatriptan for acute treatment of migraine attack in adults

Meta-analysis: Xu 2016(41), Network meta-analysis of migraine disorder treatment by NSAIDs and triptans

Definition of migraine:

Inclusion criteria: Articles were included if they: (1) were randomized clinical trials (RCTs); (2) were categorized as double blind; (3) included relevant clinical outcomes and treatments; (4) contained comparisons between different treatments.

Search strategy: We employed search strategies to explore the medical literature for relevant studies in PubMed and EMBASE systematically, and 2,967 records were identified using the following terms: “migraine disorders”, “tryptans”, “non-steroidal anti-inflammatory agents”, “ergot alkaloids”, “opioid analgesics”, “sumatriptan”, “zolmitriptan”, “almotriptan”, “rizatriptan”, “naratriptan”, “ibuprofen”, “eletriptan”, “diclofenac-potassium” and “aspirin” in PubMed. Reviewers also provided 3 additional references.

Assessment of quality of included trials: yes

Other methodological remarks:
We initially carried out a conventional pair-wise metanalysis which directly compares each pair of treatments.
The corresponding odds ratios (ORs) and 95% confidence intervals (CIs) for each study were pooled in order to obtain the overall effect size. Furthermore, a NMA was performed for each endpoint with a Bayesian framework using R 3.2.3 software.

Ref	Comparison	N/n	Outcomes	Result

Xu 2016 Design: SR+MA Search date:	Naratriptan Vs Rizatriptan	N = 1 n = 522	Pain free at 1h	**OR (95% CI): 0.35 (0.14 to 0.84)** **SS in favour of rizatriptan**
			Pain relief at 1h	OR (95% CI): 0.73 (0.49 to 1.08) NS
			Pain free at 2 h	**OR (95% CI): 0.46 (0.31, 0.69)** **SS in favour of rizatriptan**
			Pain relief at 2h	**OR (95% CI): 0.70 (0.51 to 0.97)** **SS in favour of rizatriptan**
			Nausea absence at 2h	OR (95% CI): 0.86 (0.63 to 1.18) NS
			Migraine recurrence	**OR (95% CI): 0.63 (0.41 to 0.96)** **SS in favour of naratriptan (less with naratriptan)**
			Adverse events	OR (95% CI): 0.70 (0.44 to 1.09) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Bomhof 1999 DB-PG-RCT	522	Diagnosis according to IHS		Naratriptan 2.5 mg Vs Rizatriptan 10 mg	Jadad quality score: 4 (as rated in Ashcroft 2004)

				Vs Placebo Single migraine attack treated	

Remarks:
Authors initially carried out a conventional pair-wise meta-analysis which directly compares each pair of treatments. The corresponding odds ratios (ORs) and 95% confidence intervals (CIs) for each study were pooled in order to obtain the overall effect size. Furthermore, a NMA was performed for each endpoint with a Bayesian framework using R 3.2.3 software. In the present document we only reported results from the pair-wise comparisons.

Author's conclusions:
"From pairwise meta-analysis between different medications, rizatriptan is more efficacious than naratriptan concerning 1 h-pain-free, 2 h-pain-free and 2 h-pain-relief. However, naratriptan manifests a lower recurrence than rizatriptan."

12.7.4 Naratriptan versus sumatriptan for acute treatment of migraine attack in adults

Meta-analysis: Ashcroft 2004 (73), Naratriptan for the treatment of acute migraine: meta-analysis of randomised controlled trials Definition of migraine: diagnosed according to the International Headache Society criteria. Inclusion criteria: Only randomised controlled trials (RCTs) of naratriptan taken for symptomatic relief of acute attacks of migraine were considered. Multiple-attack and multiple-dose trials were included provided that single dose information was available separately. Trials were only included if patients in one arm of the trial received a single dose of naratriptan for a single migraine attack. The analysis included only drugs and dosages that are commercially available. Population: Included patients were adults (18–65 years of age) with migraine with or without aura

Search strategy: Reports of RCTs were identified through a systematic electronic search of Medline, Embase and the Cochrane Controlled Trials Register. Medline was searched from 1966 onwards to October 2002 using an optimally sensitive search strategy for identifying RCTs. Text words that were applied to the search included naratriptan, Naramig and Amerge. This was supplemented by searching the reference lists of all retrieved RCTs and contacting the manufacturer of naratriptan. Trial eligibility was determined independently by the two authors. Abstracts were considered; attempts were made to obtain relevant information not included in the published reports by either contacting the principal author of the trial or the manufacturer.

Assessment of quality of included trials: yes

Other methodological remarks:
Single dose of naratriptan for a single migraine attack.
The method of DerSimonian and Laird was used to calculate the pooled estimates and their corresponding 95% CIs.

Ref	Comparison	N/n	Outcomes	Result
Ashcroft 2004 Design: SR+MA Search date: October 2002	Naratriptan 2.5 mg Vs Sumatriptan 100 mg	N = 2 n = 635 (Bates 1998, Havanka 2000)	Pain free at 2 h	**RR (95% CI): 0.69 (0.53 to 0.91)** **SS in favour of sumatriptan**
		N = 2 n = 635 (Bates 1998, Havanka 2000)	Headache relief at 2 h	RR (95% CI): 0.86 (0.74 to 1.00) NS

		N = 2 n = 635 (Bates 1998, Havanka 2000)	Pain free at 4 h	Naratriptan: 124/296 Sumatriptan: 180/339 **RR (95% CI): 0.79 (0.67 to 0.93**) **SS in favour of sumatriptan** I^2: 0%
		N = 2 n = 635 (Bates 1998, Havanka 2000)	Headache relief at 4 h	Naratriptan: 186/296 Sumatriptan: 251/339 **RR (95% CI): 0.85 (0.76 to 0.95)** **SS in favour of sumatriptan** I^2: 3.5%
		N = 2 n = 635 (Bates 1998, Havanka 2000)	Sustained pain relief up to 24h	Naratriptan: 146/296 Sumatriptan: 161/339 RR (95% CI): 1.04 (0.88 to 1.22) NS I^2: 0%
		ND	Adverse events	Naratriptan: 81/285 Sumatriptan: 131/318 **RR (95% CI): 0.68 (0.55 to 0.86)** **SS in favour or naratriptan (less adverse events with naratriptan)**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology

Bates 1998 DB-PG-RCT	1222			Naratriptan 0.1 mg Vs Naratriptan 0.25 mg Vs Naratritptan 1 mg Vs Naratriptan 2.5 mg Vs Sumatriptan 100 mg Placebo Up to three migraine attacks treated	Jadad quality score: 5
Havanka 2000 DB-PG-RCT	643			Naratriptan 1 mg Vs Naratriptan 2.5 mg Vs Naratriptan 5 mg Vs Naratriptan 7.5 mg Vs Naratriptan 10mg Vs Sumatriptan 100 mg Vs Placebo Single migraine attack treated	Jadad quality score: 5
Gobel, 2000a DB, CO-RCT	253	patients with a history of frequent headache recurrence		Naratriptan 2.5 mg Vs Sumatriptan	Jadad quality score: 5

				100mg	

Remarks:

- Given that migraine trials often include patients who are randomised to treatment but who do not have a migraine attack during the study period, the denominator was the number of patients randomised who had a migraine attack of moderate or severe intensity.
- The SR also identified comparison of naratriptan 1 mg over sumatriptan 100mg. This comparison was not reported in the present reported because this is not available/ recommended dose in BE.
- The SR identifies an additional RCT (Gobel 2000 a) that was not pooled in the MA because this included different population: patients with a history of frequent headache recurrence. The results of this population was also not reported in the present document as they are not part of the general population of patient with migraine
- For most of the comparisons reported in this SR, data on specific adverse events were provided including chest pain/symptoms and tightness. As it was not explicitly described if these symptom refers to cardiovascular events, no data were reported in the present document.

Author's conclusions:

"Rizatriptan 10 mg and sumatriptan 100 mg were superior to naratriptan in terms of headache relief, while zolmitriptan 2.5 mg seemed to have comparable efficacy. "

"The assessment of therapeutic efficacy was based on several endpoints. In terms of headache relief and painfree response, rizatriptan 10 mg and sumatriptan 100 mg were significantly superior to naratriptan, while zolmitriptan was not. In contrast, results based on sustained response from 4 to 24 hours found no significant differences between naratriptan and rizatriptan, sumatriptan or zolmitriptan."

"Although naratriptan was associated with adverse effects, the incidence rates were significantly lower than those associated with rizatriptan, sumatriptan or zolmitriptan."

12.7.5 Naratriptan versus zolmitriptan for acute treatment of migraine attack in adults

Meta-analysis: Ashcroft 2004 (73), Naratriptan for the treatment of acute migraine: meta-analysis of randomised controlled trials

Definition of migraine: diagnosed according to the International Headache Society criteria.

Inclusion criteria: Only randomised controlled trials (RCTs) of naratriptan taken for symptomatic relief of acute attacks of migraine were considered. Multiple-attack and multiple-dose trials were included provided that single dose information was available separately.
Trials were only included if patients in one arm of the trial received a single dose of naratriptan for a single migraine attack. The analysis included only drugs and dosages that are commercially available.

Population: Included patients were adults (18–65 years of age) with migraine with or without aura

Search strategy: Reports of RCTs were identified through a systematic electronic search of Medline, Embase and the Cochrane Controlled Trials Register. Medline was searched from 1966 onwards to October 2002 using an optimally sensitive search strategy for identifying RCTs. Text words that were applied to the search included naratriptan, Naramig and Amerge. This was supplemented by searching the reference lists of all retrieved RCTs and contacting the manufacturer of naratriptan. Trial eligibility was determined independently by the two authors. Abstracts were considered; attempts were made to obtain relevant information not included in the published reports by either contacting the principal author of the trial or the manufacturer.

Assessment of quality of included trials: yes

Other methodological remarks:
Single dose of naratriptan for a single migraine attack.
The method of DerSimonian and Laird was used to calculate the pooled estimates and their corresponding 95% CIs.

Ref	Comparison	N/n	Outcomes	Result

Ashcroft 2004 Design: SR+MA Search date: October 2002	Naratriptan 2.5 mg Vs Zolmitriptan 2.5 mg	N = 1 n = 154 (Schoenen 1999)	Pain free at 4 h	Naratriptan: 20/79 Zolmitriptan: 18/75 RR (95% CI): 1.05 (0.61 to 1.83) NS
		N = 1 n = 154 (Schoenen 1999)	Headache relief at 4 h	Naratriptan: 46/79 Zolmitriptan: 43/75 RR (95% CI) : 1.02 (0.78 to 1.33) NS
		N = 1 n = 154 (Schoenen 1999)	Sustained pain relief up to 24h	Naratriptan: 32/79 Zolmitriptan: 29/75 RR (95% CI) : 1.05 (0.71 to 1.55) NS
		N = 1 n = 154 (Schoenen 1999)	Adverse events	Naratriptan: 18/79 Zolmitriptan: 34/75 **RR (95% CI) : 0.50 (0.31 to 0.81)** **SS in favour of naratriptan (less adverse events with naratriptan)**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Schoenen 1999	181			Naratriptan 2.5 mg	Jadad quality score: 5

DB-PG-RCT				Vs Zolmitriptan 2.5 mg Vs Placebo Up to three migraine attacks treated	

Remarks:

- Given that migraine trials often include patients who are randomised to treatment but who do not have a migraine attack during the study period, the denominator was the number of patients randomised who had a migraine attack of moderate or severe intensity.
- Given that this trial was stopped early due to difficulties in obtaining supplies of one of the trial drugs, it is important that these results are interpreted
  with caution.

  Note that Bird 2014 identified a non-published trial (311CIL/0099 2000) for the same comparison. The MA Bird 2014 has not analysed data for this comparison. No other results are presented for this comparison in the present report.
- For most of the comparisons reported in this SR, data on specific adverse events were provided including chest pain/symptoms and tightness. As it was not explicitly described if these symptom refers to cardiovascular events, no data were reported in the present document.

Author's conclusions:

"Rizatriptan 10 mg and sumatriptan 100 mg were superior to naratriptan in terms of headache relief, while zolmitriptan 2.5 mg seemed to have comparable efficacy. "

"The assessment of therapeutic efficacy was based on several endpoints. In terms of headache relief and painfree response, rizatriptan 10 mg and sumatriptan 100 mg were significantly superior to naratriptan, while zolmitriptan was not. In contrast, results based on sustained response from 4 to 24 hours found no significant differences between naratriptan and rizatriptan, sumatriptan or zolmitriptan."

"Although naratriptan was associated with adverse effects, the incidence rates were significantly lower than those associated with rizatriptan, sumatriptan or zolmitriptan."

12.7.6 Rizatriptan versus zolmitriptan for acute treatment of migraine attack in adults

Meta-analysis: Xu 2016(41), Network meta-analysis of migraine disorder treatment by NSAIDs and triptans

Definition of migraine:

Inclusion criteria: Articles were included if they: (1) were randomized clinical trials (RCTs); (2) were categorized as double blind; (3) included relevant clinical outcomes and treatments; (4) contained comparisons between different treatments.

Search strategy: We employed search strategies to explore the medical literature for relevant studies in PubMed and EMBASE systematically, and 2,967 records were identified using the following terms: “migraine disorders”, “tryptans”, “non-steroidal anti-inflammatory agents”, “ergot alkaloids”, “opioid analgesics”, “sumatriptan”, “zolmitriptan”, “almotriptan”, “rizatriptan”, “naratriptan”, “ibuprofen”, “eletriptan”, “diclofenac-potassium” and “aspirin” in PubMed. Reviewers also provided 3 additional references.

Assessment of quality of included trials: yes

Other methodological remarks:
We initially carried out a conventional pair-wise metaanalysis which directly compares each pair of treatments.
The corresponding odds ratios (ORs) and 95% confidence intervals (CIs) for each study were pooled in order to obtain the overall effect size. Furthermore, a NMA was performed for each endpoint with a Bayesian framework using R 3.2.3 software.

Ref	Comparison	N/n	Outcomes	Result
Xu 2016 Design: SR+MA Search date:	Rizatriptan Vs Zolmitriptan	N = 1 n = 727	Pain free at 1h	OR (95% CI): 1.22 (0.73 to 2.02) NS
			Pain relief at 1h	OR (95% CI): 1.20 (0.88 to 1.63) NS

			Pain free at 2 h	OR (95% CI): 1.22 (0.90 to 1.66) NS
			Pain relief at 2h	OR (95% CI): 1.05 (0.81 to 1.35) NS
			Nausea absence at 2h	OR (95% CI): 1.12 (0.87 to 1.44) NS
			Migraine recurrence	OR (95% CI): 0.96 (0.68 to 1.36) NS
			Adverse events	OR (95% CI): 0.89 (0.63 to 1.27) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Pascual 2000 DB, PC RCT	766	Meeting IHS criteria for migraine (1988) with or without aura. Participants required to have a history of migraine for ar least six months and usually experience 1 to 8 attacks/month No MAOI or methysergide within 2 weeks, propranolol within 3 days,	Assessment up to 24 h	zolmitriptan 2.5 mg Vs rizatriptan 10 mg Vs Placebo Single dose to treat single attack	RANDOMIZATION: **Unclear risk** not described" ALLOCATION CONCEALMENT: **Unclear risk** not described" BLINDING: performance bias and detection bias, all outcomes **Unclear risk** not described"

		triptan, ergot or opiate within 24 h and any other analgesic or antiemetic within 6 h. Other stable prophylaxis permitted Excluded participants with cerebrovascular or cardiovascular disease n = 727 for efficacy zolmitriptan 2.5 mg, n = 304 (289 for efficacy) rizatriptan 10 mg, n = 308 (292 for efficacy) placebo, n = 154 (146 for efficacy) F 83% Mean age 39 years With aura 12%		Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication allowed after 2 h	INCOMPLETE OUTCOME DATA: **Low risk** drop-outs described, missing data 5%

Remarks:
Authors initially carried out a conventional pair-wise meta-analysis which directly compares each pair of treatments. The corresponding odds ratios (ORs) and 95% confidence intervals (CIs) for each study were pooled in order to obtain the overall effect size. Furthermore, a NMA was performed for each endpoint with a Bayesian framework using R 3.2.3 software. In the present document we only reported results from the pair-wise comparison

Author's conclusions:
"We can derive that rizatriptan and eletriptan tend to show effective performance with respect to outcomes including 1 h-pain-relief and rescue medication."

12.7.7 Oral sumatriptan versus almotriptan for acute treatment of migraine attack of moderate to severe baseline pain intensity in adults

Meta-analysis: Derry 2012(87), Sumatriptan (oral route of administration) for acute migraine attacks in adults (Review)

Definition of migraine: We used the definition of migraine specified by the International Headache Society (IHS 1988; IHS 2004), although we accepted diagnostic criteria equivalent to those of IHS 1988 where a specific reference was not provided.

Inclusion criteria: We included randomised, double-blind, placebo- and/or active controlled studies using oral sumatriptan to treat a migraine headache episode. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data for at least one of the outcomes specified below. We accepted studies reporting treatment of consecutive headache episodes if outcomes for the first, or each, episode were reported separately. Cross-over studies were accepted if there was adequate washout (N 48 hours) between treatments.

Population : Studies enrolled adults (at least 18 years of age) with migraine. There were no restrictions on migraine frequency, duration, or type (with or without aura). Participants taking stable prophylactic therapy to reduce migraine frequency were accepted. All included studies used one or more of these standard scales (reported in remarks) and reported outcomes as defined above.

Exclusion: We excluded studies designed to demonstrate prophylactic efficacy in reducing the number or frequency of migraine headaches.

Search strategy: We searched the following databases: •the Cochrane Central Register of Controlled Trials (CENTRAL) (2011, Issue 10); • MEDLINE (via OVID) (to 13 October 2011); • EMBASE (via OVID) (to 13 October 2011); • Oxford Pain Relief Database (Jadad 1996a).
We searched reference lists of retrieved studies and review articles for additional studies. We also searched online databases of clinical trials (www.gsk-clinicalstudyregister.com and www.clinicaltrials.gov). We made a written request for information about both published and unpublished data from the manufacturer of sumatriptan (GlaxoSmithKline), and asked specifically for further details on a number of studies published only on their clinical trial database. We did not search grey literature and short abstracts.

Assessment of quality of included trials: yes

Other methodological remarks:
We accepted randomisation at the individual patient level only.
The most likely source of missing data was in cross-over studies.
Where this might be problematic (e.g. where data were missing for > 10% of participants), we used only first-period data where available.

We calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants. We calculated relative risk of benefit or harm with 95% confidence intervals (CIs) using a fixed effect model. We calculated NNT, NNTp, and NNH with 95% CIs using the pooled number of events by the method of Cook and Sackett.

Ref	Comparison	N/n	Outcomes	Result
Derry 2012 Design: SR+MA Search date: October 2011	Sumatriptan 50 mg Vs Almotriptan 12.5 mg	N = 1 n = 1173 (Spierings 2001)	Pain free at 2 h (PO)	Sumatriptan: 143/582 (25%) Almotriptan: 106/591 (18%) Insufficient data for analysis (*P* = 0.005, **SS in favour of sumatriptan** reported in the original study)
		N = 1 n = 1173 (Spierings 2001)	Pain relief at 2 h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	Sumatriptan: 333/582 (57%) Almotriptan: 343/591 (58%) **Insufficient data for analysis**
		N = 1 n = 1173 (Spierings 2001)	Use of rescue medication up to 24 h	Sumatriptan: 193/582 (33%) Almotriptan: 217/591 (37%) **Insufficient data for analysis**
		N = 1 n = 1173	Adverse events over 24 h	Sumatriptan: 113/582 (19%) Almotriptan: 90/591 (15%) Insufficient data for analysis

		(Spierings 2001)		(P = 0.06, **NS** as reported in the original study)
		N = 1 n = 1173 (Spierings 2001)	Palpitation	Sumatriptan: 0/582 (1.3%) Almotriptan: 2/591 (1.0%) **Insufficient data for analysis**
		N = 1 n = 1173 (Spierings 2001)	Vasodilation	Sumatriptan: 8/582 (1.3%) Almotriptan: 6/591 (1.0%) **Insufficient data for analysis**

* Characteristics of included studies: see below

Ref	Comparison	N/n	Outcomes	Result
Derry 2012 Design: SR+MA Search date: October 2011	Sumatriptan 100 mg Vs Almotriptan 12.5 mg	N = 2 n = 754 (Dodick 2002, Dowson 2002)	Pain free at 2h (PO)	Sumatriptan: 129/387 Almotriptan: 102/367 RR (95% CI): 1.2 (0.97 to 1.49) NS I^2: 0%
		N = 2 n = 754 (Dodick 2002, Dowson 2002)	Sustained pain-free over 24 h (PO) (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	Sumatriptan: 111/387 Almotriptan: 110/367 RR (95% CI): 0.96 (0.77 to 1.19) NS I^2: 0%

		N = 1 n = 378 (Dowson 2002)	Adverse events over 24 h	Sumatritpan: 43/194 (22%) Almotritptan: 16/184 (8.6%) Insufficient data for analysis

Ref + design	n	Population	Duration	Comparison	Methodology
Spierings 2001 DB, PC, PG-RCT	1173	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity N moderate) and suffering at least 2 attacks per month, with a minimum interval of 24 h between consecutive attacks. Preventative migraine treatment was allowed, with the exception of monoamine oxidase inhibitors,		Sumatriptan 50 mg Vs Almotriptan 12.5 mg Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity Second dose of study medication available to	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes**: Low risk** Identical-looking capsules Pharmaceutical industry support: Pharmacia

		lithium carbonate, cyproheptadine hydrochloride, methysergide maleate, ergotamine tartrate, and dihydroergotamine mesylate which had to be discontinued at least 2 weeks before enrolment. Participants were excluded if they had ever taken almotriptan before, but could not be triptan naïve Sumatriptan 50 mg, n = 582 Almotriptan 12.5 mg, n = 591 M 129, F 1044 (89%) Mean age 41 years		treat recurrence between 2 and 24h Rescue medication (excluding triptans or ergotamine) available 2 h after taking study medication if migraine pain had not decreased to mild or none	
Dodick 2002 DB, PC, PG-RCT	475	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate) with an average of 1 to 6 attacks per month, each separated by at least a 24-h headache-free period. Exclusion: Participants were excluded if they had a history of migraine with prolonged aura or if they experienced more than 6 headaches per month. No migraine medications (e.g. analgesics, NSAIDS, 5-HT1B/1D receptor agonists, or dopamine	Assessment up to 24 h	Sumatriptan 100 mg Vs Almotriptan 12.5 mg Vs Placebo Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity Second dose of study medication available to	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes**:** **Unclear risk** Not reported

		agonists) for 2 days prior to intake of study medication. No antipsychotic or antidepressant medication within the 3 months preceding study enrolment, or any investigational drug within 1 month of study enrolment Sumatriptan 100 mg, n = 193 Almotriptan 12.5 mg, n = 183 Placebo, n = 99 M 69 F 406 (85%) Mean age 43 years Without aura 79%		treat recurrence within 24 h Rescue medication (excluding ergot alkaloids and 5-HT1B/1D agonists) was available if moderate-to-severe migraine pain persisted 2 h after initial dosing Of the 3 studies reported, only protocol CL13 is relevant	
Dowson 2002 DB, PC, PG-RCT	668	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N moderate) with an average of 1 to 6 attacks per month, each separated by at least a 24-h headache-free period. Exclusion: Participants were excluded if they had a history of migraine with prolonged aura or if they needed symptomatic medication for migraine in the 2 days before taking study medication.	Assessment up to 24 h	Sumatriptan 100 mg Vs Almotriptan 12.5 mg Vs Almotriptan 25 mg Vs Placebo Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes**:** **Unclear risk** Not reported Pharmaceutical industry support: Almirall SA

		No investigational drug within 1 month of study treatment. No monoamine oxidase inhibitors, lithium,selective serotonin reuptake inhibitors, ergots or derivatives, or methysergide in the 2 weeks prior to study medication Sumatriptan 100 mg, n = 194 Almotriptan 12.5 mg, n = 184 Almotriptan 25 mg, n = 191 Placebo, n = 99 M 101 F 567 (85%) Mean age 42 years Without aura 78%		Second dose of study medication available to treat recurrence within 24 h Rescue medication (excluding ergot-derivatives) available if migraine pain did not disappear or become mild within 2 h of treatment	

Remarks:

- We analysed studies using a single dose of sumatriptan in established pain of at least moderate intensity **separately** from studies in which medication was taken before pain became well established or in which a second dose of medication was permitted. All the study includes for this comparison were performed in patient having basal pain of least moderate intensity.
- Only 1 study was found in this SR comparing sumatriptan 50 mg versus almotriptan 12.5 mg. As authors calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants, no analysis was performed for this comparison.
- 2 studies were found comparing sumatriptan 100 mg versus almotriptan 12.5 mg. These studies are reported in the corresponding table. However only Dowson 2002 reported adverse event. As authors calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants, no analysis was performed for this comparison for adverse events.
- The SR only found 1 study comparing sumatriptan 100 mg versus almotriptan 25 mg but was not reported in the present document because it is not an available dosage in BE.
- For most of the comparisons reported in this SR, data on specific adverse events were provided including chest pain/symptoms. As it was not explicitly described if this symptom refers to cardiovascular events no data were reported in the present document.

- Pain intensity or pain relief had to be measured by the patient (not the investigator or carer). Pain measures accepted for the primary outcomes were:

• pain intensity: four-point categorical scale, with wording equivalent to none, mild, moderate, and severe; or 100 mm visual analogue scale (VAS);

• pain relief: five-point categorical scale, with wording equivalent to none, a little, some, a lot, complete; or 100 mm VAS.

12.7.8 Oral sumatriptan versus eletriptan for acute treatment of migraine attack of moderate to severe baseline pain intensity in adults

Meta-analysis: Derry 2012(87), Sumatriptan (oral route of administration) for acute migraine attacks in adults (Review)

Definition of migraine: We used the definition of migraine specified by the International Headache Society (IHS 1988; IHS 2004), although we accepted diagnostic criteria equivalent to those of IHS 1988 where a specific reference was not provided.

Inclusion criteria: We included randomised, double-blind, placebo- and/or active controlled studies using oral sumatriptan to treat a migraine headache episode. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data for at least one of the outcomes specified below. We accepted studies reporting treatment of consecutive headache episodes if outcomes for the first, or each, episode were reported separately. Cross-over studies were accepted if there was adequate washout (N 48 hours) between treatments.

Population : Studies enrolled adults (at least 18 years of age) with migraine. There were no restrictions on migraine frequency, duration, or type (with or without aura). Participants taking stable prophylactic therapy to reduce migraine frequency were accepted. All included studies used one or more of these standard scales (reported in remarks) and reported outcomes as defined above.

Exclusion: We excluded studies designed to demonstrate prophylactic efficacy in reducing the number or frequency of migraine headaches.

Search strategy: We searched the following databases: •the Cochrane Central Register of Controlled Trials (CENTRAL) (2011, Issue 10); • MEDLINE (via OVID) (to 13 October 2011); • EMBASE (via OVID) (to 13 October 2011); • Oxford Pain Relief Database (Jadad 1996a).
We searched reference lists of retrieved studies and review articles for additional studies. We also searched online databases of clinical trials (www.gsk-clinicalstudyregister.com and www.clinicaltrials.gov). We made a written request for information about both published and unpublished data from the manufacturer of sumatriptan (GlaxoSmithKline), and asked specifically for further details on a number of studies published only on their clinical trial database. We did not search grey literature and short abstracts.

Assessment of quality of included trials: yes

<u>Other methodological remarks:</u> We accepted randomisation at the individual patient level only. The most likely source of missing data was in cross-over studies. Where this might be problematic (e.g. where data were missing for > 10% of participants), we used only first-period data where available. We calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants. We calculated relative risk of benefit or harm with 95% confidence intervals (CIs) using a fixed effect model. We calculated NNT, NNTp, and NNH with 95% CIs using the pooled number of events by the method of Cook and Sackett.

Ref	Comparison	N/n	Outcomes	Result
Derry 2012 Design: SR+MA Search date: October 2011	Sumatriptan 50 mg Vs Eletriptan 40 mg	N = 2 n = 721 (160-104; Sandrini 2002)	Pain free at 2 h (PO)	Sumatriptan: 18% (64/362) Eletriptan: 24% (86/359) **RR (95% CI): 0.74 (0.55 to 0.98)** NNT (95% CI): 16 (8.2 to 270) **SS in favour of eletriptan** I^2: 48%
		N = 2 n = 721 (160-104; Sandrini 2002)	Pain relief at 2 h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	Sumatriptan: 51% (186/362) Eletriptan: 60% (217/359) **RR (95% CI):** 0.85 (0.75 to 0.97) NNT (95% CI): 11 (6.1 to 54) **SS in favour of eletriptan** I^2: 19%
		N = 2 n = 721	Pain relief at 1 h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	Sumatriptan: 25% (90/362) Eletriptan: 25% (90/359) RR (95% CI): 0.99 (0.77 to 1.3)

		(160-104; Sandrini 2002)		NS I^2:73%
		N = 2 n = 374 (160-104; Sandrini 2002)	Relief of nausea	Sumatriptan: 71/188 Eletriptan: 93/186 **RR (95% CI): 0.76 (0.6 to 0.95)** NNT: 8.2 **SS in favour of eletriptan** I^2:46%
		N = 2 n = 528 (160-104; Sandrini 2002)	Relief of photophobia	Sumatriptan: 107/261 Eletriptan: 132/267 RR (95% CI): 0.83 (069 to 1.00) NS I^2: 60%
		N = 2 n = 513 (160-104; Sandrini 2002	Relief of phonophobia	Sumatriptan: 120/257 Eletriptan: 139/260 RR (95% CI): 0.87 (073 to 1.04) NS I^2: 66%

		N = 2 n = 590 (160-104; Sandrini 2002)	Relief of functional disability at 2h	Sumatriptan: 51% (153/298 Eletriptan: 62% (180/292 **RR (95% CI): 0.83 (0.72 to 0.96)** NNT (95% CI): 9.7 (5.5 to 43) **SS in favour of eletriptan** I^2: 73%

* Characteristics of included studies: see below

Ref	Comparison	N/n	Outcomes	Result
Derry 2012 Design: SR+MA Search date: October 2011	Sumatriptan 100 mg Vs Eletritpan 40 mg	N = 3 n = 2263 (Goadsby 2000; Mathew 2003; Sandrini 2002)	Pain free at 2h (PO)	Sumatriptan: 24% (271/1130) Eletritpan: 32% (366/1133) **RR (95% CI):** 0**.74 (0.65 to 0.85)** NNT (95% CI): 12 (8.3 to 22) **SS in favour of eletriptan** I^2: 0%
		N = 3 n = 2263 (Goadsby 2000;	Pain relief at 2 h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	Sumatriptan: 55% (622/1130) Eletritpan: 62% (706/1133) **RR (95% CI): 0.88 (0.82 to 0.95)** NNT (95% CI): 14 (8.9 to 31)

		Mathew 2003; Sandrini 2002)		**SS in favour of eletriptan** I^2: 0%
		N = 3 n = 2263 (Goadsby 2000; Mathew 2003; Sandrini 2002)	Pain free at 1 h	Sumatriptan: 5% (59/1130) Eletritpan: 7% (75/1133) RR (95% CI): 0.79 (0.57 to 1.1) NS I^2: 0%
		N = 3 n = 2263 (Goadsby 2000; Mathew 2003; Sandrini 2002)	Pain relief at 1 h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	Sumatriptan: 25% (282/1130) Eletritpan: 32% (368/1133) **RR (95% CI): 0.77 (0.67 to 0.88)** NNT (95% CI): 13 (8.9 to 26) **SS in favour of eletriptan** I^2: 32%
		N = 2 n = 1998 (Mathew 2003; Sandrini 2002)	Sustained pain-relief over 24 h (PO) (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.)	Sumatriptan: 34% (340/1001) Eletritpan: 43% (430/997) **RR (95% CI): 0.79 (0.70 to 0.88)** NNT (95% CI): 11 (7.5 to 20) **SS in favour of eletriptan**

				I^2: 0%
		N = 3 n = 1478 (Goadsby 2000; Mathew 2003; Sandrini 2002)	Relief of nausea	Sumatriptan: 352/719 Eletritpan: 420/759 **RR (95**% CI): 0.87 (0.79 to 0.96) NNT 16 **SS in favour of eletriptan** I^2: 87%
		N = 3 n = 1692 (Goadsby 2000; Mathew 2003; Sandrini 2002)	Relief of photophobia	Sumatriptan: 438/855 Eletritpan: 500/837 **RR (95% CI):** 0.85 (0.78 to 0.93) NNT 12 **SS in favour of eletriptan** I^2: 0%
		N = 3 n = 1361 (Goadsby 2000; Mathew 2003; Sandrini 2002)	Relief of phonophobia	Sumatriptan: 352/691 Eletritpan: 405/670 **RR (95% CI): 0.84 (0.76 to 0.92)** NNT 11 **SS in favour of eletriptan** I^2: 0%

		N = 3 n = 2263 (Goadsby 2000; Mathew 2003; Sandrini 2002)	Relief of functional disability at 2h	Sumatriptan: 59% (553/936) Eletritpan: 68% (645/944) **RR (95% CI): 0.86 (0.81 to 0.92)** NNT (95% CI): 11 (7.4 to 20) **SS in favour of eletriptan** I^2: 36%
		N = 2 n = 1998 (Mathew 2003; Sandrini 2002)	Use of rescue medication	Sumatriptan: 27% (261/960) Eletritpan: 21% (203/958) **RR (95% CI): 1.3 (1.1 to 1.5)** NNT (95% CI): 17 (10 to 46) **SS in favour of eletriptan (more rescue medication with sumatriptan)** I^2: 50%

Ref + design	n	Population	Duration	Comparison	Methodology
160-104 DB, double-dummy, PC, PG-RCT	818 (treated first attack)	Aged 18 years or over and suffering at least 1 acute attack of migraine, with or without aura (IHS 1988),every 6 weeks.	Assessment up to 4 h	Sumatriptan 25 mg Vs Sumatriptan 50 mg Vs Eletriptan 40 mg	RANDOMIZATION: **Low risk** Computer-generated pseudo-random code using the method of random permuted blocks

		Exclusions: participants excluded if ever taken sumatriptan before (any formulation) or oral eletriptan No prescription analgesic or antiemetic within 6 hours prior to study treatment No sumatriptan, ergotamine, or ergotamine-like agent within previous 48 hours Sumatriptan 25 mg, n = 180 Sumatriptan 50 mg, n = 181 Eletriptan 40 mg, n = 184 Eletriptan 80 mg, n = 180 Placebo, n = 93 M 150 F 668 (82%) Mean age 35 years Without aura 86%		Vs Eletriptan 80 mg Vs Placebo Single dose to treat each of up to 3 separate attacks Medication administered when migraine headache pain was of moderate or severe intensity Second dose (either same as first dose of study medication or a double-blind placebo) available after 2 hours for inadequate response, or for recurrence of headache within 24 hours of initial dosing Alternative rescue medication available 2 hours after second dose if appropriate	ALLOCATION CONCEALMENT: **Low risk** Next consecutive number corresponding to study drug in blister card BLINDING: performance bias and detection bias, all outcomes**: Low risk** Double-dummy Pharmaceutical industry support: Pfizer
Sandrini 2002 DB, double dummy, PC, PG-RCT	774	Aged 18 years or older, meeting IHS criteria for migraine (1988) with or without aura, and suffering at least 1 attack every 6 weeks.	Assessment up to 24 h	Sumatriptan 50 mg Vs Sumatriptan 100 mg Vs Eletriptan 40 mg Vs	RANDOMIZATION**: Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported

		Exclusion: Participants were excluded if they had previously taken oral eletriptan or any formulation of sumatriptan. No ergotamine or any ergotamine-like agent within 48 h before, or 24 h after, taking study medication. No proprietary analgesic or antiemetic within 6 h of taking study medication. Sumatriptan 50 mg, n = 181 Sumatriptan 100 mg, n = 170 Eletriptan 40 mg, n = 175 Eletriptan 80 mg, n = 164 Placebo, n = 84 M 93 F 681 (88%) Mean age 38 years Without aura 65%		Eletriptan 80 mg Vs Placebo Single dose to treat each of up to 3 successive attacks Medication administered within 6 h of onset of a migraine attack, when the headache pain was of moderate or severe intensity, and if any aura phase had ended Second, blinded and randomised dose of study medication was available if there was no response to treatment after 2 h, or if there was a recurrence of headache within 24 h Rescue medication was available 2 h after the second dose if there was still no improvement in headache	BLINDING: performance bias and detection bias, all outcomes **Low risk** Double-dummy technique Pharmaceutical industry support: Pfizer Ltd
Goadsby 2000 DB, double dummy, PC, PG-RCT	692	Aged 18 or over, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity N	Assessment up to 2 h	Sumatriptan 100 mg Vs Eletriptan 20 mg Vs	RANDOMIZATION: **Low risk** Computer-generated pseudorandom code using method of random permuted

		moderate) with frequency of at least one attack every 6 weeks. Exclusion: Participants were excluded if they had more than 6 attacks per month No sumatriptan or any ergotamine-like compound within 48 h of taking study medication Sumatriptan 100 mg, n = 129 Eletriptan 20 mg, n = 144 Eletriptan 40 mg, n = 136 Eletriptan 80 mg, n = 141 Placebo, n = 142 M 124 F 568 (82%) Mean age 40 years Without aura 68%		Eletriptan 40 mg Vs Eletriptan 80 mg Vs Placebo Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity, and only if the aura phase had ended. Second blinded dose of study medication was available to treat recurrence within 24 h Rescue medication (analgesics, NSAIDs, or antiemetics) available as needed beginning 2 h after initial dosing	Blocks ALLOCATION CONCEALMENT: **Low risk** Study medication supplied pre-packed, dispensed as next consecutive number BLINDING: performance bias and detection bias, all outcomes**: Low risk** Double-dummy technique Pharmaceutical industry support: Pfizer Inc
Mathew 2003 DB, Double-dummy, PC, PG-RCT	2113	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura and a monthly frequency of 1 to 6 attacks.	Assessment up to 24 h	Sumatriptan 100 mg Vs Eletriptan 40 mg Vs Placebo	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Low risk** Double-dummy technique

		No use of potent CYP3A4 inhibitors or monoamine oxidase inhibitors within 2 weeks prior to study entry. No analgesic or antiemetic within 6 h, or triptan, ergotamine-containing or ergot-type medication within 48 h of taking study medication n = 2072 analysed for efficacy Sumatriptan 100 mg, n = 831 Eletriptan 40 mg, n = 822 Placebo, n = 419 M 277 F 1795 (87%) Mean age 42 years Without aura 65%		Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity Second dose of study medication available to treat recurrence after 2 h Rescue medication available after 2 h for inadequate headache relief, although participants not permitted to take any other triptan, ergotamine, or ergotamine-like substance for 24 h after initial dosing	Pharmaceutical industry support: Pfizer Ltd

Remarks:

- We analysed studies using a single dose of sumatriptan in established pain of at least moderate intensity **separately** from studies in which medication was taken before pain became well established or in which a second dose of medication was permitted. All the study includes for this comparison were preformed in patient having basal pain of least moderate intensity.
- 160-104 is a clinical trial report provided by the manufacturer.
- Other comparisons between sumatriptan and eletriptan were found in the SR for other dosages (sumatriptan 25 mg and eletritpan 80 mg) but were not reported in the present document because these are not available dosages in BE.
- For most of the comparisons reported in this SR, data on specific adverse events were provided including chest pain/symptoms. As it was not explicitly described if this symptom refers to cardiovascular events no data were reported in the present document. Adverse events were not report in the MA for these comparisons.

- Pain intensity or pain relief had to be measured by the patient (not the investigator or carer). Pain measures accepted for the primary outcomes were:

• pain intensity: four-point categorical scale, with wording equivalent to none, mild, moderate, and severe; or 100 mm visual analogue scale (VAS);
• pain relief: five-point categorical scale, with wording equivalent to none, a little, some, a lot, complete; or 100 mm VAS.

Author's conclusion:
"Eletriptan 40 mg and 80 mg were superior to sumatriptan 50 mg and 100 mg for most reported outcomes, including pain-free at two hours, and headache relief at one and two hours. However, there was no significant difference between sumatriptan 50 mg and eletriptan 40 mg for headache relief at one hour, or sumatriptan 100 mg and eletriptan 40 mg for pain-free at one hour. "

12.7.9 Oral sumatriptan versus rizatriptan for acute treatment of migraine attack of moderate to severe baseline pain intensity in adults

Meta-analysis: Derry 2012(87), Sumatriptan (oral route of administration) for acute migraine attacks in adults (Review)

Definition of migraine: We used the definition of migraine specified by the International Headache Society (IHS 1988; IHS 2004), although we accepted diagnostic criteria equivalent to those of IHS 1988 where a specific reference was not provided.

Inclusion criteria: We included randomised, double-blind, placebo- and/or active controlled studies using oral sumatriptan to treat a migraine headache episode. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data for at least one of the outcomes specified below. We accepted studies reporting treatment of consecutive headache episodes if outcomes for the first, or each, episode were reported separately. Cross-over studies were accepted if there was adequate washout (N 48 hours) between treatments.

Population : Studies enrolled adults (at least 18 years of age) with migraine. There were no restrictions on migraine frequency, duration, or type (with or without aura). Participants taking stable prophylactic therapy to reduce migraine frequency were accepted. All included studies used one or more of these standard scales (reported in remarks) and reported outcomes as defined above.

Exclusion: We excluded studies designed to demonstrate prophylactic efficacy in reducing the number or frequency of migraine headaches.

Search strategy: We searched the following databases: •the Cochrane Central Register of Controlled Trials (CENTRAL) (2011, Issue 10); • MEDLINE (via OVID) (to 13 October 2011); • EMBASE (via OVID) (to 13 October 2011); • Oxford Pain Relief Database (Jadad 1996a).

We searched reference lists of retrieved studies and review articles for additional studies. We also searched online databases of clinical trials (www.gsk-clinicalstudyregister.com and www.clinicaltrials.gov). We made a written request for information about both published and unpublished data from the manufacturer of sumatriptan (GlaxoSmithKline), and asked specifically for further details on a number of studies published only on their clinical trial database. We did not search grey literature and short abstracts.

Assessment of quality of included trials: yes

Other methodological remarks:
We accepted randomisation at the individual patient level only.
The most likely source of missing data was in cross-over studies. Where this might be problematic (e.g. where data were missing for > 10% of participants), we used only first-period data where available.
We calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants.
We calculated relative risk of benefit or harm with 95% confidence intervals (CIs) using a fixed effect model. We calculated NNT, NNTp, and NNH with 95% CIs using the pooled number of events by the method of Cook and Sackett.

Ref	Comparison	N/n	Outcomes	Result
Derry 2012 Design: SR+MA Search date: October 2011	Sumatriptan 50 mg Vs Rizatriptan 10 mg	N = 2 n = 2230 (Goldstein 1998; Kolodny 2004)	Pain free at 2 h (PO)	Sumatriptan: 35% (394/1116) Rizatriptan: 39% (440/1114) RR (95% CI): 0.89 (0.80 to 1.0) NS I^2: 0%
		N = 2 n = 2230 (Goldstein 1998; Kolodny 2004)	Pain relief at 2 h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	Sumatriptan: 64% (710/1116) Rizatriptan: 70% (780/1114) **RR (95% CI): 0.91 (0.86 to 0.97)** NNT (95% CI): 16 (9.9 to 43) **SS in favour of rizatriptan**

				I^2: 72%
		N = 2 n = 2230 (Goldstein 1998; Kolodny 2004)	Pain relief at 1 h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	Sumatriptan: 37% (409/1116) Rizatriptan: 41% (456/1114) **RR (95% CI): 0.90 (0.81 to 0.99)** **SS in favour of rizatriptan** I^2: 0%
		N = 2 n = 2230 (Goldstein 1998; Kolodny 2004)	Presence of nausea at 2 h	RR (95% CI): 1.2 (1.0 to 1.4) NS
		N = 2 n = 2230 (Goldstein 1998; Kolodny 2004)	Presence of photophobia	RR (95% CI): 1.1 (0.96 to 1.2) NS
		N = 2 n = 2230 (Goldstein 1998; Kolodny 2004)	Presence of phonophobia	RR (95% CI): 1.1 (0.96 to 1.2) NS
		N = 2 n = 1714 (Goldstein 1998; Kolodny 2004)	Use of rescue medication up to 4h	Sumatriptan: 20% (167/851) Rizatriptan: 20% (175/863) RR (95% CI): 0.97 (0.80 to 1.2) NS I^2: 0%

		N = 2 n = 1177 (Goldstein 1998; Kolodny 2004)	Adverse events within 24h	Sumatriptan: 48% (276/578) Rizatriptan: 46% (276/599 RR (95% CI): 1.0 (0.92 to 1.2) NS I^2: 0%

* Characteristics of included studies: see below

Ref	Comparison	N/n	Outcomes	Result
Derry 2012 Design: SR+MA Search date: October 2011	Sumatriptan 100 mg Vs Rizatriptan 10 mg	N = 2 n = 936 (Tfelt-Hansen 1998; Visser 1996)	Pain free at 2h (PO)	Sumatriptan: 31% (143/460) Rizatriptan: 37% (178/476) **RR (95% CI): 0.82 (0.69 to 0.98)** NNT (95% CI): 16 (8.1 to 41) **SS in favour of rizatriptan** I^2: 0%
		N = 2 n = 936 (Tfelt-Hansen 1998; Visser 1996)	Pain relief at 1 h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	Sumatriptan: 26% (120/460) Rizatriptan: 34% (163/476) **RR (95% CI): 0.76 (0.62 to 0.92)** NNT (95% CI): 12 (7.1 to 43) **SS in favour of rizatriptan** I^2: 0%

		N = 2 n = 856 (Tfelt-Hansen 1998; Visser 1996)	Adverse events within 24 h	Sumatriptan: 52% (217/421) Rizatriptan: 47% (203/435) RR (95% CI): 1.1 (0.96 to 1.3) NS I^2: 0%

Ref + design	n	Population	Duration	Comparison	Methodology
Goldstein 1998 DB, PC, CO-RCT	1329	Aged 18 to 91, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity N moderate) with an average of 1 to 8 attacks per month. No monoamine oxidase inhibitors, propranolol, or lithium within 2 weeks; no sumatriptan, ergot derivatives, or opiates within 24 h; and no other form of analgesia or antiemetic within 6 h of taking study medication Standard migraine prophylaxis was permitted with the exception of NSAIDs and propranolol n = 1205 analysed for efficacy Sumatriptan 25 mg, n = 563 Sumatriptan 50 mg, n = 566	Assessment up to 4 h	Sumatriptan 25 mg Vs Sumatriptan 50 mg Vs Rizatriptan 5 mg Vs Rizatriptan 10 mg Vs Placebo Single dose to treat each of 2 successive attacks Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication available after 2 h for inadequate headache response	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** Not reported Pharmaceutical industry support: Merck Research Laboratories (supplies of sumatriptan provided by Glaxo Wellcome)

		Rizatriptan 5 mg, n = 557 Rizatriptan 10 mg, n = 567 Placebo, n = 141 M 162, F 1167 (88%) Mean age 40 years Without aura 89%		Each treated attack was separated by a minimum of 5 days	
Kolodny 2004 DB, PC, CO-RCT	1447	Aged 18 years or older, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity N moderate) No monoamine oxidase inhibitors, methysergide, or propranolol during the study period Standard antimigraine prophylactic medications (with the exception of NSAIDs, daily analgesics, or propanolol) were permitted n = 1287 analysed for efficacy Sumatriptan 25 mg, n = 554 (290 1st attack only) Sumatriptan 50 mg, n = 550 (285 1st attack only) Rizatriptan 5 mg, n = 536 (288 1st attack only) Rizatriptan 10 mg, n = 547 (296 1st attack only) Placebo, n = 288	Assessment up to 4 h	Sumatriptan 25 mg Vs Sumatriptan 50 mg Vs Rizatriptan 5 mg Vs Rizatriptan 10 mg Vs Placebo Single dose to treat each of 2 consecutive attacks Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication (analgesics or antiemetics) was permitted from 2 h onwards in case of treatment failure or headache recurrence	RANDOMIZATION: **Low risk** Computer-generated randomisation schedules ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Low risk** Matched placebos Pharmaceutical industry support: Merck & Co.

		M 203 F 1244 (86%) Mean age 40 years			
Tfelt-Hansen 1998 DB, trible dummy, PC, PG-RCT	1099	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity N moderate) and suffering an average of 1 to 8 attacks per month Exclusion: Participants were excluded if they had ever been exposed to rizatriptan before No monoamine oxidase inhibitors, methysergide, or lithium within 2 weeks; sumatriptan, Midrin, or ergot derivatives within 48 h; any opiate within 24 h; or any other form of analgesia or antiemetic within 6 h of taking study medication Standard migraine prophylaxis was permitted with the exception of NSAIDs Sumatriptan 100 mg, n = 388 Rizatriptan 5 mg, n = 164 Rizatriptan 10 mg, n = 387 Placebo, n = 160 M 201	Assessment up to 4 h	Sumatriptan 100 mg Vs Rizatriptan 5 mg Vs Rizatriptan 10 mg Vs Placebo Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication was available to treat non-response at 2 h, or recurrence within 24 of initial dosing. Sumatriptan, Midrin, and ergot derivatives were prohibited as rescue medications until 24 after initial dosing.	RANDOMIZATION: **Low risk** Computer-generated schedule ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: ***Low risk*** Triple-dummy technique Pharmaceutical industry support: Merck & Co.

		F 898 (82%) Mean age 38 years Without aura 84%			
Visser 1996; DB, PC, PG-RCT	449	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity N moderate) and suffering 8 or fewer migraine attacks per month. No fluoxetine hydrochloride within 6 weeks, prophylactic antimigraine treatment within 2 weeks, ergot derivatives or sumatriptan within 48 h, opiate within 24 h, or any other form of analgesia within 6 h of taking study medication Sumatriptan 100 mg, n = 72 Rizatriptan 10 mg, n = 89 Rizatriptan 20 mg, n = 82 Rizatriptan 40 mg, n = 121 Placebo, n = 85 M 47 F 402 (90%) Mean age 40 years Proportion with/without aura not reported	Assessment up to 2 h	Sumatriptan 100 mg Vs Rizatriptan 10 mg Vs Rizatriptan 20 mg Vs Rizatriptan 40 mg Vs Placebo Single dose to treat single attack Medication administered when migraine headache pain was of moderate or severe intensity Second, blinded dose of study medication available after 2 h for inadequate headache response Rescue medication (opiates, acetaminophen, or NSAIDs) available after 4 h, and sumatriptan or ergotamine-derivatives available after 24h.	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: ***Low risk*** Matching capsules Study Pharmaceutical industry support: Merck Research Laboratories

Remarks:

- We analysed studies using a single dose of sumatriptan in established pain of at least moderate intensity **separately** from studies in which medication was taken before pain became well established or in which a second dose of medication was permitted. All the study includes for this comparison were preformed in patient having basal pain of least moderate intensity.
- 160-104 is a clinical trial report provided by the manufacturer.
- For most of the comparisons reported in this SR, data on specific adverse events were provided including chest pain/symptoms. As it was not explicitly described if this symptom refers to cardiovascular events no data were reported in the present document.
- Other comparisons between sumatriptan and rizatriptan were found in the SR for other dosages (sumatriptan 25 mg and rizatriptan 5 mg) but were not reported in the present document because these are not available dosages in BE.
- Pain intensity or pain relief had to be measured by the patient (not the investigator or carer). Pain measures accepted for the primary outcomes were:

• pain intensity: four-point categorical scale, with wording equivalent to none, mild, moderate, and severe; or 100 mm visual analogue scale (VAS);

• pain relief: five-point categorical scale, with wording equivalent to none, a little, some, a lot, complete; or 100 mm VAS.

Author's conclusion:

"Rizatriptan 10 mg was superior to sumatriptan 25 mg, 50 mg, and 100 mg for all reported outcomes, including pain-free at two hours and headache relief at one and two hours."

12.7.10 Zolmitriptan versus frovatriptan for acute treatment of migraine attack in adults

Meta-analysis: Bird 2014 (158), Zolmitriptan for acute migraine attacks in adults.

Definition of migraine: We used the definition of migraine specified by the International Headache Society (IHS 1988; IHS 2004), although we accepted diagnostic criteria equivalent to those of IHS 1988 where a specific reference was not provided.

Inclusion criteria: We included randomised, double-blind, placebo- and/or active controlled studies using zolmitriptan to treat a migraine headache episode. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data for at least one of the outcomes specified

below. We accepted studies reporting treatment of consecutive headache episodes if outcomes for the first, or each, episode were reported separately. Cross-over studies were accepted if there was adequate washout (N 48 hours) between treatments.

Population : Studies enrolled adults (at least 18 years of age) with migraine. There were no restrictions on migraine frequency, duration, or type (with or without aura). Participants taking stable prophylactic therapy to reduce migraine frequency were accepted. All included studies used one or more of these standard scales (reported in remarks) and reported outcomes as defined above.

Exclusion: We excluded studies designed to demonstrate prophylactic efficacy in reducing the number or frequency of migraine headaches.

Search strategy: We searched the following electronic databases: • the Cochrane Central Register of Controlled Trials (CENTRAL), *The Cochrane Library* (Issue 3 of 12, 2014). • MEDLINE (via Ovid) (1990 to 12 March 2014). • EMBASE (via Ovid) (1990 to 12 March 2014). • Oxford Pain Relief Database, searched on 22 May 2013. Searches of MEDLINE and EMBASE started in 2009 because we were looking only for randomised controlled trials and these two databases are routinely searched and all controlled trials added to CENTRAL. This may not capture studies that have been published or indexed in the previous year, but searching back to 2009 provided a considerable overlap. We did not apply any language restrictions.
We searched for additional studies in reference lists of retrieved studies and review articles, and in three clinical trials databases (www.astrazenecaclinicaltrials.com, www.clinicaltrials.gov, and apps.who.int/trial search). AstraZeneca, the manufacturer of Zomig, provided a database search of publications relating to zolmitriptan in migraine; no mention of unpublished data was made. No studies, published or unpublished, were identified in the list they provided that were not identified by our searches.

Assessment of quality of included trials: yes

Other methodological remarks:
We accepted randomisation to the individual patient only.
For analysis of studies with more than one treatment arm contributing to any one analysis (for example two formulations of the same dose of zolmitriptan in the same study with a single placebo group), we would split the placebo group equally between the two treatment arms so as not to double-count placebo participants.
Where participants treated more than one attack we used first attack data preferentially. When that was not reported we have used data from combined attacks and have considered how this might fect the results.
The most likely source of missing data was in cross-over studies; we planned to use only the first-period data where possible, but where that was not provided we treated the results as if they were parallel group results.
For all outcomes we carried out analyses, as far as possible, on a modified intention-to-treat (ITT) basis. Where sufficient information was reported, we re-included missing data in the analyses we undertook. We planned to exclude data from outcomes where data from 10% or more of participants were missing with no acceptable reason provided or apparent.

We calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants. Relative risk (RR) of benefit ('relative benefit') or harm ('relative risk') was calculated with 95% confidence intervals (CIs) using a fixed-effect model. We calculated NNT, NNTp, and NNH with 95% CIs, where possible, using the pooled number of events by the method of Cook and Sackett.

Ref	Comparison	N/n	Outcomes	Result
Bird 2014 Design: SR+MA Search date: March 2014	Zolmitriptan 2.5 mg Vs Frovatriptan 2.5 mg	N = 1 n = 493 (Tullo 2010)	Pain free at 2h (PO)	Zolmitriptan: 94/303 Frovatriptan: 80/308 No statistical analysis reported
		N = 1 n = 493 (Tullo 2010)	Pain relief at 2h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	Zolmitriptan: 142/245 Frovatriptan: 141/247 No statistical analysis reported
		N = 1 n = 121 (Tullo 2010)	Adverse events	Zolmitriptan: 5/121 Frovatriptan: 2/121 No statistical analysis reported
		N = 1 n = 121 (Tullo 2010)	Angina-like symptoms (tachycardia, thoracic constriction, or pain)	Zolmitriptan: 4/121 Frovatriptan: 0/121 No statistical analysis reported

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Tullo 2010 DB, CO-RCT	121	Aged 18 - 65 years, meeting IHS criteria for migraine with or without aura. Participants were required to have at least 1 attack/month for the previous 6 months No MAOI Excluded participants with uncontrolled hypertension or cardiac, vascular, liver or renal impairment. Also excluded those with a history of previous inadequate response to Q2 triptans 107 for efficacy zolmitriptan 2.5 mg, n = 107 frovatriptan 2.5 mg, n = 107 M 22, F 85 (79%) Mean age 38 years With aura 15%	Assessment up to 48 h	zolmitriptan 2.5 mg Vs frovatriptan 2.5 mg Single dose to treat each of 3 attacks, as soon as possible after onset, in a maximum of 3 months for each treatment period 2nd dose allowed after 2 h if insufficient relief obtained Rescue medication (not triptan, ergot) allowed 1 h after 2nd dose	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** Not reported INCOMPLETE OUTCOME DATA: **Unclear risk** ITT analysis, but denominators unclear

Remarks:

- Authors analysed studies using a single dose of zolmitriptan in established pain of at least moderate intensity s**eparately** from studies in which the medication was taken before pain became well established, or in which a second dose of medication was required. Tullo 2010 treated 'as soon as possible', reporting for mixed baseline pain intensities.
- Only on study was found in the SR for this comparison, as authors calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants, no analysis was performed for this comparison.

- Tullo 2010 scored 2/5 Oxford Quality Scale. Tullo 2010 did there appear to be potential for missing data.
- Tullo 2010 reported events per treatment group, but it was unclear how multiple attacks were combined.
- Pain intensity or pain relief had to be measured by the patient (not the investigator or carer). Pain measures accepted for the primary outcomes were:

• pain intensity: four-point categorical scale, with wording equivalent to none, mild, moderate, and severe; or 100 mm visual analogue scale (VAS);
• pain relief: five-point categorical scale, with wording equivalent to none, a little, some, a lot, complete; or 100 mm VAS.

12.7.11 Zolmitriptan versus sumatriptan for acute treatment of migraine attack of moderate to severe basal pain intensity in adults

Meta-analysis: Bird 2014(158), Zolmitriptan for acute migraine attacks in adults.

Definition of migraine: We used the definition of migraine specified by the International Headache Society (IHS 1988; IHS 2004), although we accepted diagnostic criteria equivalent to those of IHS 1988 where a specific reference was not provided.

Inclusion criteria: We included randomised, double-blind, placebo- and/or active controlled studies using zolmitriptan to treat a migraine headache episode. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data for at least one of the outcomes specified below. We accepted studies reporting treatment of consecutive headache episodes if outcomes for the first, or each, episode were reported separately. Cross-over studies were accepted if there was adequate washout (N 48 hours) between treatments.

Population : Studies enrolled adults (at least 18 years of age) with migraine. There were no restrictions on migraine frequency, duration, or type (with or without aura). Participants taking stable prophylactic therapy to reduce migraine frequency were accepted. All included studies used one or more of these standard scales (reported in remarks) and reported outcomes as defined above.

Exclusion: We excluded studies designed to demonstrate prophylactic efficacy in reducing the number or frequency of migraine headaches.

Search strategy: We searched the following electronic databases: • the Cochrane Central Register of Controlled Trials (CENTRAL), *The Cochrane Library* (Issue 3 of 12, 2014). • MEDLINE (via Ovid) (1990 to 12 March 2014). • EMBASE (via Ovid) (1990 to 12 March 2014). • Oxford Pain Relief Database, searched on 22 May 2013. Searches of MEDLINE and EMBASE started in 2009 because we were looking only for randomised controlled trials and these two databases are routinely searched and all controlled trials added to CENTRAL. This may not capture studies that have been published or indexed in the previous year, but searching back to 2009 provided a considerable overlap. We did not apply any language restrictions.
We searched for additional studies in reference lists of retrieved studies and review articles, and in three clinical trials databases (www.astrazenecaclinicaltrials.com, www.clinicaltrials.gov, and apps.who.int/trialsearch). AstraZeneca, the manufacturer of Zomig, provided a database

search of publications relating to zolmitriptan in migraine; no mention of unpublished data was made. No studies, published or unpublished, were identified in the list they provided that were not identified by our searches.

Assessment of quality of included trials: yes

Other methodological remarks:
We accepted randomisation to the individual patient only.
For analysis of studies with more than one treatment arm contributing to any one analysis (for example two formulations of the same dose of zolmitriptan in the same study with a single placebo group), we would split the placebo group equally between the two treatment arms so as not to double-count placebo participants.
Where participants treated more than one attack we used first attack data preferentially. When that was not reported we have used data from combined attacks and have considered how this might fect the results.
The most likely source of missing data was in cross-over studies; we planned to use only the first-period data where possible, but where that was not provided we treated the results as if they were parallel group results.
For all outcomes we carried out analyses, as far as possible, on a modified intention-to-treat (ITT) basis. Where sufficient information was reported, we re-included missing data in the analyses we undertook. We planned to exclude data from outcomes where data from 10% or more of participants were missing with no acceptable reason provided or apparent.
We calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants. Relative risk (RR) of benefit ('relative benefit') or harm ('relative risk') was calculated with 95% confidence intervals (CIs) using a fixed-effect model. We calculated NNT, NNTp, and NNH with 95% CIs, where possible, using the pooled number of events by the method of Cook and Sackett.

Ref	Comparison	N/n	Outcomes	Result
Bird 2014 Design: SR+MA Search date:	Zolmitriptan 2.5 mg Vs	N = 1 n = 1008 attacks (Gruffyd-Jones 2001)	Pain free at 2h (PO)	Zolmitriptan: 160/500 Sumatriptan: 187/508 **No statistical analysis**

March 2014	Sumatriptan 50 mg	N = 2 n = 1609 attacks (Gallagher 2000; Gruffyd-Jones 2001)	Pain relief at 2h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	Zolmitriptan: 66% (521/795) Sumatriptan: 68% (554/814) RR (95% CI): 0.96 (0.90 to 1.03) NS I^2: 73%
		N = 1 n = 1008 attacks (Gruffyd-Jones 2001)	Sustained pain-free over 24h (PO) (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	Zolmitriptan: 126/500 Sumatriptan: 138/508 OR 0.90 (0.73 to 1.12) NS
		N = 1 n = 3474 attacks (Gruffyd-Jones 2001)	Sustained pain relief over 24 h (PO) (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.)	Zolmitriptan: 705/1680 Sumatriptan: 780/1794 OR 0.94 (0.78 to 1.14) NS
		N = 1 n = 2964 attacks (Gruffyd-Jones 2001)	Use of rescue medication	Zolmitriptan: 631/1271 Sumatriptan: 620/1693 **No statistical analysis**
		N = 2 n = 1777 attacks (Gallagher 2000;	Adverse events	Zolmitriptan: 32% (283/878) Sumatriptan: 28% (251/893) RR (95% CI): 1.1 (0.99 to 1.3) NS

		Gruffyd-Jones 2001)		

* Characteristics of included studies: see below

Ref	Comparison	N/n	Outcomes	Result
Bird 2014 Design: SR+MA Search date: March 2014	Zolmitriptan 5 mg Vs Sumatriptan 50 mg	N = 1 n = 1022 attacks (Gruffyd-Jones 2001)	Pain free at 2h (PO)	Zolmitriptan: 190/514 Sumatriptan: 187/508 **No statistical analysis**
		N = 2 n = 1633 attacks (Gallagher 2000; Gruffyd-Jones 2001)	Pain relief at 2h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	Zolmitriptan: 67% (545/819) Sumatriptan: 68% (554/814) RR (95% CI): 0.98 (0.92 to 1.1) NS
		N = 1 n = 1022 attacks (Gruffyd-Jones 2001)	Sustained pain-free over 24h (PO) (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	Zolmitriptan: 125/514 Sumatriptan: 138/508 OR 1.09 (0.88 to 1.36) NS

		N = 1 n = 3597 attacks (Gruffyd-Jones 2001)	Sustained pain relief over 24 h (PO) (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.)	Zolmitriptan: 803/1803 Sumatriptan: 780/1794 OR 1.07 (0.89 to 1.29) NS
		N = 1 n = 3437 attacks (Gruffyd-Jones 2001)	Use of rescue medication	Zolmitriptan: 608/2744 Sumatriptan: 620/2693 **No statistical analysis**
		N = 2 n = 1789 attacks (Gallagher 2000; Gruffyd-Jones 2001)	Adverse events	Zolmitriptan: 31% (280/896) Sumatriptan: 28% (251/893) RR (95% CI): 1.1 (0.96 to 1.3) NS

* Characteristics of included studies: see below

Ref	Comparison	N/n	Outcomes	Result
Bird 2014 Design: SR+MA Search date:	Zolmitriptan 5 mg Vs	N = 1 n = 1002 (Geraud 2000)	Pain free at 2h (PO)	Zolmitriptan: 144/491 Sumatriptan: 150/499 P<0.05 **SS in favour of sumatriptan 100 mg**

March 2014	Sumatriptan 100 mg	N = 1 n = 1002 (Geraud 2000)	Pain relief at 2h (PO) (Headache relief was defined as a decrease from an initial moderate or severe headache to mild or none.)	Zolmitriptan: 288/491 Sumatriptan: 304/498 P<0.05 **SS in favour of sumatriptan 100 mg**
		N = 1 n = 1002 (Geraud 2000)	Sustained pain relief over 24 h (PO) (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.)	Zolmitriptan: 180/498 Sumatriptan: 195/504 No statistical analysis
		N = 1 n = 1002 (Geraud 2000)	Use of rescue medication	Zolmitriptan: 189/498 Sumatriptan: 192/504 No statistical analysis
		N = 1 n = 983 (Geraud 2000)	Adverse events	Zolmitriptan: 287/491 Sumatriptan: 279/492 No statistical analysis

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Gallagher 2000 DB, PG-RCT	1338	Aged 18- 65 years, meeting IHS criteria for migraine (1988) with or without aura. Patients required to have a history of attacks for at least 1 year No MAOI, methysergide, methylergonovine, (dex)fenfluramine	Assessment up to 24 h	zolmitriptan 2.5 mg Vs zolmitriptan 5 mg Vs sumatriptan 25 mg Vs sumatriptan 50 mg,	RANDOMIZATION: **Unclear risk** Not reported ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Unclear risk** Not reported

		Excluded participants with hypertension or cardiovascular problems 1212 treated 2 attacks - 6187 attacks in total zolmitriptan 2.5 mg, n = 327 (295 for efficacy) zolmitriptan 5 mg, n = 337 (305 for efficacy) sumatriptan 25 mg, n = 336 (306 for efficacy) sumatriptan 50 mg, n = 338 (306 for efficacy) F 87% Mean age 40 years Without aura ˜57%		Single dose to treat each of up to six attacks. Second identical dose was available for recurrence 4 to 24 h Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication permitted after 2 h (but no acute antimigraine treatments)	INCOMPLETE OUTCOME DATA: **Unclear risk** ITT analysis, ITT population comprised participants treating > 2 attacks
Gruffyd-Jones 2001 DB, PG-RCT	1666	Aged 18- 65 years, meeting IHS criteria of migraine (2004) with or without aura Participants required to have a history of migraine for at least 1 year, with onset < 50 years and 2 to 6 attacks/month in the previous 2 months No MAOI, methysergide or methylergonovine within 2 weeks. No ergot derivative, sumatriptan or opiate	Assessment up to 24 h	zolmitriptan 2.5 mg vs zolmitriptan 5 mg Vs sumatriptan 50 mg Single dose to treat each of up to six attacks. 2nd identical dose available for recurrence 2 to 24 h Medication administered when migraine headache	RANDOMIZATION: **Low risk** "computer-generated random numbers scheme" ALLOCATION CONCEALMENT: **Unclear risk** Not reported BLINDING: performance bias and detection bias, all outcomes: **Low risk** Double dummy INCOMPLETE OUTCOME DATA: **Unclear risk** ITT analysis, ITT population comprised participants treating > 2 attacks

		within 24 h, other analgesic within 6 h. Other medications (including prophylaxis?) at discretion of investigator Excluded participants with cardiovascular disease, uncontrolled hypertension and moderate or severe renal or hepatic disease 1522 treated > 2 attacks zolmitriptan 2.5 mg, n = 555 (500 treated 2 attacks (ITT), total attacks 2671) zolmitriptan 5 mg, n = 551 (514 treated 2 attacks (ITT), total attacks_ 2744) sumatriptan 50 mg, n = 560 (508 treated 2 attacks (ITT), total attacks_ 2693) M 223, F 1299 (85%) Mean age 42 years Without aura 57%_		pain was of moderate or severe intensity Rescue medication permitted after 2 h (but no ergotamine within 6 h)	
Geraud 2000 DB, double-dummy, PC, PG-RCT	1058	Aged 18- 65 years, meeting IHS criteria for migraine (1988) with or without aura. Patients required to have a history of migraine for at least 1 year, with an onset at < 50 years and with 1 to 6 attacks/month in the previous 6 months. Triptan naïve participants only	Assessment up to 24 h	zolmitriptan 5 mg Vs sumatriptan 100 mg Vs placebo Single dose to treat single attack	RANDOMIZATION: **Unclear risk** not described" ALLOCATION CONCEALMENT **Unclear risk** not described" BLINDING: performance bias and detection bias, all outcomes: **Low risk** "double dummy technique"

		Prophyalxis with beta-blockers, calcium channel blockers (except flunarizine), clonidine and valproic acid was allowed. No psychoactive drugs or drugs with a clinically important action at 5-HT receptor were permitted in the previous 4 weeks Excluded participants with cardiovascular disease, uncontrolled hypertension and severe renal or hepatic disease zolmitriptan 5 mg, n = 498 sumatriptan 100 mg, n = 504 placebo, n = 56 M 174 F 884 (84%) Mean age 38 years Without aura ˜73%		Medication administered when migraine headache pain was of moderate or severe intensity Rescue medication permitted after 2 h if symptoms persisted (no ergot for 12 h, no sumatriptan)	INCOMPLETE OUTCOME DATA: **Low risk** drop-outs described, missing data 2%

Remarks:

- Authors analysed studies using a single dose of zolmitriptan in established pain of at least moderate intensity s**eparately** from studies in which the medication was taken before pain became well established, or in which a second dose of medication was required.
- Gallagher 2000 did not state pain intensity in the methods, but reported results for reduction from at least moderate to no greater than mild.
- Oral tablet formulation was used in the different studies.
- 2 studies were found in the SR comparing zolmitriptan 2.5 mg to sumatriptan 50 mg and zolmitriptan 5 mg to sumatriptan 50 mg. One study was found for the comparison zolmitriptan 5 mg vs sumatriptan 100 mg. As authors calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants, no analysis was performed for the comparison zolmitriptan

5 mg vs sumatriptan 100 mg and for several outcomes of the comparisons zolmitriptan 2.5 mg to sumatriptan 50 mg and zolmitriptan 5 mg to sumatriptan 50 mg; where there was only one study per outcomes, the results were extracted from the original study.

- Other comparisons were found in the SR for other doses of sumatriptan. AS these doses are not available/recommended in BE we have not reported these comparisons in the present document.
- Pain intensity or pain relief had to be measured by the patient (not the investigator or carer). Pain measures accepted for the primary outcomes were:

• pain intensity: four-point categorical scale, with wording equivalent to none, mild, moderate, and severe; or 100 mm visual analogue scale (VAS);
• pain relief: five-point categorical scale, with wording equivalent to none, a little, some, a lot, complete; or 100 mm VAS.

Author's conclusions:
There were no significant differences between zolmitriptan 2.5 mg and sumatriptan 50 mg or zolmitriptan 5 mg and sumatriptan 50 mg for headache relief at two hours, any adverse event, or withdrawals due to adverse events.

12.8 Combinations with triptans

12.8.1 Sumatriptan + naproxen versus placebo for acute treatment of migraine attack of moderate to severe baseline pain intensity or of mild baseline pain intensity in adults

Meta-analysis: Law 2016(184), Sumatriptan plus naproxen for the treatment of acute migraine attacks in adults.

Definition of migraine: We used the definition of migraine specified by the International Headache Society (IHS 1988; IHS 2004), although we accepted diagnostic criteria equivalent to those of IHS 1988 where a specific reference was not provided.

Inclusion criteria: We included randomised, double-blind, placebo- and/or active controlled studies using oral sumatriptan plus naproxen to treat a migraine headache episode. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data for at least one of the outcomes specified below. We accepted studies reporting treatment of consecutive headache episodes if outcomes for the first, or each, episode were reported separately. Cross-over studies were accepted if there was adequate washout (N 48 hours) between treatments.

Population : Studies enrolled adults (at least 18 years of age) with migraine. There were no restrictions on migraine frequency, duration, or type (with or without aura). Participants taking stable prophylactic therapy to reduce migraine frequency were accepted. All included studies used one or more of these standard scales (reported in remarks) and reported outcomes as defined above.
We considered only data obtained directly from the patient.

Exclusion: We excluded studies designed to demonstrate prophylactic efficacy in reducing the number or frequency of migraine headaches. We excluded trials evaluating treatments for chronic migraine.

Search strategy: This is an updated version of the original Cochrane review published in October 2013. We searched the following databases. • the Cochrane Central Register of Controlled Trials (CENTRAL), *The Cochrane Library,* (Issue 6 of 12, 2013 for the original review, and on 28 October 2015 via CRSO for this update). • MEDLINE (via Ovid) (1946 to 28 October 2015). • EMBASE (via Ovid) (1974 to 28 October 2015). We searched for additional studies in reference lists of retrieved studies and review articles, and in two clinical trials databases (www.clinicaltrials.gov and www.gsk-clinicalstudyregister.com).
For the original review we contacted the manufacturer of the fixed-dose combination agent (GlaxoSmithKline) for information about both published and unpublished data, but no additional studies were identified in their response. We did not search grey literature and abstracts.

Assessment of quality of included trials: yes

Other methodological remarks:
We planned to analyse data using the individual participant as the unit of analysis. In cross-over studies we planned to use only first-period data where possible, but where that was not provided, we used headache episode as the unit of analysis and treated the results as if they were parallel group results. For all outcomes we carried out analyses, as far as possible, on a modified intention-to-treat basis; that is, we included all participants who were randomised and received an intervention. where sufficient information was reported, we re-included missing data in the analyses we undertook.
We calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants. Risk ratio (relative benefit or harm) was calculated with 95% confidence intervals (CIs) using a fixed-eFect model. We calculated NNT, NNTp, and NNH with 95% CIs using the pooled number of events by the method of Cook and Sackett.

Ref	Comparison	N/n	Outcomes	Result

Law 2016 Design: SR+MA Search date: October 2015	Sumatriptan + naproxen Vs Placebo Moderate or severe basal pain intensity	N = 4 n = 2596 attacks (Brandes 2007 Study 1; Brandes 2007 Study 2; TRX109011/13, Smith 2005)	Pain free at 2 h (PO)	Sumatriptan + naproxen: 28% (362/1293) Placebo: 7.7% (100/1303) **RR (95% CI): 3.7 (3.0 to 4.5)** NNT (95% CI): 4.9 (4.3 to 5.7) **SS in favour of sumatriptan plus naproxen** I^2: 38%
		N = 4 n = 2596 attacks (Brandes 2007 Study 1; Brandes 2007 Study 2; TRX109011/13, Smith 2005)	Pain relief at 2 h (PO) (Pain reduced from moderate or severe to none or mild without the use of rescue medication.)	Sumatriptan + naproxen: 58% (755/1293) Placebo: 27% (352/1303) **RR (95% CI): 2..2 (2.0 to 2.4)** NNT (95% CI): 3.2 (2.9 to 3.6) **SS in favour of sumatriptan plus naproxen** I^2: 0%
		N = 4 n = 2596 attacks (Brandes 2007 Study 1; Brandes 2007 Study 2; TRX109011/13, Smith 2005)	Sustained pain-free over 24 h (PO) (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	Sumatriptan + naproxen: 20% (262/1293) Placebo: 5.9% (77/1303) **RR (95% CI): 3.4 (2.7 to 4.4)** NNT (95% CI): 7.0 (5.9 to 8.7) **SS in favour of sumatriptan plus naproxen** I^2: 0%

		N = 4 n = 2596 attacks (Brandes 2007 Study 1; Brandes 2007 Study 2; TRX109011/13, Smith 2005)	Sustained pain relief over 24 h (PO) (Headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.)	Sumatriptan + naproxen: 43% (554/1293) Placebo: 16% (214/1303) **RR (95% CI): 2.6 (2.3 to 3.0)** NNT (95% CI): 3.8 (3.4 to 4.3) **SS in favour of sumatriptan plus naproxen** I^2: 0%
		N = 3 n = 1984 (Brandes 2007 Study 1; Brandes 2007 Study 2; TRX109011/13)	Relief of functional disability at 2 h	Sumatriptan + naproxen: 245/994 Placebo: 72/990 **RR (95% CI): 3.36 (2.63 to 4.29)** **SS in favour of sumatriptan + naproxen** I^2: 0%
		N = 4 n = 2793 attacks (Brandes 2007 Study 1; Brandes 2007 Study 2; TRX109011/13, Smith 2005)	Adverse events over 24 h	Sumatriptan + naproxen: 21% (291/1394) Placebo: 11% (148/1399) **RR (95% CI): 2.0 (1.6 to 2.4)** NNH (95% CI): 9.7 (7.7 to 13) **SS in favour of placebo** I^2: 61%
		N = 4 n = 2169	Use of rescue medication	Sumatriptan + naproxen: 304/1083 Placebo: 643/1086 **RR (95% CI): 0.47 (0.42 to 0.53)**

		(Brandes 2007 Study 1; Brandes 2007 Study 2; TRX109011/13, Smith 2005)		**SS in favour of sumatriptan + naproxen (less rescue medication with sumatriptan + naproxen)** I^2: 81%

* Characteristics of included studies: see below

Ref	Comparison	N/n	Outcomes	Result
Law 2016 Design: SR+MA Search date: October 2015	Sumatriptan + naproxen Vs Placebo Mild pain intensity	N = 8 n = 3395 attacks (Lipton 2009 Study 1; Lipton 2009 Study 2; Mannix 2009 Study 1; Mannix 2009 Study 2; Mathew 2009 Study 1; Mathew 2009 Study 2; Silberstein 2008 Study 1; Silberstein 2008 Study 2)	Pain free at 2h (PO)	Sumatriptan + naproxen: 50% (1008/2025) Placebo: 18% (244/1370) **RR (95% CI): 2.8 (2.4 to 3.1)** NNT (95% CI): 3.1 (2.9 to 3.5) **SS in favour of sumatriptan + naproxen** I^2: 37%

		N = 8 n = 3396 attacks (Lipton 2009 Study 1; Lipton 2009 Study 2; Mannix 2009 Study 1; Mannix 2009 Study 2; Mathew 2009 Study 1; Mathew 2009 Study 2; Silberstein 2008 Study 1; Silberstein 2008 Study 2)	Sustained pain-free over 24h (PO) (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	Sumatriptan + naproxen: 37% (741/2026) Placebo: 12% (166/1370) **RR (95% CI): 3.0 (2.6 to 3.6)** NNT (95% CI): 4.1 (3.7 to 4.6) **SS in favour of sumatriptan + naproxen** I^2: 41%
		N = 2 n = 981 (Silberstein 2008 Study 1; Silberstein 2008 Study 2)	Relief of functional disability at 2 h	Sumatriptan + naproxen: 208/496 Placebo: 71/485 **RR (95% CI): 2.91 (2.29 to 3.72)** **SS in favour of sumatriptan + naproxen** I^2: 94%
		N = 8 n = 1705	Relief of nausea at 2h	Sumatriptan + naproxen: 326/900 Placebo: 83/805 **RR (95% CI): 3.47 (2.79 to 4.32)**

		(Lipton 2009 Study 1; Lipton 2009 Study 2 Mathew 2009 Study 1; Mathew 2009 Study 2; Silberstein 2008 Study 1; Silberstein 2008 Study 2, Brandes 2007 Study 1; Brandes 2007 Study 2;)		**SS in favour of sumatriptan + naproxen** I^2: 87%
		N = 8 n = 3127 (Lipton 2009 Study 1; Lipton 2009 Study 2 Mathew 2009 Study 1; Mathew 2009 Study 2; Silberstein 2008 Study 1; Silberstein 2008 Study 2, Brandes 2007 Study 1;	Relief of photophobia at 2h	Sumatriptan + naproxen: 949/1792 Placebo: 249/1335 **RR (95% CI): 2.77 (2.44 to 3.13)** **SS in favour of sumatriptan + naproxen** I^2: 33%

		Brandes 2007 Study 2;)		
		N = 8 n = 3127 (Lipton 2009 Study 1; Lipton 2009 Study 2 Mathew 2009 Study 1; Mathew 2009 Study 2; Silberstein 2008 Study 1; Silberstein 2008 Study 2, Brandes 2007 Study 1; Brandes 2007 Study 2;)	Relief of phonophobia at 2h	Sumatriptan + naproxen: 878/1614 Placebo: 246/1242 **RR (95% CI): 2.63 (2.33 to 2.97)** **SS in favour of sumatriptan + naproxen** I^2: 51%
		N = 8 n = 2823 (Lipton 2009 Study 1; Lipton 2009 Study 2; Mannix 2009 Study 1; Mannix 2009 Study 2; Mathew 2009	Adverse events over 24 h	Sumatriptan + naproxen: 14% (241/1749) Placebo: 8.2% (88/1074) **RR (95% CI): 1.5 (1.2 to 1.9)** NNH (95% CI): 18 (13 to 30) **SS in favour of placebo** I^2: 0%

		Study 1; Mathew 2009 Study 2; Silberstein 2008 Study 1; Silberstein 2008 Study 2)		
		N = 8 n = 3396 (Lipton 2009 Study 1; Lipton 2009 Study 2; Mannix 2009 Study 1; Mannix 2009 Study 2; Mathew 2009 Study 1; Mathew 2009 Study 2; Silberstein 2008 Study 1; Silberstein 2008 Study 2)	Use of rescue medication	Sumatriptan + naproxen: 375/2026 Placebo: 698/1370 **RR (95% CI): 0.42 (0.38 to 0.47)** **SS in favour of sumatriptan + naproxen** I^2: 73%

Ref + design	n	Population	Duration	Comparison	Methodology
Studies included for comparisons for moderate to severe baseline pain intensity					

Brandes 2007 Study 1 DB, PC, PG-RCT	1461	Migraine ± aura (IHS 2004), aged 18 to 65 years. History: > 6 months with frequency of 2 to 6 per month and untreated severity > moderate Excluded: uncontrolled hypertension, cardio- or cerebrovascular disease, using MAOI, ergot, SJW, or NSAID Sumatriptan 85 mg plus naproxen 500 mg, n = 370 (364 analysed for efficacy) Sumatriptan 85 mg, n = 365 (361 for efficacy) Naproxen 500 mg, n = 361 (365 for efficacy) Placebo, n = 365 (360 for efficacy) F = 86% Mean age 40 years 72% without aura	Assessment up to 24 h	Sumatriptan 85 mg plus naproxen 500 mg Vs Sumatriptan 85 mg Vs Naproxen 500 mg Vs Placebo Single dose to treat single attack Medication taken when PI > moderate Rescue medication allowed after 2 h if necessary (as prescribed by physician but not ergot-containing, serotonin agonist, or NSAID-containing medications)	RANDOMIZATION: **Unclear risk** Not described ALLOCATION CONCEALMENT: **Unclear risk** Not described BLINDING (performance and detection bias, all outcomes): **Unclear risk** Not described INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs described
Brandes 2007 Study 2 DB, PC, PG-RCT	1495	Migraine ± aura (IHS 2004), aged 18 to 65 years. History: > 6 months with frequency of 2 to 6 per month and untreated severity > moderate Excluded: uncontrolled hypertension, cardio- or cerebrovascular disease, using MAOI, ergot, SJW, or NSAID	Assessment up to 24 h	Sumatriptan 85 mg plus naproxen 500 mg Vs Sumatriptan 85 mg Vs Naproxen 500 mg Vs Placebo	RANDOMIZATION: **Unclear risk** Not described ALLOCATION CONCEALMENT: **Unclear risk** Not described BLINDING (performance and detection bias, all outcomes): **Unclear risk** Not described INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs described

		Sumatriptan 85 mg plus naproxen 500 mg, n = 367 (362 for efficacy) Sumatriptan 85 mg, n = 370 (362 for efficacy) Naproxen 500 mg, n = 371 (364 for efficacy) Placebo, n = 387 (382 for efficacy) F = 88% Mean age 40 years 76% without aura		Single dose to treat single attack Medication taken when PI > moderate Rescue medication allowed after 2 h if necessary (as prescribed by physician but not ergot-containing, serotonin agonist, or NSAID-containing medications)	
TRX109011/13 DB, Double-dummy, 3 phase CO-RCT	375 attacks ITT; 442 attacks for safety	Migraine ± aura (IHS 2004), aged N 18 years. History of 2 to 8 attacks per month in previous 3 months Sumatriptan 50 mg plus naproxen 500 mg, n = 406 (317 for efficacy) Paracetamol (acetaminophen) 325 mg + caffeine 40 mg + butalbital 50 mg, n = 392 (304 for efficacy) Placebo, n = 405 (320 for efficacy) F = 88% Mean age 43 years	Assessment up to 48 h	Sumatriptan 50 mg plus naproxen 500 mg Vs Paracetamol (acetaminophen) 325 mg + caffeine 40 mg + butalbital 50 mg Vs Placebo Single dose of each medication to treat single attack. Washout between attacks > 72 h Medication taken when pain > moderate	RANDOMIZATION: **Low risk** "computer-generated block randomization schedule" ALLOCATION CONCEALMENT: **Unclear risk** Not described BLINDING (performance and detection bias, all outcomes): **Low risk** "3 identical tablets for each dose". DD method INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs described. All treated attacks accounted for

Smith 2005 DB, Double-dummy, PG-RCT	972	Migraine ± aura (IHS 2004), aged N 18 years. History N 1 year with 2 to 6 attacks per month, and able to tolerate oral triptan or ergot derivative Sumatriptan 50 mg plus naproxen 500 mg, n = 251 Sumatriptan 50 mg, n = 229 Naproxen 500 mg, n = 250 Placebo, n = 242 F = 91% Mean age 42 years Without aura: > 70%	Assessment up to 24 h	Sumatriptan 50 mg plus naproxen 500 mg Vs Sumatriptan 50 mg Vs Naproxen 500 mg Vs Placebo Single dose to treat single attack Medication taken when pain > moderate Rescue medication allowed after 2 h if necessary (not specified)	RANDOMIZATION: **Unclear risk** Not described ALLOCATION CONCEALMENT: **Unclear risk** Not described BLINDING (performance and detection bias, all outcomes): **Low risk** DD method, with sumatriptan encapsulated INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs described
Studies includes for comparisons for mils baseline pain intensity					
Lipton 2009 Study 1 DB, PC, CO-RCT	570	Migraine ± aura (IHS 2004), aged 18 to 65 years. History N 6 months with frequency of 2 to 6 attacks per month and untreated severity N moderate and identifiable mild phase Excluded: uncontrolled hypertension, cardio- or cerebrovascular disease 568 for efficacy Sumatriptan plus naproxen 85/500 mg (1693 attacks treated) Placebo (424 attacks treated)	Assessment up to 24 h	Sumatriptan 85 mg plus naproxen 500 mg Vs Placebo Single dose per attack. 4 attacks treated: all with active or 3 active and 1 placebo (in random order). Washout between attacks not specified, but all headache medications	RANDOMIZATION: **Unclear risk** Not described ALLOCATION CONCEALMENT: **Unclear risk** Not described BLINDING (performance and detection bias, all outcomes): **Unclear risk** Not described INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs described

		5 treatment groups with different medication sequences (Nap: naproxen; P: placebo; Sum: sumatriptan) F = 89% Mean age 42 years		prohibited within 24 h of a treated attack, and AE data collected for 72 h after treatment Medication taken within 1 h of onset when PI was mild Rescue medication allowed after 2 h if necessary (recommended 2 x 220 mg naproxen sodium with additional 1 x 220 mg 6 h later if needed)	
Lipton 2009 Study 2 DB, PC, CO-RCT	565	Migraine ± aura (IHS 2004), aged 18 to 65 years. History N 6 months with frequency of 2 to 6 attacks per month and untreated severity N moderate and identifiable mild phase Excluded: uncontrolled hypertension, cardio- or cerebrovascular disease 563 for efficacy Sumatriptan plus naproxen 85/500 mg (1687 attacks treated) Placebo (422 attacks treated) 5 treatment groups with different medication sequences (Nap:	Assessment up to 24 h	Sumatriptan 85 mg plus naproxen 500 mg Vs Placebo Single dose per attack. 4 attacks treated: all with active or 3 active and 1 placebo (in random order). Washout between attacks not specified, but all headache medications prohibited within 24 h of a treated attack, and AE	RANDOMIZATION: **Unclear risk** Not described ALLOCATION CONCEALMENT: **Unclear risk** Not described BLINDING (performance and detection bias, all outcomes): **Unclear risk** Not described INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs described

		naproxen; P: placebo; Sum: sumatriptan) F = 90% Mean age 41 years		data collected for 72 h after treatment Medication taken within 1 h of onset when PI was mild Rescue medication allowed after 2 h if necessary (recommended 2 x 220 mg naproxen sodium with additional 1 x 220 mg 6 h later if needed)	
Mannix 2009 Study 1 DB, PC, PG-RCT	312	Migraine ± aura (IHS 2004), aged N 18 years. History: frequency of migraines 1 to 6 per month with menstrual migraine in 2/3 previous cycles and dysmenorrhoea in 2/3 cycles. Untreated severity > moderate, with identifiable mild phase 311 for efficacy Sumatriptan 85 mg plus naproxen 500 mg, n = 152 Placebo, n = 160 F = 100% Mean age 37 years	Assessment up to 48 h	Sumatriptan 85 mg plus naproxen 500 mg Vs Placebo Single dose to treat single attack Medication taken when PI mild and within 1 h of onset Rescue medication allowed after 2 h if necessary (including second dose, sumatriptan or naproxen sodium)	RANDOMIZATION: **Low risk** "Randomly assigned by a computer generated code" ALLOCATION CONCEALMENT: **Low risk** Remote allocation (computerised registration and ordering system) BLINDING (performance and detection bias, all outcomes): **Unclear risk** Not described INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs described

		Aura: 26%; primary dysmenorrhoea: 77%		Rescue medication allowed after 2 h if necessary (including second dose, sumatriptan or naproxen sodium)	
Mannix 2009 Study 2 DB, PC, PG-RCT	311	Migraine ± aura (IHS 2004), aged N 18 years. History: frequency of migraines 1 to 6 per month with menstrual migraine in 2/3 previous cycles and dysmenorrhoea in 2/3 cycles. Untreated severity > moderate, with identifiable mild phase 310 for efficacy Sumatriptan 85 mg plus naproxen 500 mg, n = 151 Placebo, n = 160 F = 100% Mean age 37 years Aura: 40%; primary dysmenorrhoea: 92%	Assessment up to 48 h	Sumatriptan 85 mg plus naproxen 500 mg Vs Placebo Single dose to treat single attack Medication taken when PI mild and within 1 h of onset Rescue medication allowed after 2 h if necessary (including second dose, sumatriptan or naproxen sodium) Rescue medication allowed after 2 h if necessary (including second dose, sumatriptan or naproxen sodium)	RANDOMIZATION: **Low risk** "Randomly assigned by a computer generated code" ALLOCATION CONCEALMENT: **Low risk** Remote allocation (computerised registration and ordering system) BLINDING (performance and detection bias, all outcomes): **Unclear risk** Not described INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs described
Mathew 2009 Study 1	144	Migraine ± aura (IHS 2004), aged 18 to 65 years, poor response to	Assessment up to 48 h	Sumatriptan 85 mg plus naproxen 500 mg	RANDOMIZATION: **Unclear risk** Not described

DB, PC, CO-RCT		triptans with short half-life. History: frequency of 1 to 8 per month, < 15 headache days monthly. Untreated severity N mild Excluded: uncontrolled hypertension, cardio- or cerebrovascular disease 139 for efficacy Sumatriptan 85 mg plus naproxen 500 mg, n = 136 Placebo, n = 134 F = 85% Mean age 41 years Aura: 32%		Vs Placebo Single dose to treat single attack. Washout between attacks > 1 week Medication taken when PI mild and within 1 h of onset Rescue medication allowed after 2 h if necessary (not specified)	ALLOCATION CONCEALMENT: **Unclear risk** Not described BLINDING (performance and detection bias, all outcomes): **Unclear risk** Not described INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs described
Mathew 2009 Study 2 DB, PC, CO-RCT	137	Migraine ± aura (IHS 2004), aged 18 to 65 years, poor response to triptans with short half-life. History: frequency of 1 to 8 per month, < 15 headache days monthly. Untreated severity N mild Excluded: uncontrolled hypertension, cardio- or cerebrovascular disease 131 for efficacy Sumatriptan 85 mg plus naproxen 500 mg, n = 134 Placebo, n = 133 F = 93%	Assessment up to 48 h	Sumatriptan 85 mg plus naproxen 500 mg Vs Placebo Single dose to treat single attack. Washout between attacks > 1 week Medication taken when PI mild and within 1 h of onset Rescue medication allowed after 2 h if necessary (not specified)	RANDOMIZATION: **Unclear risk** Not described ALLOCATION CONCEALMENT: **Unclear risk** Not described BLINDING (performance and detection bias, all outcomes): **Unclear risk** Not described INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs described

		Mean age 41 years Aura: 27%			
Silberstein 2008 Study 1 DB, PC, PG-RCT	580	Migraine ± aura (IHS 2004), aged 18 to 65 years. History: > 6 months with frequency of 2 to 6 attacks per month, and < 15 per month. Untreated severity > moderate, with identifiable mild pain phase Excluded: uncontrolled hypertension, cardio- or cerebrovascular disease, gastrointestinal history 576 for efficacy Sumatriptan 85 mg plus naproxen 500 mg, n = 283 Placebo, n = 297 F = 87.5% Mean age 40 years Aura: 20%	Assessment up to 24 h	Sumatriptan 85 mg plus naproxen 500 mg Vs Placebo Single dose to treat single attack Medication taken when PI mild and within 1 h of onset Rescue medication allowed after 2 h if necessary (not triptans, NSAID-containing, ergot-containing or ergot-like medication)	RANDOMIZATION: **Low risk** "Computer-generated randomization schedule" ALLOCATION CONCEALMENT: **Unclear risk** Not described BLINDING (performance and detection bias, all outcomes): **Low risk** “Matching placebo" INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs described
Silberstein 2008 Study 2 DB, PC, PG-RCT	542	Migraine ± aura (IHS 2004), aged 18 to 65 years. History: N 6 months with frequency of 2 to 6 attacks per month, and _ 15 per month. Untreated severity N moderate, with identifiable mild pain phase Excluded: uncontrolled hypertension, cardio- or cerebrovascular disease, gastrointestinal history	Assessment up to 24 h	Sumatriptan 85 mg plus naproxen 500 mg Vs Placebo Single dose to treat single attack Medication taken when PI mild and within 1 h of onset	RANDOMIZATION: **Low risk** "Computer-generated randomization schedule"ALLOCATION CONCEALMENT: **Unclear risk** Not described BLINDING (performance and detection bias, all outcomes): **Low risk** “Matching placebo" INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs described

		535 for efficacy Sumatriptan 85 mg plus naproxen 500 mg, n = 278 Placebo, n = 264 F = 90.5% Mean age 41 years 66% without aura		Rescue medication allowed after 2 h if necessary (not triptans, NSAID-containing, ergot-containing or ergot-like medication)	

Remarks:

- Authors included studies in which self-administered sumatriptan plus naproxen was used either as separate tablets administered together, or as a fixed-dose combination tablet to treat a migraine headache episode. Most studies gave sumatriptan 85 mg plus naproxen 500 mg formulated as a combination tablet, while Smith 2005 gave sumatriptan 50 mg plus naproxen 500 mg as separate tablets taken together. In the study TRX109011/13 sumatriptan 50 mg plus naproxen 500 mg was also used.
- Authors analysed studies using a single dose of sumatriptan plus naproxen in established pain of at least moderate intensity **separately f**rom studies in which medication was taken before pain became well established, or in which a second dose of medication. No studies employed multiple dosing strategies for a single attack was analysed.
- According to the definition, pain relief cannot be evaluated for mild pain intensity baseline population.
- Two studies included only participants with menstrual migraine (Mannix 2009 Study 1; Mannix 2009 Study 2).
- All studies reported some information about participants who experienced one or more adverse events, but the reporting was inconsistent. Since there was no obvious relationship between numbers of participants with adverse events and the time over which the data were collected, authors have combined data from different time periods for analysis.
- One participant, who had several cardiovascular risk factors, experienced heart palpitations and was admitted to hospital after receiving sumatriptan 85 mg; the event was judged probably related to study medication (Brandes 2007 Study 1).
- For the outcomes regarding relief of associated symptom, only pooled date for both patients having mild intensity and moderate to severe migraine attacks were pooled. As majority of the studies concerned patients with mild intensity attacks when using medication, data were reported with for this population.
- Pain intensity or pain relief had to be measured by the patient (not the investigator or carer). Pain measures accepted for the primary outcomes were:

• pain intensity: four-point categorical scale, with wording equivalent to none, mild, moderate, and severe; or 100 mm visual analogue scale (VAS);

• pain relief: five-point categorical scale, with wording equivalent to none, a little, some, a lot, complete; or 100 mm VAS.

Author's conclusions:

"Combination treatment was effective in the acute treatment of migraine headaches. The effect was greater than for the same dose of either sumatriptan or naproxen alone, but additional benefits over sumatriptan alone were not large.
More participants achieved good relief when medication was taken early in the attack, when pain was still mild.
Adverse events were more common with the combination and sumatriptan alone than with placebo or naproxen alone."

12.8.2 Sumatriptan + naproxen versus sumatriptan for acute treatment of migraine attack of moderate to severe baseline pain intensity in adults

Meta-analysis: Law 2016(184), Sumatriptan plus naproxen for the treatment of acute migraine attacks in adults.

Definition of migraine: We used the definition of migraine specified by the International Headache Society (IHS 1988; IHS 2004), although we accepted diagnostic criteria equivalent to those of IHS 1988 where a specific reference was not provided.

Inclusion criteria: We included randomised, double-blind, placebo- and/or active controlled studies using oral sumatriptan plus naproxen to treat a migraine headache episode. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data for at least one of the outcomes specified below. We accepted studies reporting treatment of consecutive headache episodes if outcomes for the first, or each, episode were reported separately. Cross-over studies were accepted if there was adequate washout (N 48 hours) between treatments.

Population : Studies enrolled adults (at least 18 years of age) with migraine. There were no restrictions on migraine frequency, duration, or type (with or without aura). Participants taking stable prophylactic therapy to reduce migraine frequency were accepted. All included studies used one or more of these standard scales (reported in remarks) and reported outcomes as defined above.
We considered only data obtained directly from the patient.

Exclusion: We excluded studies designed to demonstrate prophylactic efficacy in reducing the number or frequency of migraine headaches. We excluded trials evaluating treatments for chronic migraine.

Search strategy: This is an updated version of the original Cochrane review published in October 2013. We searched the following databases. • the Cochrane Central Register of Controlled Trials (CENTRAL), *The Cochrane Library,* (Issue 6 of 12, 2013 for the original review, and on 28 October 2015 via CRSO for this update). • MEDLINE (via Ovid) (1946 to 28 October 2015). • EMBASE (via Ovid) (1974 to 28 October 2015). We searched for additional studies in reference lists of retrieved studies and review articles, and in two clinical trials databases (www.clinicaltrials.gov and www.gsk-clinicalstudyregister.com).
For the original review we contacted the manufacturer of the fixed-dose combination agent (GlaxoSmithKline) for information about both published and unpublished data, but no additional studies were identified in their response. We did not search grey literature and abstracts.

Assessment of quality of included trials: yes

Other methodological remarks:
We planned to analyse data using the individual participant as the unit of analysis. In cross-over studies we planned to use only first-period data where possible, but where that was not provided, we used headache episode as the unit of analysis and treated the results as if they were parallel group results. For all outcomes we carried out analyses, as far as possible, on a modified intention-to-treat basis; that is, we included all participants who were randomised and received an intervention. where sufficient information was reported, we re-included missing data in the analyses we undertook.
We calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants. Risk ratio (relative benefit or harm) was calculated with 95% confidence intervals (CIs) using a fixed-eFect model. We calculated NNT, NNTp, and NNH with 95% CIs using the pooled number of events by the method of Cook and Sackett.

Ref	Comparison	N/n	Outcomes	Result

Law 2016 Design: SR+MA Search date: October 2015	Sumatriptan + naproxen Vs Sumatriptan Moderate or severe basal pain intensity	N = 3 n = 1925 (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005)	Pain free at 2 h (PO)	Sumatriptan plus naproxen: 32% (317/976) Sumatriptan: 23% (217/949) **RR (95% CI): 1.4 (1.2 to 1.7)** NNT (95% CI): 10 (7.4 to 18) **SS in favour of sumatriptan + naproxen** I^2: 0%
		N = 3 n = 1925 (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005)	Pain relief at 2 h (PO) (Pain reduced from moderate or severe to none or mild without the use of rescue medication.)	Sumatriptan + naproxen: 62% (607/976) Sumatriptan: 52% (493/949) **RR (95% CI): 1.2 (1.1 to 1.3)** NNT (95% CI): 9.8 (6.8 to 17) **SS in favour of sumatriptan + naproxen** I^2: 10%
		N = 3 n = 1925 (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005)	Sustained pain-free over 24 h (PO) (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	Sumatriptan + naproxen: 24% (236/976) Sumatriptan: 14% (135/949) **RR (95% CI): 1.7 (1.4 to 2.1)** NNT (95% CI): 10 (7.4 to 15) **SS in favour of sumatriptan + naproxen** I^2: 19%
		N = 3 n = 1925	Sustained pain relief over 24 h (PO) (Headache relief at two hours, sustained for 24 hours, with no use of	Sumatriptan + naproxen: 46% (447/976) Sumatriptan: 33% (314/949) **RR (95% CI): 1.39 (1.24 to 1.55)** **NNT (95% CI): 7.9 (5.9 to 12)**

		(Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005)	rescue medication or a second dose of study medication.)	**SS in favour of sumatriptan + naproxen** I^2: 0%
		N = 2 n = 718 (Brandes 2007 Study 1; Brandes 2007 Study 2)	Relief of nausea at 2 h	Sumatriptan + naproxen: 148/377 Sumatriptan: 89/381 **RR (95% CI):** **1.51 (1.21 to 1.87)** **SS in favour of sumatriptan + naproxen** I^2: 0%
		N = 2 n = 1186 (Brandes 2007 Study 1; Brandes 2007 Study 2)	Relief of photophobia at 2 h	Sumatriptan + naproxen: 253/588 Sumatriptan: 214/598 **RR (95% CI):** **1.20 (1.04 to 1.39)** **SS in favour of sumatriptan + naproxen** I^2: 0%
		N = 2 n = 1186 (Brandes 2007 Study 1; Brandes 2007 Study 2)	Relief of phonophobia at 2 h	Sumatriptan + naproxen: 275/574 Sumatriptan: 217/572 **RR (95% CI):** **1.26 (1.10 to 1.45)** **SS in favour of sumatriptan + naproxen** I^2: 7%
		N = 2 n = 1353 (Brandes 2007 Study 1; Brandes 2007 Study 2)	Relief of functional disability at 2 h	Sumatriptan + naproxen: 220/685 Sumatriptan: 152/669 **RR (95% CI):** **1.41 (1.18 to 1.69)** **SS in favour of sumatriptan + naproxen** I^2: 24%

		N = 3 n = 1952 (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005)	Adverse events over 24 h	Sumatriptan + naproxen: 26% (255/988) Sumatriptan: 26% (249/964) **RR (95% CI): 1.0 (0.9 to 1.2)** **NS** I^2: 0%
		N = 3 n = 1925 (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005)	Use of rescue medication	Sumatriptan + naproxen: 252/976 Sumatriptan: 367/949 **RR (95% CI): 0.66 (0.58 to 0.76)** **SS in favour of sumatriptan + naproxen** I^2: 0%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Brandes 2007 Study 1 DB, PC, PG-RCT	1461	Migraine ± aura (IHS 2004), aged 18 to 65 years. History: > 6 months with frequency of 2 to 6 per month and untreated severity > moderate Excluded: uncontrolled hypertension, cardio- or cerebrovascular disease, using MAOI, ergot, SJW, or NSAID Sumatriptan 85 mg plus naproxen 500 mg, n = 370 (364 analysed for efficacy) Sumatriptan 85 mg, n = 365 (361 for efficacy)	Assessment up to 24 h	Sumatriptan 85 mg plus naproxen 500 mg Vs Sumatriptan 85 mg Vs Naproxen 500 mg Vs Placebo Single dose to treat single attack Medication taken when PI > moderate	RANDOMIZATION: **Unclear risk** Not described ALLOCATION CONCEALMENT: **Unclear risk** Not described BLINDING (performance and detection bias, all outcomes): **Unclear risk** Not described INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs described

		Naproxen 500 mg, n = 361 (365 for efficacy) Placebo, n = 365 (360 for efficacy) F = 86% Mean age 40 years 72% without aura		Rescue medication allowed after 2 h if necessary (as prescribed by physician but not ergot-containing, serotonin agonist, or NSAID-containing medications)	
Brandes 2007 Study 2 DB, PC, PG-RCT	1495	Migraine ± aura (IHS 2004), aged 18 to 65 years. History: > 6 months with frequency of 2 to 6 per month and untreated severity > moderate Excluded: uncontrolled hypertension, cardio- or cerebrovascular disease, using MAOI, ergot, SJW, or NSAID Sumatriptan 85 mg plus naproxen 500 mg, n = 367 (362 for efficacy) Sumatriptan 85 mg, n = 370 (362 for efficacy) Naproxen 500 mg, n = 371 (364 for efficacy) Placebo, n = 387 (382 for efficacy) F = 88% Mean age 40 years 76% without aura	Assessment up to 24 h	Sumatriptan 85 mg plus naproxen 500 mg Vs Sumatriptan 85 mg Vs Naproxen 500 mg Vs Placebo Single dose to treat single attack Medication taken when PI > moderate Rescue medication allowed after 2 h if necessary (as prescribed by physician but not ergot-containing, serotonin agonist, or NSAID-containing medications)	RANDOMIZATION: **Unclear risk** Not described ALLOCATION CONCEALMENT: **Unclear risk** Not described BLINDING (performance and detection bias, all outcomes): **Unclear risk** Not described INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs described

Smith 2005 DB, Double-dummy, PG-RCT	972	Migraine ± aura (IHS 2004), aged N 18 years. History N 1 year with 2 to 6 attacks per month, and able to tolerate oral triptan or ergot derivative Sumatriptan 50 mg plus naproxen 500 mg, n = 251 Sumatriptan 50 mg, n = 229 Naproxen 500 mg, n = 250 Placebo, n = 242 F = 91% Mean age 42 years Without aura: > 70%	Assessment up to 24 h	Sumatriptan 50 mg plus naproxen 500 mg Vs Sumatriptan 50 mg Vs Naproxen 500 mg Vs Placebo Single dose to treat single attack Medication taken when pain > moderate Rescue medication allowed after 2 h if necessary (not specified)	RANDOMIZATION: **Unclear risk** Not described ALLOCATION CONCEALMENT: **Unclear risk** Not described BLINDING (performance and detection bias, all outcomes): **Low risk** DD method, with sumatriptan encapsulated INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs described

Remarks:

- Authors included studies in which self-administered sumatriptan plus naproxen was used either as separate tablets administered together, or as a fixed-dose combination tablet to treat a migraine headache episode. Most studies gave sumatriptan 85 mg plus naproxen 500 mg formulated as a combination tablet, while Smith 2005 gave sumatriptan 50 mg plus naproxen 500 mg as separate tablets taken together. In the study TRX109011/13 sumatriptan 50 mg plus naproxen 500 mg was also used.
- Authors analysed studies using a single dose of sumatriptan plus naproxen in established pain of at least moderate intensity **separately f**rom studies in which medication was taken before pain became well established, or in which a second dose of medication. No studies employed multiple dosing strategies for a single attack was permitted. For the comparison with sumatriptan alone, all studies were performed in a population having moderate to severe migraine attack when taking medication.
- All studies reported some information about participants who experienced one or more adverse events, but the reporting was inconsistent. Since there was no obvious relationship between numbers of participants with adverse events and the time over which the data were collected, authors have combined data from different time periods for analysis.

- One participant, who had several cardiovascular risk factors, experienced heart palpitations and was admitted to hospital after receiving sumatriptan 85 mg; the event was judged probably related to study medication (Brandes 2007 Study 1).
- Pain intensity or pain relief had to be measured by the patient (not the investigator or carer). Pain measures accepted for the primary outcomes were:

• pain intensity: four-point categorical scale, with wording equivalent to none, mild, moderate, and severe; or 100 mm visual analogue scale (VAS);
• pain relief: five-point categorical scale, with wording equivalent to none, a little, some, a lot, complete; or 100 mm VAS.

Author's conclusions:
"The combination of sumatriptan plus naproxen is better than naproxen alone, and probably better than sumatriptan alone. It is not clear whether there is any clinical significance to the benefits observed with the combination over sumatriptan alone.
Adverse events are more common with the combination and sumatriptan alone than with placebo or naproxen alone, but these events do not usually stop people from taking the medicine.
The combination tablet is not available in most countries, but the individual components are widely available and can be taken together. Although sumatriptan alone is available only in 50 and 100 mg doses. The included study using separate tablets used the 50 mg dose."

12.8.3 Sumatriptan + naproxen versus naproxen for acute treatment of migraine attack of moderate to severe basel pain intensity in adults

Meta-analysis: Law 2016(184), Sumatriptan plus naproxen for the treatment of acute migraine attacks in adults.

Definition of migraine: We used the definition of migraine specified by the International Headache Society (IHS 1988; IHS 2004), although we accepted diagnostic criteria equivalent to those of IHS 1988 where a specific reference was not provided.

Inclusion criteria: We included randomised, double-blind, placebo- and/or active controlled studies using oral sumatriptan plus naproxen to treat a migraine headache episode. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data for at least one of the outcomes specified below. We accepted studies reporting treatment of consecutive headache episodes if outcomes for the first, or each, episode were reported separately. Cross-over studies were accepted if there was adequate washout (N 48 hours) between treatments.

Population : Studies enrolled adults (at least 18 years of age) with migraine. There were no restrictions on migraine frequency, duration, or type (with or without aura). Participants taking stable prophylactic therapy to reduce migraine frequency were accepted. All included studies used one or more of these standard scales (reported in remarks) and reported outcomes as defined above.
We considered only data obtained directly from the patient.

Exclusion: We excluded studies designed to demonstrate prophylactic efficacy in reducing the number or frequency of migraine headaches. We excluded trials evaluating treatments for chronic migraine.

Search strategy: This is an updated version of the original Cochrane review published in October 2013. We searched the following databases. • the Cochrane Central Register of Controlled Trials (CENTRAL), *The Cochrane Library,* (Issue 6 of 12, 2013 for the original review, and on 28 October 2015 via CRSO for this update). • MEDLINE (via Ovid) (1946 to 28 October 2015). • EMBASE (via Ovid) (1974 to 28 October 2015). We searched for additional studies in reference lists of retrieved studies and review articles, and in two clinical trials databases (www.clinicaltrials.gov and www.gsk-clinicalstudyregister.com).
For the original review we contacted the manufacturer of the fixed-dose combination agent (GlaxoSmithKline) for information about both published and unpublished data, but no additional studies were identified in their response. We did not search grey literature and abstracts.

Assessment of quality of included trials: yes

Other methodological remarks:
We planned to analyse data using the individual participant as the unit of analysis. In cross-over studies we planned to use only first-period data where possible, but where that was not provided, we used headache episode as the unit of analysis and treated the results as if they were parallel group results. For all outcomes we carried out analyses, as far as possible, on a modified intention-to-treat basis; that is, we included all participants who were randomised and received an intervention. where sufficient information was reported, we re-included missing data in the analyses we undertook.
We calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants. Risk ratio (relative benefit or harm) was calculated with 95% confidence intervals (CIs) using a fixed-eFect model. We calculated NNT, NNTp, and NNH with 95% CIs using the pooled number of events by the method of Cook and Sackett.

Ref	Comparison	N/n	Outcomes	Result

Law 2016 Design: SR+MA Search date: October 2015	Sumatriptan + naproxen Vs Naproxen Moderate or severe basal pain intensity	N = 3 n = 1944 (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005)	Pain free at 2 h (PO)	Sumatriptan + naproxen: 32% (317/976) Naproxen: 16% (155/968) **RR (95% CI): 2.0 (1.7 to 2.4)** NNT (95% CI): 6.1 (5.0 to 7.9) **SS in favour of sumatriptan + naproxen** I^2: 0%
		N = 3 n = 1944 (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005)	Pain relief at 2 h (PO) (Pain reduced from moderate or severe to none or mild without the use of rescue medication.)	Sumatriptan + naproxen: 62% (607/976) Naproxen: 44% (426/968) **RR (95% CI): 1.4 (1.2 to 1.5)** NNT (95% CI): 5.5 (4.4 to 7.2) **SS in favour of sumatriptan + naproxen** I^2: 0%
		N = 3 n = 1944 (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005)	Sustained pain-free over 24 h (PO) (Pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.)	Sumatriptan + naproxen: 24% (236/976) Naproxen: 11% (104/968) **RR (95% CI): 2.3 (1.8 to 2.8)** NNT (95% CI): 7.4 (6.0 to 9.9) **SS in favour of sumatriptan + naproxen** I^2: 0%
		N = 3 n = 1944	Sustained pain relief over 24 h (PO) (Headache relief at two hours, sustained for 24 hours, with no use of	Sumatriptan + naproxen: 46% (447/976) Naproxen: 28% (271/968) **RR (95% CI): 1.6 (1.5 to 1.9)** NNT (95% CI): 5.6 (4.5 to 7.4)

		(Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005)	rescue medication or a second dose of study medication.)	**SS in favour of sumatriptan + naproxen** I^2: 0%
		N = 2 n = 726 (Brandes 2007 Study 1; Brandes 2007 Study 2)	Relief of nausea at 2 h	Sumatriptan + naproxen: 148/377 Naproxen: 126/349 **RR (95% CI):** **1.09 (0.90 to 1.32)** **NS** I^2: 0%
		N = 2 n = 1176 (Brandes 2007 Study 1; Brandes 2007 Study 2)	Relief of photophobia at 2 h	Sumatriptan + naproxen:253/588 Naproxen: 182/588 **RR (95% CI):** **1.39 (1.19 , 1.62)** **SS in favour of sumatriptan + naproxen** I^2: 0%
		N = 2 n = 1135 (Brandes 2007 Study 1; Brandes 2007 Study 2)	Relief of phonophobia at 2 h	Sumatriptan + naproxen: 275/574 Naproxen: 181/561 **RR (95% CI):** **1.48 (1.28 to 1.72)** **SS in favour of sumatriptan + naproxen** I^2: 0%
		N = 2 n = 1352 (Brandes 2007 Study 1; Brandes 2007 Study 2)	Relief of functional disability at 2 h	Sumatriptan + naproxen: 220/685 Naproxen: 131/667 **RR (95% CI):** **1.63 (1.35 to 1.97)** **SS in favour of sumatriptan + naproxen** I^2: 0%

		N = 3 n = 1990 (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005)	Adverse events over 24 h	Sumatriptan + naproxen: 255/988 Naproxen: 143/9982 **RR (95% CI):** **1.77 (1.47 to 2.13)** **SS in favour of naproxen** I^2: 39 %
		N = 3 n = 1944 (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005)	Use of rescue medication	Sumatriptan + naproxen: 252/976 Naproxen: 407/968 **RR (95% CI):** **0.61 (0.54 to 0.70)** **SS in favour of sumatriptan + naproxen** I^2: 0%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Brandes 2007 Study 1 DB, PC, PG-RCT	1461	Migraine ± aura (IHS 2004), aged 18 to 65 years. History: > 6 months with frequency of 2 to 6 per month and untreated severity > moderate Excluded: uncontrolled hypertension, cardio- or cerebrovascular disease, using MAOI, ergot, SJW, or NSAID Sumatriptan 85 mg plus naproxen 500 mg, n = 370 (364 analysed for efficacy)	Assessment up to 24 h	Sumatriptan 85 mg plus naproxen 500 mg Vs Sumatriptan 85 mg Vs Naproxen 500 mg Vs Placebo Single dose to treat single attack	RANDOMIZATION: **Unclear risk** Not described ALLOCATION CONCEALMENT: **Unclear risk** Not described BLINDING (performance and detection bias, all outcomes): **Unclear risk** Not described INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs described

		Sumatriptan 85 mg, n = 365 (361 for efficacy) Naproxen 500 mg, n = 361 (365 for efficacy) Placebo, n = 365 (360 for efficacy) F = 86% Mean age 40 years 72% without aura		Medication taken when PI > moderate Rescue medication allowed after 2 h if necessary (as prescribed by physician but not ergot-containing, serotonin agonist, or NSAID-containing medications)	
Brandes 2007 Study 2 DB, PC, PG-RCT	1495	Migraine ± aura (IHS 2004), aged 18 to 65 years. History: > 6 months with frequency of 2 to 6 per month and untreated severity > moderate Excluded: uncontrolled hypertension, cardio- or cerebrovascular disease, using MAOI, ergot, SJW, or NSAID Sumatriptan 85 mg plus naproxen 500 mg, n = 367 (362 for efficacy) Sumatriptan 85 mg, n = 370 (362 for efficacy) Naproxen 500 mg, n = 371 (364 for efficacy) Placebo, n = 387 (382 for efficacy) F = 88% Mean age 40 years 76% without aura	Assessment up to 24 h	Sumatriptan 85 mg plus naproxen 500 mg Vs Sumatriptan 85 mg Vs Naproxen 500 mg Vs Placebo Single dose to treat single attack Medication taken when PI > moderate Rescue medication allowed after 2 h if necessary (as prescribed by physician but not ergot-containing,	RANDOMIZATION: **Unclear risk** Not described ALLOCATION CONCEALMENT: **Unclear risk** Not described BLINDING (performance and detection bias, all outcomes): **Unclear risk** Not described INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs described

				serotonin agonist, or NSAID-containing medications)	
Smith 2005 DB, Double-dummy, PG-RCT	972	Migraine ± aura (IHS 2004), aged N 18 years. History N 1 year with 2 to 6 attacks per month, and able to tolerate oral triptan or ergot derivative Sumatriptan 50 mg plus naproxen 500 mg, n = 251 Sumatriptan 50 mg, n = 229 Naproxen 500 mg, n = 250 Placebo, n = 242 F = 91% Mean age 42 years Without aura: > 70%	Assessment up to 24 h	Sumatriptan 50 mg plus naproxen 500 mg Vs Sumatriptan 50 mg Vs Naproxen 500 mg Vs Placebo Single dose to treat single attack Medication taken when pain > moderate Rescue medication allowed after 2 h if necessary (not specified)	RANDOMIZATION: **Unclear risk** Not described ALLOCATION CONCEALMENT: **Unclear risk** Not described BLINDING (performance and detection bias, all outcomes): **Low risk** DD method, with sumatriptan encapsulated INCOMPLETE OUTCOME DATA: **Low risk** Drop-outs described

Remarks:

- Authors included studies in which self-administered sumatriptan plus naproxen was used either as separate tablets administered together, or as a fixed-dose combination tablet to treat a migraine headache episode. Most studies gave sumatriptan 85 mg plus naproxen 500 mg formulated as a combination tablet, while Smith 2005 gave sumatriptan 50 mg plus naproxen 500 mg as separate tablets taken together. In the study TRX109011/13 sumatriptan 50 mg plus naproxen 500 mg was also used.
- Authors analysed studies using a single dose of sumatriptan plus naproxen in established pain of at least moderate intensity **separately f**rom studies in which medication was taken before pain became well established, or in which a second dose of medication. No studies employed multiple dosing strategies for a single attack was permitted. For the comparison with naproxen alone, all studies were performed in a population having moderate to severe migraine attack when taking medication.

- All studies reported some information about participants who experienced one or more adverse events, but the reporting was inconsistent. Since there was no obvious relationship between numbers of participants with adverse events and the time over which the data were collected, authors have combined data from different time periods for analysis.
- One participant, who had several cardiovascular risk factors, experienced heart palpitations and was admitted to hospital after receiving sumatriptan 85 mg; the event was judged probably related to study medication (Brandes 2007 Study 1).
- Pain intensity or pain relief had to be measured by the patient (not the investigator or carer). Pain measures accepted for the primary outcomes were:

• pain intensity: four-point categorical scale, with wording equivalent to none, mild, moderate, and severe; or 100 mm visual analogue scale (VAS);
• pain relief: five-point categorical scale, with wording equivalent to none, a little, some, a lot, complete; or 100 mm VAS.

Author's conclusions:
"The combination of sumatriptan plus naproxen is better than naproxen alone, and probably better than sumatriptan alone. It is not clear whether there is any clinical significance to the benefits observed with the combination over sumatriptan alone.
Adverse events are more common with the combination and sumatriptan alone than with placebo or naproxen alone, but these events do not usually stop people from taking the medicine.
The combination tablet is not available in most countries, but the individual components are widely available and can be taken together. Although sumatriptan alone is available only in 50 and 100 mg doses. The included study using separate tablets used
the 50 mg dose."

12.8.4 Naratriptan + naproxen versus naratriptan for acute treatment of migraine attack in adults

Meta-analysis: Ashcroft 2004 (73), Naratriptan for the treatment of acute migraine: meta-analysis of randomised controlled trials Definition of migraine: diagnosed according to the International Headache Society criteria. Inclusion criteria: Only randomised controlled trials (RCTs) of naratriptan taken for symptomatic relief of acute attacks of migraine were considered. Multiple-attack and multiple-dose trials were included provided that single dose information was available separately. Trials were only included if patients in one arm of the trial received a single dose of naratriptan for a single migraine attack. The analysis included only drugs and dosages that are commercially available.

Population: Included patients were adults (18–65 years of age) with migraine with or without aura

Search strategy: Reports of RCTs were identified through a systematic electronic search of Medline, Embase and the Cochrane Controlled Trials Register. Medline was searched from 1966 onwards to October 2002 using an optimally sensitive search strategy for identifying RCTs. Text words that were applied to the search included naratriptan, Naramig and Amerge. This was supplemented by searching the reference lists of all retrieved RCTs and contacting the manufacturer of naratriptan. Trial eligibility was determined independently by the two authors. Abstracts were considered; attempts were made to obtain relevant information not included in the published reports by either contacting the principal author of the trial or the manufacturer.

Assessment of quality of included trials: yes

Other methodological remarks:
Single dose of naratriptan for a single migraine attack.
The method of DerSimonian and Laird was used to calculate the pooled estimates and their corresponding 95% CIs.

Remarks:
One trial compared naratriptan 2.5 mg against naratriptan 2.5 mg plus naproxen 500 mg in 50 patients was identifies in the SR. This trial does not meet our inclusion criteria and is not reported in the present document.

12.9 Gepants

12.9.1 Rimegepant versus placebo for acute treatment of migraine in adults

Meta-analysis: Gao 2019(190), Efficacy and Safety of Rimegepant for the Acute Treatment of Migraine: Evidence From Randomized Controlled Trials

Definition of migraine:/

Inclusion criteria: Inclusion criteria were as follows: (a) study type: RCTs; (b) language restriction: no language restriction was applied in our study; (c) participants: patients aged >18 years with migraine for at least 1 year; (d) intervention: rimegepant and placebo; (e) outcomes: efficacy outcomes including freedom from pain,
freedom from most bothersome symptom and pain relief at 2hr, and safety outcomes. Exclusion criteria were as follows: (a) study types: case reports, case reviews, post-hoc analyses studies, retrospective studies, and cohort studies; (b) patients with a history of any clinically significant or unstable medical condition; and patients who received nonbiologic investigational agents within 30 days of the baseline visit or received biologic investigational agents within 90 days before the baseline visit.

Search strategy: A search was made for several terms in Pubmed, Embased, and Cochrane Library until August 2019 to find potentially eligible studies. In addition, we manually screened reference lists from RCTs and systematic reviews to ensure all relevant studies had been included in this study.

Assessment of quality of included trials: yes

Other methodological remarks:
Random effects model was used

Ref	Comparison	N/n	Outcomes	Result
Gao 2019 Design: SR+MA Search date: August 2019	Rimegepant Vs Placebo	N = 4 n = 3827 (Marcus 2014, Croop 2019, Lipton 2019, Lipton 2018)	Pain free (2h) (PO)	Rimegepant: 20.6% Placebo: 12.5% **RR (95% CI): 1.70 (1.39 to 2.08)** **SS in favour of rimegepant** I^2: 43%
		N = 4	Pain relief (2h) (PO)	Rimegepant: 58.6%

		n = 3827 (Marcus 2014, Croop 2019, Lipton 2019, Lipton 2018)		Placebo: 44.6% **RR (95% CI): 1.34 (1.25 to 1.44)** **SS in favour of rimegepant** I^2: 17.1 %
		N = 4 n = 3827 (Marcus 2014, Croop 2019, Lipton 2019, Lipton 2018)	Freedom from most bothersome symptom at 2 h (PO)	Rimegepant: 36% Placebo: 25.1% **RR (95% CI): 1.44 (1.23 to 1.68)** **SS in favour of rimegepant** I^2: 54.5%
		N = 4 n = 3827 (Marcus 2014, Croop 2019, Lipton 2019, Lipton 2018)	Freedom from nausea at 2 h	Rimegepant: 50.3% Placebo: 44.7% **RR (95% CI): 1.16 (1.07 to 1.26)** **SS in favour of rimegepant** I^2: 0%
		N = 4 n = 3827 (Marcus 2014, Croop 2019, Lipton	Freedom from photophobia at 2 h	Rimegepant: 35.5% Placebo: 23.9% **RR (95% CI): 1.49 (1.33 to 1.68)** **SS in favour of rimegepant** I^2: 14.3%

		2019, Lipton 2018)		
		N = 4 n = 3827 (Marcus 2014, Croop 2019, Lipton 2019, Lipton 2018)	Freedom from phonophobia at 2 h	Rimegepant: 40.1% Placebo: 29.1% **RR (95% CI): 1.41 (1.23 to 1.62)** **SS in favour of rimegepant** I^2: 39.1%
		N = 4 n = 3827 (Marcus 2014, Croop 2019, Lipton 2019, Lipton 2018)	Sustained pain free (24 h)	Rimegepant: 22.1% Placebo: 12.3% **RR (95% CI): 2.18 (1.38 to 3.44)** **SS in favour of rimegepant** I^2: 86%
		N = 4 n = 3827 (Marcus 2014, Croop 2019, Lipton 2019, Lipton 2018)	Sustained pain free (48 h)	Rimegepant: 12.9% Placebo: 5.9% **RR (95% CI): 2.45 (1.56 to 3.84)** **SS in favour of rimegepant** I^2: 66.1%

		N = 4 n = 3827 (Marcus 2014, Croop 2019, Lipton 2019, Lipton 2018)	Sustained pain relief (24 h)	Rimegepant: 47.1% Placebo: 29.4% **RR (95% CI): 1.69 (1.53 to 1.87)** **SS in favour of rimegepant** I^2: 0%
		N = 4 n = 3827 (Marcus 2014, Croop 2019, Lipton 2019, Lipton 2018)	Sustained pain relief (48 h)	Rimegepant: 39.6% Placebo: 24.1% **RR (95% CI): 1.64 (1.46 to 1.86)** **SS in favour of rimegepant** I^2: 0%
		N = 4 n = 3827 (Marcus 2014, Croop 2019, Lipton 2019, Lipton 2018)	Total adverse events	Rimegepant: 4.4% Placebo: 3.7% **RR (95% CI): 1.17 (0.88 to 1.55)** **NS** I^2: 40.5%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Marcus 2014	885	Acute migraine Age:18-65 years old	7 days	Rimegepant 10m Vs	**As reported in Vanderpluym 2021 (Rob tool)**

RCT Multi-center		At least one-year history of migraine Two to seven attacks in each 3 months Exclusion: History of basilar-type migraine; history of stroke/transient ischemic attacks		Rimegepant 25mg Vs Rimegepant 75mg Vs Rimegepant 150mg Vs Rimegepant 300mg Vs Rimegepant 600mg Vs Sumatriptan 100mg Vs Placebo	Overall: **High** Randomization: **High Risk** Deviation from intended intervention: **Low risk** Missing outcome data: **Low risk** Measurement of outcome: **Moderate risk** Selection of reported results: **Low risk**
Croop 2019 RCT Multi-center	1466	Acute migraine Age>18 years old At least one-year history of migraine At least two attacks in each month Exclusion: History of serious illness; alcohol or drug abuse	7-9 days	Rimegepant 75mg Vs Placebo	**As reported in Vanderpluym 2021 (Rob tool)** Overall: **High** Randomization: **Low risk** Deviation from intended intervention: **Low risk** Missing outcome data: **Low risk** Measurement of outcome: **Low risk** Selection of reported results: **High risk**
Lipton 2019 RCT Multi-center	1186	Acute migraine Age>18 years old At least one-year history of migraine Two to eight attacks in each month Exclusion: History of any clinically significant or unstable medical	7 days	Rimegepant 75mg Vs Placebo	**As reported in Vanderpluym 2021 (Rob tool)** Overall: Moderate Randomization: **Moderate risk** Deviation from intended intervention: **Low risk** Missing outcome data: **Low risk**

		condition, alcohol or drug abuse and substance-use disorder			Measurement of outcome: **Moderate risk** Selection of reported results: **Low risk**
Lipton 2018 RCT Multi-center		Acute migraine Age>18 years old At least one-year history of migraine Two to eight attacks in each month Exclusion: History of any clinically significant or unstable medical condition, alcohol or drug abuse and substance-use disorder		Rimegepant 75mg Vs Placebo	Missing outcome data: **High risk** **"**The risk for incomplete outcome data bias is high in the Lipton study (2018). " Selective reporting: **Moderate risk** "For selective reporting, the Lipton study had an unclear risk of bias."

Remarks:

- A dose a 75 mg was used in these different studies.
- Large majority of the subjects of these four RCTs were roughly 40-year-old, non-Hispanic and non-Latino white women with a BMI of about 31.
- Risk of bias is evaluated but details of the evaluation have not been reported. Evaluation reported in Vanderpluym2021 have been used. Lipton 2018 is not reported in VanderPluym 2021 has it is only published as congress abstract, no additional information have been found.

Author's conclusions:

"Rimegepant exhibits good efficacy and safety for the acute treatment of migraine. A dose of 75 mg rimegepant was proven to be effective against acute migraine headache as measured by freedom from pain and bothersome symptoms or pain relief 2 hours post dose after drug ingestion as compared to the placebo. The use of 75 mg rimegepant was not related to a significant increase in these specific adverse events."

12.9.2 Ubrogepant versus placebo for acute treatment of migraine in adults (population ??? check for this MA)

Meta-analysis: VanderPluym 2021(1), Acute Treatments for Episodic Migraine in Adults A Systematic Review and Meta-analysis

Definition of migraine: the definition used in the original studies was accepted as long as it also fit the current *International Classification of Headache Disorders,*
Third Edition criteria for episodic migraine (defined as the presence of headache 14 or fewer days per month in someone who has migraine).

Inclusion criteria: Eligible studies (1) included adult patients (≥18 years)with episodic migraine; (2) evaluated abortive pharmacologic therapy or noninvasive nonpharmacologic abortive therapy; (3) involved comparisons of the intervention with placebo, usual care, another pharmacologic therapy, noninvasive nonpharmacologic therapy, wait list, no treatment, or attention control, (4) reported short-term outcomes of interest (≤4 weeks after the end of treatments); and (5) were published in English.

Exclusion:
Invasive treatments (defined as surgically implanted), preventive treatments, in vitro studies, studies without original data, and single-group studies were excluded. Therapies in development, with terminated development, or unavailable in the United States were also excluded.
Studies that randomized migraine attacks instead of patients were not meta-analyzed because correlations between attacks could not be controlled.

Search strategy: EMBASE, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, PsycINFO, and Scopus from database inception to February 24, 2021, were searched. Clinical trial registries, government databases and websites, conference proceedings, patient advocate group websites, and medical society websites were also searched. Reference mining of existing systematic reviews/meta-analyses, clinical trial registries, and relevant primary studies was conducted to identify additional literature.

Assessment of quality of included trials: yes

Other methodological remarks:
All statistical analyses for RCTs involved analyzing participants according to their original allocation group. For crossover RCTs, outcomes before crossover were used in meta-analysis. Studies that randomized migraine attacks instead of patients were not meta-analyzed because correlations between attacks could not be controlled. DerSimonian-Laird random-effects model with Hartung- Knapp-Sidik-Jonkman variance correction was used to combine direct comparisons between treatments if the number of studies included in the analysis was larger than 3. The fixed-effect method based on the Mantel-Haenszel method was adopted when the number of studies was 3 or fewer.

Ref	Comparison	N/n	Outcomes	Result
VanderPluym2021 Design: SR+MA Search date: February 2021	Ubrogepant Vs Placebo	N = 3 n = 4192 (Dodick 2019, Lipton 2019, Voss 2016)	Pain free (2h)	Ubrogepant: 459/2931 Placebo: 129/1261 RR (95% CI): 1.58 (1.31 to 1.90) **SS in favour of ubrogepant** I^2=0.00%
		N = 3 n = 4192 (Dodick 2019, Lipton 2019, Voss 2016)	Pain relief (2h) (Improvement of pain from moderate to severe at baseline to mild or none or pain scale improved at least 50% from baseline at defined assessment time)	Ubrogepant: 1357/2931 Placebo: 494/1261 RR (95% CI): 1.21 (1.12 to 1.31) **SS in favour of ubrogepant** I^2=0.00%
		N = 1 n = 1686 (Lipton 2019)	Pain relief (24h) (Improvement of pain from moderate to severe at baseline to mild or none or pain scale improved at least 50% from baseline at defined assessment time)	Ubrogepant : 303/1123 Placebo : 93/563 RR (95% CI): 1.63 (1.33 to 2.01) **SS in favour of ubrogepant**
		N = 3 n = 4192 (Dodick 2019, Lipton 2019, Voss 2016)	Sustained pain free (24h) (No pain at initial assessment and remains at follow-up assessment with no use of rescue medication or relapse)	Ubrogepant: 310/2931 Placebo: 83/1261 RR (95% CI): 1.63 (1.29 to 2.07) **SS in favour of ubrogepant** I^2=0.00%

		N = 1 n = 834 (Voss 2016)	Sustained pain free (1 week), (No pain at initial assessment and remains at follow-up assessment with no use of rescue medication or relapse)	Ubrogepant : 66/695 Placebo : 7/139 RR (95% CI): 1.89 (0.88 to 4.02) **NS**
		N = 2 n = 2506 (Voss 2016, Dodick 2019)	Sustained pain relief (24h) (pain relief at defined assessment time that remains improved at follow-up assessment with no use of rescue medication or relapse)	Ubrogepant: 509/1808 Placebo: 125/698 RR (95% CI): 1.55 (1.30 to 1.85) **SS in favour of ubrogepant** I^2= 66.05%
		N = 1 n = 834 (Voss 2016)	Sustained pain relief (1 week) (Pain relief at defined assessment time that remains improved at follow-up assessment with no use of rescue medication or relapse)	Ubrogepant: 181/695 Placebo: 28/139 RR (95% CI): 1.29 (0.91 to 1.84) **NS**
		N = 2 n = 3358 (Dodick 2019, Lipton 2019)	Restored function (2h) (No restriction to perform work or usual activities)	Ubrogepant : 737/2236 Placebo : 292/1122 RR (95% CI): 1.27 (1.13 to 1.42) **SS in favour of ubrogepant** I^2= 0.00%
		N = 2 n = 3358 (Dodick 2019, Lipton 2019)	Restored function (24h) (No restriction to perform work or usual activities)	Ubrogepant: 1331/2236 Placebo: 573/1122 RR (95% CI): 1.17 (1.09 to 1.25) **SS in favour of ubrogepant**

				I^2= 0.00%
		N = 1 n = 834 (Voss 2016)	Cardiovascular adverse events	Rate Ratio: 2.00 95% CI: 0.11 to 36.61 **NS**
		N = 2 n = 3358 (Dodick 2019, Lipton 2019)	Serious adverse events.	Rate Ratio: 2.54 95% CI: 0.28 to 23.11 **NS** I^2=N/A
		N = 3 n = 4192 (Dodick 2019, Lipton 2019, Voss 2016)	Total adverse events	Rate Ratio: 1.11 95% CI: 0.96 to 1.28 **NS** I^2=0%
		N = 2 n = 3358 (Dodick 2019, Lipton 2019)	Withdrawal due to adverse events	RR: 0.63 95% CI: 0.17 to 2.33 **NS** I^2=4.68

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Dodick 2019 RCT	1672	Outpatients	4 weeks	Ubrogepant 100 mg Vs Ubrogepant 50 mg vs	Overall: Low Randomization: Low risk Deviation from intended intervention: Low risk

		Ubrogepant 100 mg: n = 557, 40.6±12 years, 86.2% female, 80.8% white, BMI 30.4±8. **Ubrogeptant 50 mg:** n = 556, 40.1±11.7 years, 89.7% female, 82.2% white, BMI 30.2±8.1 **Placebo:** n = 559, 40.9±11.7 years, 88.7% female, 84.5% White, BMI 30±7.4		Placebo Ubrogepant: 2 or 1 tablet(s) of ubrogepant 50 mg, once. Placebo: 2 placebo tablets, once. An optional second dose of the same treatment was allowed.	Missing outcome data: Low risk Measurement of outcome: Low risk Selection of reported results: Low risk FOLLOW-UP: Not reported ITT: Not reported FUNDING: Not reported
Lipton 2019 RCT	1686	Outpatients **Ubrogepant 50 mg**: n= 562, 41.2±12.5 years, 91% female, 16.8% African American, 81.6% white, 0.4% Asian, 21.9% Hispanic, 0.4% American Indian or Alaska Native, 0.2% Native Hawaiian or other Pacific Islander, 0.6% multiple, BMI 30.5±7.5, 3.9% previous opioid use **Ubrogepant 25 mg:** n = 561, 41.6±12.4 years, 90.2% female, 14% African American, 83.5% White, 1.3% Asian, 23% Hispanic, 0.2% American Indian or Alaska Native, 0.2% Native Hawaiian or other Pacific Islander, 0.8% multiple, BMI 29.6±7, 3.6 % previous opioid use **Placebo:** n = 563, 41.7±12.1 years, 88.6% female, 16.4% African	42 days	Ubrogepant 50 mg Vs Ubrogepant 25 mg Vs Placebo Once within 4 hours of a qualifying migraine attack	Overall: Low Randomization: Low risk Deviation from intended intervention: Low risk Missing outcome data: Low risk Measurement of outcome: Low risk Selection of reported results: Low risk FOLLOW-UP: Not reported ITT: Not reported FUNDING: Not reported

		American, 80% White, 1.4% Asian, 19.8% Hispanic, 0.6% American Indian or Alaska Native, 0.2% Native Hawaiian or other Pacific Islander, 1.4% multiple, BMI 29.8±7.7, 3.8% previous opioid use			
Voss 2016 RCT	834	Outpatients **Ubrogepant 1 mg**: n = 138, 39.6 ± 10.7 years, 88.8% female, BMI 29.4±7.3 **Ubrogepant 10 mg:** n = 139, 41.1 ± 10.9 years, 85.2% female, 29.6±7.1 **Ubrogepant 25 mg:** n = 139, 41.4 ± 11.5 years, 86.8% female, BMI 29.2±8.1 **Ubrogepant 50 mg:** n = 139, 40.7 ± 12.3 years, 88.2% female, BMI 27.8±8.1 **Ubrogepant 100 mg:** n = 140, 41.9 ± 11 years, 83.3% female, BMI 29.2±7 **Placebo:** n= 139, 40.5 ± 11.7 years, 87.65% female, BMI 28.5±7		Ubrogepant 1 mg vs Ubrogepant 10 mg vs Ubrogepant 25 mg vs Ubrogepant 50 mg vs Ubrogepant 100 mg vs Placebo Oral once	Overall: Low Randomization: Low risk Deviation from intended intervention: Low risk Missing outcome data: Low risk Measurement of outcome: Low risk Selection of reported results: Low risk FOLLOW-UP: Not reported ITT: Not reported FUNDING: Not reported

Remarks:

- 2 different doses of ubrogepant were investigated in Dodick 2019 as well as in Lipton 2019. 5 different doses were compared in Voss 2016. For the purpose of this report we have only reported the effect of ubrogepant as a pooled group. The comparison of each individual dose, to placebo or to each other, was done in a subgroup analysis of the reported MA (not included in the methodology of this report).

Author's conclusions:

“In particular, use of triptans, NSAIDs, acetaminophen, dihydroergotamine, calcitonin generelated peptide antagonists, lasmiditan, and remote electrical neuromodulation was associatedwith improved pain and function with relatively robust SOE.”

13 Appendix. Evidence tables. Prophylactic treatment of migraine in adults.

13.1 Beta-blockers

Meta-analysis: Jackson 2019(198) :” Beta-blockers for the prevention of headache in adults, a systematic review and meta-analysis”

Migraine definition: articles were reviewed by at least two authors to determine if the headache could be reasonably classified as migraine or tension-type headache and as either frequent episodic or chronic according to the most recent IHS criteria.

Inclusion criteria:
Study design: RCTs at least 4 weeks in duration
Population: adults with migraine or tension-type headache
Intervention: beta-blocker used for the prevention of migraine or tension-type headache

Search strategy: Cochrane Register of Controlled Trials; MEDLINE; EMBASE; ISI Web of Science, clinical trial registries, CNKI, Wanfang and CQVIP were searched up until August 2018

Assessment of quality of included trials: y, JADAD and Cochrane risk of bias tool

Other methodological remarks:

Remarks:

Conclusion authors: “There is high quality evidence that propranolol is better than placebo for episodic migraine headache. Other comparisons were underpowered, rated as low-quality based on only including single trials, making definitive conclusions about comparative effectiveness impossible. There were few trials examining beta-blocker effectiveness for chronic migraine or tension-type headache though there was limited evidence of benefit”

13.1.1 Atenolol vs placebo

Ref	Comparison	N/n	Outcomes	Result
Jackson 2019(198) Design: SR Search date: August 2018	atenolol vs placebo	N= 2 n=96 (Forssman 1983, Johansson 1987)	Headache frequency (headache days per month) At week 12	**WMD -1.7 (-3.0 to -0.32)** **SS in favour of atenolol**
		N= 2 n=96 (Forssman 1983, Johansson 1987)	50% improvement in headaches At week 12	**RR 1.8 (1.0 to 3.2)** **SS in favour of atenolol**

		N= 2 n=96 (Forssman 1983, Johansson 1987)	Headache index At 12 weeks	**SMD -0.65 (-1.3 to -0.01)** **SS in favour of atenolol**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Jackson 2019)
Forssman 1983 Crossover RCT	24	Migraine – unspecified Mean age 40 y Rescue medication allowed	13 weeks	Atenolol (100) vs Placebo	RCT did not meet our inclusion criteria (sample size)
Johannsson 1987 Crossover RCT	72	Episodic migraine Mean age 43 y Rescue medication allowed	12 weeks	Atenolol (100) vs Placebo	Jadad score (0-8): 4 ITT: no ADHERENCE ASSESSED: no RANDO: unclear risk ALLOCATION CONC: unclear risk BLINDING: unclear risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: unclear risk OTHER BIAS unclear risk

					INDUSTRY SPONSORED: unclear

13.1.2 Bisoprolol vs placebo

Ref	Comparison	N/n	Outcomes	Result
Jackson 2019(198) Design: SR Search date: August 2018	bisoprolol vs placebo	N= 1 n= 226 (van de Ven 1997)	Headache frequency (headache days per month) At week 12	Bisoprolol 5 mg **WMD -0.90 (-1.53 to -0.27)** **SS in favour of bisoprolol** Bisoprolol 10 mg **WMD -0.90 (-1.6 to -0.24)** **SS in favour of bisoprolol**

		N= 1 n= 226 (van de Ven 1997)	Headache duration (hours per month) At week 12	WMD -1.9 (-6.5 to 2.5) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Jackson 2019)
Van de Ven 1997 Parallel group RCT	226	Episodic migraine HIS 1988 classification Rescue medication allowed Mean age 38.7y	12 weeks	Bisoprolol 5 mg vs Bisoprolol 10 mg vs Placebo	Jadad score (0-8): 4 ITT: yes ADHERENCE ASSESSED: Yes RANDO: unclear risk ALLOCATION CONC: unclear risk BLINDING: unclear risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS Low risk INDUSTRY SPONSORED: yes

13.1.3 Metoprolol vs placebo

Ref	Comparison	N/n	Outcomes	Result
Jackson 2019(198) Design: SR Search date: August 2018	Metoprolol vs placebo	N= 3 n= 140 (Li 2006, Siniatchkin 2007, Yang 2006)	Headache frequency (headache days per month) At week 12	WMD -0.90 (-2.2 to 0.41) NS
		N= 3 n= 140 (Li 2006, Siniatchkin 2007, Yang 2006)	50% improvement in headaches At week 12	**RR 1.7 (1.0 to 2.9)** **SS in favour of metoprolol** **I^2 =66.1%**

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Jackson 2019)

Li 2006 Parallel group RCT	60	Migraine – unspecified Mean age 48.5 y Rescue medication allowed	12 weeks	Metoprolol (125 mg) vs Placebo	RCT does not meet our inclusion criteria (sample size)
Siniatchkin 2007 Parallel group RCT	20	Migraine – unspecified Mean age 37 y Rescue medication allowed	12 weeks	Metoprolol (200 mg) vs Placebo	RCT does not meet our inclusion criteria (sample size)
Yang 2006 Parallel group RCT	60	Episodic migraine	12 weeks	Metoprolol (90 mg) vs Placebo	RCT does not meet our inclusion criteria (sample size)

13.1.4 Propranolol vs placebo

Ref	Comparison	N/n	Outcomes	Result
Jackson 2019(198) Design: SR Search date:	propranolol vs placebo	N= 9 n= 811 (Borgesen 1974, Diener 2004, Johnson 1986,	Headache frequency (headache days per month) At week 12	**WMD -1.2 (-1.8 to-0.60)** **SS in favour of propranolol** **I^2 = 77%**

August 2018		Mikkelsen 1986, Pradalier 1989, Standnes 1982, Stovner 2014, Tfelt-Hansen 1984, Wideroe 1974) N= 1 n= 575 (Diener 2004)	At week 24	**WMD -0.9 (-1.5 to -0.32)** **SS in favour of propranolol**
		N= 9 n= 811 (Borgesen 1974, Diener 2004, Johnson 1986, Mikkelsen 1986, Pradalier 1989, Standnes 1982, Stovner 2014, Tfelt-Hansen 1984, Wideroe 1974)	50% improvement in headaches At week 12	**RR 1.4 (1.1 to 1.8)** **SS in favour of propranolol** **I^2 = 59.5%**

		N= 9 n= 811 (Borgesen 1974, Diener 2004, Johnson 1986, Mikkelsen 1986, Pradalier 1989, Standnes 1982, Stovner 2014, Tfelt-Hansen 1984, Wideroe 1974)	Analgesic medication consumption (number of doses per month) At week 12	**WMD -2.1 (-3.2 to -0.95)** **SS in favour of propranolol** **I^2 = 85.2%**
		N= 9 n= 811 (Borgesen 1974, Diener 2004, Johnson 1986, Mikkelsen 1986, Pradalier 1989, Standnes 1982, Stovner 2014, Tfelt-Hansen 1984, Wideroe 1974)	Headache Index At week 12	**SMD -0.41 (-0.65 to -0.17)** **SS in favour of propranolol** **I^2 =0%**

		N= 9 n= 811 (Borgesen 1974, Diener 2004, Johnson 1986, Mikkelsen 1986, Pradalier 1989, Standnes 1982, Stovner 2014, Tfelt-Hansen 1984, Wideroe 1974)	Headache severity At week 12	SMD 0.18 (-0.30 to 0.01) NS I^2 = 46.0%
		N= 9 n= 811 (Borgesen 1974, Diener 2004, Johnson 1986, Mikkelsen 1986, Pradalier 1989, Standnes 1982, Stovner 2014, Tfelt-Hansen 1984, Wideroe 1974)	Headache duration (hours per month) At week 12	**WMD -1.6 (-3.0 to -0.11)** **SS in favour of propranolol** **I^2 = 0%**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Jackson 2019)
Borgesen 1974 Crossover RCT	12	Episodic migraine Mean age 37.6 y Rescue medication allowed	12 weeks	Propranolol (120 mg) vs Placebo	RCT doesn not meet our inclusion criteria (sample size)
Diener 2004 Parallel group RCT	575	Episodic migraine Mean age 41 y Rescue medication allowed	26 weeks	Propranolol (160 mg) vs. Topiramate (100 mg) vs Topiramate (200 mg) vs Placebo	Jadad score (0-8): 6 ITT: yes ADHERENCE ASSESSED: no RANDO: unclear risk ALLOCATION CONC: unclear risk BLINDING: low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS high risk INDUSTRY SPONSORED: yes
Johnson 1986 Crossover RCT	29	Episodic migraine Mean age 42 y Rescue medication allowed	12 weeks	Propranolol (240) vs Mefenamic Acid (1500) vs Placebo	RCT does not meet our inclusion criteria (sample size)
Mikkelsen 1986 Crossover RCT	31	Episodic migraine Mean age 39.4 y	12 weeks	Propranolol (120) vs Tolfenamic Acid (300) vs	RCT does not meet our inclusion criteria (sample size)

		Rescue medication allowed		Placebo	
Pradalier 1989 Parallel group RCT	74	Episodic migraine Mean age 37.4 y Unclear whether rescue medication allowed	12 weeks	Propranolol (160) vs Placebo	RCT does not meet our inclusion criteria (sample size)
Standnes 1982 Crossover RCT	25	Episodic migraine Mean age 41.4 y Rescue medication allowed	12 weeks	Propranolol 80 mg vs Timolol 10 mg vs Placebo	RCT does not meet our inclusion criteria (sample size)
Stovner 2014 Crossover RCT	72	Episodic migraine Mean age 37 y Rescue medication allowed	12 weeks	Propranolol (160 mg) vs Candesartan (16 mg) vs Placebo	Jadad score (0-8): 8 ITT: yes ADHERENCE ASSESSED: Yes RANDO: low risk ALLOCATION CONC: low risk BLINDING: low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS unclear risk INDUSTRY SPONSORED: yes
Tfelt-Hansen 1984 Crossover RCT	96	Episodic migraine Mean age 39.5 y	12 weeks	Propranolol 160 mg vs Timolol 20 mg vs	Jadad score (0-8): 6 ITT: no ADHERENCE ASSESSED: no

		Rescue medication allowed		Placebo	RANDO: unclear risk ALLOCATION CONC: unclear risk BLINDING: low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: high risk OTHER BIAS unclear risk INDUSTRY SPONSORED: unclear
Wideroe 1974 Crossover RCT	30	Episodic migraine Mean age 40 y Rescue medication allowed	12 weeks	Propranolol (160) vs Placebo	RCT does not meet our inclusion criteria (sample size)

13.1.5 Timolol vs placebo

Ref	Comparison	N/n	Outcomes	Result
Jackson 2019(198) Design: SR Search date: August 2018	timolol vs placebo	N= 2 n= 121 (Standnes 1982, Tfelt-Hansen 1984)	Headache frequency (headache days per month) At week 12	**WMD -1.53 (-2.5 to -0.78)** **SS in favour of timolol** **I^2 = 0%**

		N= 2 n= 121 (Standnes 1982, Tfelt-Hansen 1984)	50% improvement in headaches At week 12	**RR 1.8 (1.4 to 2.3)** **SS in favour of timolol** **I^2 =0%**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Jackson 2019)
Standnes 1982 Crossover RCT	25	Episodic migraine Mean age 41.4 y Rescue medication allowed	12 weeks	Propranolol 80 mg vs Timolol 10 mg vs Placebo	RCT does not meet our inclusion criteria (sample size)
Tfelt-Hansen 1984 Crossover RCT	96	Episodic migraine Mean age 39.5 y Rescue medication allowed	12 weeks	Propranolol 160 mg vs Timolol 20 mg vs Placebo	Jadad score (0-8): 6 ITT: no ADHERENCE ASSESSED: no RANDO: unclear risk ALLOCATION CONC: unclear risk BLINDING: low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: high risk OTHER BIAS unclear risk

					INDUSTRY SPONSORED: unclear

13.1.6 Metoprolol vs bisoprolol

Ref	Comparison	N/n	Outcomes	Result
Jackson 2019(198) Design: SR Search date: August 2018	Metoprolol vs bisoprolol	N= 1 n= 125 (Worz 1992)	Headache frequency (headache days per month) At week 12	WMD -0.09 (-0.62 to 0.44) NS
		N= 1 n= 125 (Worz 1992)	Medication use (doses/month)	WMD 0.01 (-0.30 to 0.32) NS
		N= 1 n= 125 (Worz 1992	Headache severity	WMD 0.19 (-0.13 to 0.3) NS
		N= 1 n= 125 (Worz 1992	Headache duration (hours per month)	WMD 0.30 (-4.2 to 4.8) NS

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Jackson 2019)

Worz 1992 Crossover RCT	125	Episodic migraine Mean age 38.5 y Rescue medication allowed	12 weeks	Metoprolol (200 mg) vs Bisoprolol (10 mg)	Jadad score (0-8): 2 ITT: unclear ADHERENCE ASSESSED: unclear RANDO: high risk ALLOCATION CONC: high risk BLINDING: unclear risk INCOMPLETE OUTCOME DATA: high risk SELECTIVE REPORTING: Low risk OTHER BIAS unclear risk INDUSTRY SPONSORED: no

13.1.7 Propranolol vs metoprolol

Jackson 2019 reported results for propranolol vs metoprolol for some outcomes at a time points of 16 weeks, 24 weeks and 28 weeks. However, we believe this to be an inaccuracy: it is unclear which studies these results are extracted from, as the only studies presented in Jackson 2019 that compare propranolol to metoprolol are short in duration (8 weeks or less). As the RCTs do not meet our inclusion criteria (for duration and sample size), we did not report this comparison.

13.1.8 Timolol vs propranolol

Ref	Comparison	N/n	Outcomes	Result
Jackson 2019(198) Design: SR Search date: August 2018	timolol vs propranolol	N= 2 n= 121 (Standnes 1982, Tfelt-Hansen 1984)	Headache frequency (headache days per month) At week 12	WMD 0.37 (-0.45 to 1.2) NS I^2 = 0%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Jackson 2019)
Standnes 1982 Crossover RCT	25	Episodic migraine Mean age 41.4 y Rescue medication allowed	12 weeks	Propranolol 80 mg vs Timolol 10 mg vs Placebo	RCT does not meet our inclusion criteria (sample size)
Tfelt-Hansen 1984 Crossover RCT	96	Episodic migraine Mean age 39.5 y Rescue medication allowed	12 weeks	Propranolol 160 mg vs Timolol 20 mg vs Placebo	Jadad score (0-8): 6 ITT: no ADHERENCE ASSESSED: no RANDO: unclear risk ALLOCATION CONC:

					unclear risk BLINDING: low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: high risk OTHER BIAS unclear risk INDUSTRY SPONSORED: unclear

13.1.9 Propranolol vs riboflavin

Ref	Comparison	N/n	Outcomes	Result
Jackson 2019(198) Design: SR Search date: August 2018	propranolol vs riboflavine	N= 1 n= 100 (Nambiar 2011)	Headache frequency (headache days per month) At week 12	WMD -0.04 (-0.59 to 0.51) NS
		N= 1 n= 100 (Nambiar 2011)	Headache severity 12 weeks	**WMD 0.42 (0.02 to 0.82)** **SS in favour of riboflavin** **Lower headache severity with riboflavin**
		N= 1 n= 100 (Nambiar 2011)	Headache severity 24 weeks	WMD 0.11 (-0.29 to 0.50) NS

		N= 1 n= 100 (Nambiar 2011) 12 weeks	Headache duration (hours per month)	WMD -0.10 (-0.39 to 0.19) NS
		N= 1 n= 100 (Nambiar 2011) 24 weeks	Headache duration (hours per month)	WMD 0.30 (-0.06 to 6.6) NS

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Jackson 2019)
Nambiar 2011 Parallel group RCT	100	Episodic migraine Mean age 31 y Rescue medication allowed	24 weeks	Propranolol (80 mg) vs Riboflavin (100 mg)	Jadad score (0-8): 3 ITT: yes ADHERENCE ASSESSED: no RANDO: high risk ALLOCATION CONC: high risk BLINDING: high risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: high risk OTHER BIAS unclear risk INDUSTRY SPONSORED: no

13.1.10 Propranolol vs topiramate

Ref	Comparison	N/n	Outcomes	Result
Jackson 2019(198) Design: SR Search date: August 2018	propranolol vs topiramate	N= 2 n= 642 (Diener 2004, Yuan 2005) N=1 n= 575 (Diener 2004)	Headache frequency (headache days per month) At week 12 At week 24	WMD 0.10 (-0.98 to 1.2) NS WMD -0.75 (-1.6 to 0.13) NS
		N=2 n= 642 (Diener 2004, Yuan 2005)	50% reduction in headache At week 12	RR 1.2 (0.98 to 1.4) NS I^2 = 0%

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Jackson 2019)
Diener 2004 Parallel group RCT	575	Episodic migraine Mean age 41 y Rescue medication allowed	26 weeks	Propranolol (160 mg) vs. Topiramate (100 mg) vs Topiramate (200 mg) vs Placebo	Jadad score (0-8): 6 ITT: yes ADHERENCE ASSESSED: no RANDO: unclear risk ALLOCATION CONC: unclear risk BLINDING:

					low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS high risk INDUSTRY SPONSORED: yes
Yuan 2005 Parallel group RCT	67	Migraine – unspecified Mean age 29.9 y Rescue medication NOT allowed	12 weeks	Propranolol (120) vs Topiramate (150)	RCT does not meet our inclusion criteria (sample size)

13.2 Sartans

Meta-analysis: Jackson 2015(217) “A Comparative Effectiveness Meta-Analysis of Drugs for the Prophylaxis of Migraine Headache”

Definition of migraine: two authors independently reviewed each included article's headache definition and, where possible, classified it according to the 3rd edition of the International Headache Society (IHS) criteria (ICDH-III) and included only those that could reasonably be defined based on these diagnostic criteria

Inclusion criteria:
Study design: RCTs, at least 4 weeks in duration
Population: episodic or chronic migraine
Comparisons: active treatments versus placebo or active controls for the preventive treatment of migraine

Search strategy: PUBMED, EMBASE, Cochrane Trial Registry were searched up until May 2014. Assessment of quality of included trials: yes, JADAD and Cochrane risk of bias tools Other methodological remarks: this was a network meta-analysis; we only reported the analyses of direct comparisons.

13.2.1 Candesartan vs placebo

Ref	Comparison	N/n	Outcomes	Result
Jackson 2015(217) Design: SR Search date: May 2014	Candesartan Vs placebo	N= 2 n= 118 (Stovner 2013, Tronvik 2003)	Headache frequency (number of headaches per month) at 12 weeks	MD -0.9 (-1.8 to 0.03) NS I^2 = 31.7%
		N= 1 n= 57 (Tronvik 2003)	>50% improvement at 12 weeks	**RR 18.0 (2.5 to 130.4)** **SS in favour of candesartan**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Jackson 2015)
Stovner 2013	61	Episodic migraine	12 weeks	Candesartan 16 mg vs	Jadad score (0-8): 8) ITT: yes

RCT crossover				propranolol 160 mg vs placebo	ADHERENCE ASSESSED: Yes RANDO: low risk ALLOCATION CONC: low risk BLINDING: low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS unclear risk INDUSTRY SPONSORED: yes
Tronvik 2003 RCT crossover	57	Episodic migraine	12 weeks	Candesartan 16 mg vs placebo	Jadad score (0-8): 8 ITT: yes RANDO: low risk ALLOCATION CONC: low risk BLINDING: low risk INCOMPLETE OUTCOME DATA: unclear risk SELECTIVE REPORTING: unclear risk OTHER BIAS unclear risk INDUSTRY SPONSORED: yes

13.2.2 Telmisartan vs placebo

Ref	Comparison	N/n	Outcomes	Result
Jackson 2015(217) Design: SR Search date: May 2014	Telmisartan Vs placebo	N= 1 n= 95 (Diener 2009)	Headache frequency (number of headaches per month)	**MD -1.9 (-3.6 to -0.23)** **SS in favour of telmisartan**
		N= 1 n= 95 (Diener 2009)	>50% improvement	RR 1.6 (0.85 to 3.0) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Jackson 2015)
Diener 2009 RCT Parallel group	95	Episodic migraine	12 weeks	Telmisartan 80 mg Vs placebo	Jadad score (0-8): 3 ITT: no RANDO: unclear risk ALLOCATION CONC: unclear risk BLINDING: unclear risk INCOMPLETE OUTCOME DATA: unclear risk

					SELECTIVE REPORTING: unclear risk OTHER BIAS unclear risk INDUSTRY SPONSORED: yes

13.3 Calcium antagonists

Meta-analysis: SR Stubberud 2019(220) “Flunarizine as prophylaxis for episodic migraine: a systematic review with meta-analysis”

Definition of migraine: Included studies were not required to have strictly applied the International Headache Society diagnostic criteria as long as the migraine diagnoses were based on their list of distinctive features, such as nausea/vomiting, severe pain, pulsating pain, unilaterality, photophobia/phonophobia, or aura

Inclusion criteria:
Study design: prospective, randomized or pseudo-RCTs
Population: episodic migraine
Intervention: flunarizine as a prophylactic drug for migraine
Comparison: placebo or other pharmacological and nonpharmacological treatments with proven efficacy

Search strategy: MEDLINE, Embase, and CENTRAL were searched up until November 2017

Assessment of quality of included trials: yes, Cochrane risk of bias tool
Other methodological remarks:

Remarks:

This SR also found RCTs comparing flunarizine to valproate. However, none of these RCTs met our inclusion criteria (sample size).

13.3.1 Flunarizine vs placebo

Ref	Comparison	N/n	Outcomes	Result
Stubberud 2019(220) Design: SR Search date: November 2017	Flunarizine vs placebo	N= 5 n= 249 (Diamond 1993, Frenken 1984, Louis 1981, Pini 1985, Sørensen 1986)	Mean reduction in migraine frequency (after 3 months of treatment)	**MD -0.44 (-0.61 to -0.26)** **SS in favour of flunarizine** **I^2 = 27%**
		N= 3 n= 113 (Frenken 1984, Louis 1981, Mendenopoulos 1985)	Proportion of responders (≥50% reduction in migraine frequency)	Flunarazine: 36/55 Placebo: 11/58 **OR 8.86 (3.57 to 22.00)** **SS in favour of flunarizine** **I^2 = 0%**
		N= 3 n= 113 (Frenken 1984, Louis 1981, Mendenopoulos 1985)	Adverse events	Flunarazine: 12/55 Placebo: 10/58 RD 0.04 (-0.08 to 0.17) NS I^2 = 0%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Diamond 1993 double-blind RCT	143	migraine, with or without aura, two to eight migraines per month	20 weeks	Flunarizine 10 mg/day Vs placebo	RANDO: unclear risk (no information on method) ALLOCATION CONC: unclear risk (no information on method) BLINDING Participants/personnel: unclear risk (reported as double blind but unclear who was blinded) BLINDING Assessors : unclear risk (reported as double blind but unclear who was blinded) INCOMPLETE OUTCOME DATA: high risk (143 recruited, only 101 completers, exclusions not described) SELECTIVE REPORTING: high risk (unclear and limited reporting) OTHER BIAS High risk (only previous treatment responders were included)
Frenken 1984 double-blind RCT	35	migraine as defined by IHS	3 months	Flunarizine 10 mg/day Vs placebo	RCT did not meet our inclusion criteria (sample size)
Louis 1981 double-blind RCT	58	migraine with throbbing or pulsating attacks	3 months	Flunarizine 10 mg/day Vs	RCT did not meet our inclusion criteria (sample size)

				placebo	
Mendenopoulos 1985 double-blind RCT	30	Migraine diagnosis according to IHS criteria	4 months	Flunarizine 10 mg/day Vs placebo	RCT did not meet our inclusion criteria (sample size)
Pini 1985 double-blind RCT	20	migraine	20 days	Flunarizine 10 mg/day Vs placebo	RCT did not meet our inclusion criteria (sample size and duration)
Sørensen 1986 double-blind cross-over trial	29	Migraine diagnosis according to IHS criteria	Four weeks run-in, 16 weeks treatment, four weeks wash-out and then 16 weeks treatment	Flunarizine 10 mg/day Vs placebo	RCT did not meet our inclusion criteria (sample size)

13.3.2 Flunarazine vs metoprolol

Ref	Comparison	N/n	Outcomes	Result
Stubberud 2019(220) Design: SR Search date: November 2017	Flunarizine vs metoprolol	N= 1 n= 127 (Sørensen 1991)	Mean reduction in migraine frequency (after 3 months of treatment)	MD -0.10 (-1.08 to 0.88) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Sørensen 1991 Double-blind RCT	149	18-65 y Migraine diagnosis according to IHS criteria frequency of migraine attacks of 2-8 attacks per month.	5 months	Flunarizine 10 mg/day Vs metoprolol 200 mg/day	RANDO: Unclear risk (no information about method) ALLOCATION CONC: Unclear risk (no information about method) BLINDING Participants/personnel: Low risk BLINDING Assessors : unclear risk (no stated) INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk

13.3.3 Flunarazine vs propranolol

Ref	Comparison	N/n	Outcomes	Result
Stubberud 2019(220) Design: SR Search date: November 2017	Flunarizine vs propranolol	N= 7 n= 1151 (Bordini 1997, Ludin 1989, Soyka 1987a, Soyka 1987b, Diener 2002, Gawel 1992, Shimell 1990)	Mean reduction in migraine frequency (after 4 months of treatment)	MD -0.08 (-0.34 to 0.18) NS I^2 = 0%
		N= 2 n= 135 (Gawel 1992, Ludin 1989)	Intensity of migraine headache (after 4 months of treatment)	MD 0.22 (-0.12 to 0.57) NS
		N= 5 n= 1063 (Diener 2002, Gawel 1992, Ludin 1989, Soyka 1987a, Soyka 1987b)	Duration of migraine headache (after 4 months of treatment)	MD 0.60 (-1.48 to 2.69) NS
		N= 2 n= 583 (Diener 2002, Ludin 1989)	Doses of acute medication	SMD 0.07 (-0.09 to 0.23) NS
		N= 6 n= 1133	Adverse events	RD -0.04 (0.09 to 0.02) NS

		(Bordini 1997, Diener 2002, Gawel 1992, Shimell 1990, Soyka 1987a, Soyka 1987b)		

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Bordini 1997 double-blind RCT	45	Migraine diagnosis according to IHS criteria	4 months	Flunarizine 10 mg/day vs propranolol 60 mg/day vs flunarizine 10 mg/day + propranolol 60 mg/day	RCT does not meet our inclusion criteria (sample size)
Diener 2002 double-blind RCT	810	18-65 y Migraine diagnosis according to IHS criteria two to six migraine attacks every month	4 months	Flunarizine 5 mg/day vs flunarizine 10 mg/day vs propranolol 160 mg/day	RANDO: Low risk ALLOCATION CONC: Low risk BLINDING Participants/personnel: unclear risk (reported as double blind but unclear who was blinded) BLINDING Assessors : unclear risk (reported as double blind but unclear who was blinded) INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk
Gawel 1992	94	18-65 y	4 months	Flunarizine 10 mg/day vs	RANDO:

double-blind RCT		Migraine headache as defined by the World Federation of Neurology Research Group		propranolol 160 mg/day	unclear risk (no information on method) ALLOCATION CONC: unclear risk (no information on method) BLINDING Participants/personnel: unclear risk (reported as double blind but unclear who was blinded) BLINDING Assessors : unclear risk (reported as double blind but unclear who was blinded) INCOMPLETE OUTCOME DATA: high risk (18 non-completers, no information on reason- SELECTIVE REPORTING: high risk (limited reporting of adverse events)
Ludin 1989 double-blind RCT	71	Headache attacks with characteristic features of migraine	4 months	Flunarizine 10 mg/day vs propranolol 120 mg/day	RCT does not meet our inclusion criteria (sample size)
Shimell 1990 double-blind RCT	58	Migraine diagnosis according to IHS criteria	4 months	Flunarizine 10 mg/day vs propranolol 180 mg/day	RCT does not meet our inclusion criteria (sample size)
Soyka 1987a double-blind RCT	87	20-65 y Classic or common migraine with characteristic features	4 months	Flunarizine 10 mg/day vs propranolol 120 mg/day.	RANDO: unclear risk (no information on method) ALLOCATION CONC: unclear risk (no information on method) BLINDING Participants/personnel:

					unclear risk (reported as double blind but unclear who was blinded) BLINDING Assessors : unclear risk (reported as double blind but unclear who was blinded) INCOMPLETE OUTCOME DATA: high risk (18 non-completers, no information on reason) SELECTIVE REPORTING: high risk (limited reporting of dropouts)
Soyka 1987b double-blind RCT	434	20-65 y Classic or common migraine with characteristic features	4 months	Flunarizine 10 mg/day vs propranolol 120 mg/day.	RANDO: unclear risk (no information on method) ALLOCATION CONC: unclear risk (no information on method) BLINDING Participants/personnel: unclear risk (reported as double blind but unclear who was blinded) BLINDING Assessors : unclear risk (reported as double blind but unclear who was blinded) INCOMPLETE OUTCOME DATA: high risk (98 non-completers, no information on reason) SELECTIVE REPORTING: high risk (limited reporting of dropouts)

13.3.4 Flunarazine vs topiramate

Ref	Comparison	N/n	Outcomes	Result
Stubberud 2019(220) Design: SR Search date: November 2017	Flunarizine vs topiramate	N= 1 n= 83 (Luo 2012)	Mean reduction in migraine frequency (after 3 months of treatment)	MD -0.30 (-0.97 to 0.37) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Luo 2012 Open label RCT	150	18-65 y Migraine diagnosis according to ICHD-2 criteria Migraine two or more days per month Exclusion: overuse of analgesics and abortive migraine medication	12 months	Flunarizine 5 mg/day vs topiramate 25 to 100 mg/day vs flunarizine 5 mg/day + topiramate 25 to 100 mg/day	RANDO: unclear risk (no information) ALLOCATION CONC: unclear risk (no information) BLINDING Participants/personnel: high risk (no blinding) BLINDING Assessors : unclear risk (not stated) INCOMPLETE OUTCOME DATA: high risk (Serious attrition from flunarizine group due to ineffectiveness, and only completers are included in analyses)

					SELECTIVE REPORTING: high risk (Duration of migraine attacks is mentioned as an outcome in methods, but not reported sufficiently under results.)

13.3.5 Verapamil versus control

SR Jackson 2015 searched for RCTs comparing active treatments versus placebo or active controls for the preventive treatment of migraine. Two RCTs comparing verapamil to placebo were found. None met our inclusion criteria for sample size or duration. No RCTs comparing verapamil to an active control were found.

13.4 Anticonvulsants

13.4.1 Lamotrigine vs placebo

Meta-analysis: Cochrane Linde 2013b(256) “Antiepileptics other than gabapentin, pregabalin, topiramate, and valproate for the prophylaxis of episodic migraine in adults”

Definition of migraine: No specific set of diagnostic criteria were required, but “migraine diagnoses had to be based on at least some of the distinctive features of migraine, eg, nausea/vomiting, severe head pain, throbbing character, unilateral location, phono/photophobia, or aura. Secondary headache disorders had to be excluded using reasonable criteria.”

Inclusion criteria:
Population: adults (at least 16 years of age), meeting reasonable criteria designed to distinguish migraine from tension-type headache
Intervention: An antiepileptic drug other than gabapentin, pregabalin, topiramate, or valproate (without concomitant use of other migraine prophylactic treatment), given as prophylaxis
Comparator: placebo, no intervention, or active drug treatment

Study design: Randomized or pseudo-randomized trials

Exclusion: chronic migraine

Search strategy:

Cochrane Central Register of Controlled Trials (CENTRAL; The Cochrane Library 2012, Issue 12), PubMed/MEDLINE (1966 to 15 January 2013), MEDLINE In-Process (current week, 15 January 2013), and EMBASE (1974 to 15 January 2013) were searched; Headache and Cephalalgia were hand-searched through January 2013.

Ref	Comparison	N/n	Outcomes	Result
Cochrane Linde 2013b(256) Design: SR Search date: January 2013	Lamotrigine Vs placebo	N= 2 n= 190 (Gupta 2007, Steiner 1997)	Headache frequency	MD -0.49 (-1.83 to 0.85) NS I^2 = 72%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology

Gupta 2007 Double blind RCT CO	57	Ages 18 to 65 migraine with or without aura according to ICHD-I migraine frequency of 4 to 10 attacks/month exclusion: >8 days/month of NSAID, ergots or triptans. Rule for use of acute medication: patients were allowed to take tablets with a combination of paracetamol and diclofenac potassium	4 weeks	Topiramate 50 mg/day versus topiramate placebo versus lamotrigine 50 mg/day versus placebo	RCT does not meet our inclusion criteria (duration)
Steiner 1997 Double blind RCT PG	77	age range 18 to 60 IHS migraine criteria 2 to 8 attacks per month Exclusion: daily headache, analgesic overuse headache Rule for use of acute medication: Co-codamol encouraged, ergotamine discouraged, but some other medication also allowed	3 months	Lamotrigine versus placebo	RCT does not meet our inclusion criteria (sample size)

Author's conclusions: "Available evidence does not allow robust conclusions regarding the efficacy of antiepileptic drugs other than gabapentin, pregabalin, topiramate, and valproate in the prophylaxis of episodic migraine among adults. Acetazolamide, carisbamate, clonazepam, lamotrigine, oxcarbazepine, and vigabatrin were not more effective than placebo in reducing headache frequency. In one trial each, carbamazepine and levetiracetam were significantly superior to placebo in reducing headache frequency, and there was no significant difference in proportion of responders between zonisamide and active comparator. These three positive studies suffer from considerable methodological limitations."

13.4.2 Topiramate vs placebo

Meta-analysis: Cochrane Linde 2013a(236)

Definition of migraine: No specific set of diagnostic criteria were required, but "migraine diagnoses had to be based on at least some of the distinctive features of migraine, eg, nausea/vomiting, severe head pain, throbbing character, unilateral location, phono/photophobia, or aura. Secondary headache disorders had to be excluded using reasonable criteria."

Inclusion criteria:
Population: adults (at least 16 years of age), meeting reasonable criteria designed to distinguish migraine from tension-type headache
Intervention: Topiramate (without concomitant use of other migraine prophylactic treatment), given as prophylaxis
Comparator: placebo, no intervention, or active drug treatment
Study design: Randomized or pseudo-randomized trials

Exclusion: chronic migraine

Search strategy:

Cochrane Central Register of Controlled Trials (CENTRAL; The Cochrane Library 2012, Issue 12), PubMed/MEDLINE (1966 to 15 January 2013), MEDLINE In-Process (current week, 15 January 2013), and EMBASE (1974 to 15 January 2013) were searched; Headache and Cephalalgia were hand-searched through January 2013.

Assessment of quality of included trials: yes Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result
Cochrane Linde 2013a(236) Design: Search date: (January 2013)	Topiramate vs placebo	N= 9 n= 1793 (Brandes 2004, de Tommaso 2007, Diener 2004, Diener 2007, Edwards 2000, Gupta 2007, Lipton 2011, Silberstein 2004, Storey 2001)	Headache frequency	**MD -1.2 (1.59 to -0.8)** **SS in favour of topiramate** I^2 39%
		N= 9 n= 1246 (Brandes 2004, de Tommaso 2007, Diener 2004, Edwards 2000, Gupta 2007, Mei 2004, Silberstein 2004,	ORs for Responders (patients with ≥50% reduction in headache frequency)	Topiramate 310/660 Placebo 136/586 **OR 3.18 (2.1 to 4.82)** **SS In favour of topiramate** I^2 54%

		Silberstein 2006, Storey 2001)		
		N= 9 n= 1246 (Brandes 2004, de Tommaso 2007, Diener 2004, Edwards 2000, Gupta 2007, Mei 2004, Silberstein 2004, Silberstein 2006, Storey 2001)	RRs for Responders (patients with ≥50% reduction in headache frequency)	Topiramate 310/660 Placebo 136/586 **RR 2.02 (1.57 to 2.6)** **SS in favour of topiramate** I^2 46%
		N= 1 n= 120 (Gupta 2007)	Any adverse event	Topiramate 50 mg/day: 9/60 Placebo: 6/60 RD 0.05 (-0.07 to 0.17) NS
		N= 2 n= 883 (Diener 2007, Lipton 2011)		Topiramate 100 mg/day: 318/430 Placebo: 287/443 **RD 0.09 (0.03 to 0.15)** **SS in favour of placebo** I^2 0%

		N= 1 n= 213 (Silberstein 2006)		Topiramate 200 mg/day: 126/140 Placebo: 51/73 **RD 0.2 (0.08 to 0.32)** **SS in favour of placebo**
		N= 2 n= 463 (Brandes 2004, Silberstein 2004)	MSQ role-function restrictive	Topiramate 50 mg/day vs placebo **MD 5.83 (2.25 to 9.41)** **SS in favour of topiramate** I^2 0%
		N= 2 n= 474 (Brandes 2004, Silberstein 2004)		Topiramate 100 mg/day vs placebo **MD 10.08 (6.55 to 13.6)** **SS in favour of topiramate** I^2 0%
		N= 2 n= 458 (Brandes 2004, Silberstein 2004)		Topiramate 200 mg/day vs placebo **MD 10.36 (6.68 to 14.04)** **SS in favour of topiramate** I^2 0%
		N= 2 n= 463 (Brandes 2004, Silberstein 2004)	MSQ role-function prevention	Topiramate 50 mg/day vs placebo MD 2.84 (-0.24 to 5.92) NS

				I^2 0%
		N= 2 n= 474 (Brandes 2004, Silberstein 2004)		Topiramate 100 mg/day vs placebo **MD 6.39 (3.37 to 9.41)** **SS in favour of topiramate** I^2 0%
		N= 2 n= 458 (Brandes 2004, Silberstein 2004)		Topiramate 200 mg/day vs placebo **MD 5.06 (1.87 to 8.25)** **SS in favour of topiramate** I^2 0%
		N= 2 n= 463 (Brandes 2004, Silberstein 2004)	MSQ- emotional function	Topiramate 50 mg/day vs placebo **MD 4.58 (0.61 to 8.54)** **SS in favour of topiramate** I^2 0%
		N= 2 n= 474 (Brandes 2004, Silberstein 2004)		Topiramate 100 mg/day vs placebo **MD 10.22 (6.31 to 14.14)** **SS in favour of topiramate** I^2 0%
		N= 2 n= 458		Topiramate 200 mg/day vs placebo **MD 8.45 (4.38 to 12.52)**

		(Brandes 2004, Silberstein 2004)		**SS in favour of topiramate** I^2 0%
		N= 2 n= 463 (Brandes 2004, Silberstein 2004)	SF-36 general health	Topiramate 50 mg/day vs placebo MD 1.45 (-2.18 to 5.08) NS I^2 5.3%
		N= 2 n= 474 (Brandes 2004, Silberstein 2004)		Topiramate 100 mg/day vs placebo MD 4.18 (-1.21 to 9.57) NS I^2 58.4%
		N= 2 n= 458 (Brandes 2004, Silberstein 2004)		Topiramate 200 mg/day vs placebo MD 2.58 (-1.6 to 1.5) NS I^2 0%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Linde 2013a)
Brandes 2004 Double blind RCT	468	Age range 12-65 IHS migraine criteria	8 weeks titration + 18 weeks stable	Topiramate 50 mg/day versus	RANDO: Low risk ALLOCATION CONC:

PG		Migraine frequency 3-12 in 28 days Migraine with and without aura Exclusion: daily headache, analgesic overuse headache Rule for use of acute medication: analgesics, ergot derivatives, triptans and opioids allowed	dosage + open-label extension	topiramate 100 mg/day versus topiramate 200 mg/day versus placebo	Low risk BLINDING Participants/personnel: Low risk BLINDING Assessors : unclear risk (not clearly stated that blinding included the stage of analysis) INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk
de Tommaso 2007 Double blind RCT PG	39	Ages 18 to 49 migraine without aura according to ICHD-II; attack frequency not specified. Rule for use of acute medication: not reported	8 weeks	Topiramate 100 mg/day versus placebo versus levetiracetam	RCT does not meet our inclusion criteria (sample size and duration)
Diener 2004 Double blind RCT PG	568	Ages 12 to 65 IHS migraine criteria migraine frequency 3 to 12 per month during 28-day baseline phase exclusion: daily headache Rule for use of acute medication: aspirin, paracetamol, NSAIDs, ergot compounds, triptans, and opioids permitted	18 weeks	Topiramate 100 mg/day versus topiramate 200 mg/day versus propranolol 160 mg/day versus placebo	RANDO: unclear risk (method not described) ALLOCATION CONC: unclear risk (no information) BLINDING Participants/personnel: unclear risk (method not described) BLINDING Assessors : unclear risk (no information) INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk

Diener 2007 Double blind RCT PG	507	Ages 18 to 80 migraine with or without aura according to ICHD-II migraine frequency of ≥ 4 attacks/month exclusion: overuse of acute medication Rule for use of acute medication: individuals with medication overuse not included; triptans, ergots, opiates, and other analgesics thereafter permitted	26 weeks	Topiramate 100 mg/day versus placebo	RANDO: Low risk ALLOCATION CONC: Low risk BLINDING Participants/personnel: Low risk BLINDING Assessors : unclear risk (no information) INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk
Edwards 2000 Double blind RCT PG	30	age range 30 to 62 IHS migraine criteria Migraine frequency 2 to 8 per month Exclusion: daily headache, medication overuse headache Rule for use of acute medication: acute medication permitted; allowed types not specified	14 weeks	Topiramate 200 mg/day versus placebo	RCT does not meet our inclusion criteria (sample size)
Gupta 2007 Double blind RCT CO	57	Ages 18 to 65 migraine with or without aura according to ICHD-I	4 weeks	Topiramate 50 mg/day versus topiramate placebo versus	RCT does not meet our inclusion criteria (duration)

		migraine frequency of 4 to 10 attacks/month exclusion: >8 days/month of NSAID, ergots or triptans. Rule for use of acute medication: patients were allowed to take tablets with a combination of paracetamol and diclofenac potassium		lamotrigine 50 mg/day versus placebo	
Lipton 2011 Double blind RCT PG	330	Ages 18 to 65 migraine with or without aura according to ICHD-II Migraine frequency of 9 to 14 days/month Exclusion: < 15 total headache days/month Rule for use of acute medication: subjects were permitted to take acute headache medication as indicated.	26 weeks	Topiramate 100 mg/day versus placebo	RANDO: Low risk ALLOCATION CONC: Low risk BLINDING Participants/personnel: Low risk BLINDING Assessors : unclear risk (no information) INCOMPLETE OUTCOME DATA: unclear risk (efficacy only reported for the subgroup of participants who completed at least 28 days) SELECTIVE REPORTING: **high risk** (≥ 50% and ≥ 75% reduction in headache days and migraine days were collected but only reported as "higher in the topiramate group compared with the placebo treatment group". For MSQ and MIDAS results, the authors refer to www.clinicaltrials.gov (study identifier: NCT00212810). More

					than 5 years after study completion, no results from this study have yet been posted there. Corresponding author requested twice by Cochrane authors about the numbers of subjects with 50% or greater reduction in 28-day migraine day frequency in both groups without providing data
Mei 2004 Double blind RCT PG	72	age range 20 to 60 IHS migraine criteria migraine frequency of 2 to 6 per month Rule for use of acute medication: NSAID and triptan use monitored	16 weeks	Topiramate 100 mg/day versus placebo	RCT does not meet our inclusion criteria (sample size)
Silberstein 2004 Double blind RCT PG	469	age range 12 to 65 IHS migraine criteria; migraine frequency of 3 to 12 in 28-days Exclusion: daily headache, analgesic overuse headache Rule for use of acute medication: analgesics, ergot derivatives, triptans, and opioids allowed	8 weeks titration + 18 weeks stable dosage	Topiramate 50 mg/day versus topiramate 100 mg/day versus topiramate 200 mg/day versus placebo	RANDO: unclear risk (Randomisation in permutation blocks of 4 stratified by centre) ALLOCATION CONC: Low risk BLINDING Participants/personnel: Low risk BLINDING Assessors : unclear risk (no information) INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk

Silberstein 2006 Double blind RCT PG	211	age range 18 to 64 migraine with or without aura according to ICHD-I average migraine frequency of 3 to 8 migraine episodes/month Exclusion: > 15 headache days/month during the 3 months; triptan use on > 8 days/month Rule for use of acute medication: use of acute medications was allowed	20 weeks	Topiramate 200 mg/day versus placebo	RANDO: unclear risk (no information) ALLOCATION CONC: unclear risk (no information) BLINDING Participants/personnel: unclear risk (no description of method) BLINDING Assessors : unclear risk (no information) INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: high risk; Data on mean migraine frequencies during the double-blind period lacking
Storey 2001 Double blind RCT PG	40	allowed age range 18 to 65 years IHS migraine criteria 2 or more attacks per month for previous 12 months Exclusion: daily headaches, analgesic overuse headaches Rule for use of acute medication: abortive medications permitted	8 weeks titration, 8-week maintenance period	Topiramate versus placebo	RCT does not meet our inclusion criteria (sample size)

Author's conclusions: "Meta-analysis demonstrates that topiramate in a 100 mg/day dosage is effective in reducing headache frequency and reasonably well tolerated in adult patients with episodic migraine. This provides good evidence to support its use in routine clinical management. More studies designed specifically to compare the efficacy or safety of topiramate versus other interventions with proven efficacy in the prophylaxis of migraine are needed."

13.4.3 Topiramate v amitriptyline

Ref	Comparison	N/n	Outcomes	Result
Cochrane Linde 2013a(236) Design: Search date: (January 2013)	Topiramate vs amitriptyline	N= 1 n= 330 (Dodick 2009)	Responders (patients with ≥50% reduction in headache frequency)	Amitriptyline 50-100 mg 73/159 Topiramate 50-100 mg 95/171 OR 0.68 (95%CI 0.44 to 1.05) NS
		N= 1 n= 295 (Dodick 2009)	MIDAS score	Amitriptyline 50-100 mg Mean (SD) -14.2 (20.7) Topiramate 50-100 mg Mean (SD) -12.1 (23.4) MD 2.1 (-2.93 to 7.13) NS

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Linde 2013a)
Dodick 2019 RCT PG	331	Age 18 and above Migraine with or without aura according to ICD-II Migraine frequency 3 to 12 attacks/month during 3 months Rule for use of acute medication: use of acute headache medications	4 weeks titration, followed by 22 weeks maintenance, then 2 weeks taper/exit phase	Topiramate 100 mg/day Vs Amitriptyline 100 mg/day	RANDO: Low risk ALLOCATION CONC: Low risk BLINDING Participants/personnel: Low risk BLINDING Assessors : unclear risk (no information) INCOMPLETE OUTCOME DATA: unclear risk (Unclear how many

		including over-the-counter analgesics, NSAIDs, triptans, ergot derivatives, and dihydroergotamine mesylate, was permitted for symptomatic relief of headaches throughout the study, but was not to exceed 4 days per week			participants in the topiramate group contributed to the endpoint ≥ 50% reduction in headache frequency.) SELECTIVE REPORTING: Unclear risk

13.4.4 Valproate vs placebo

Meta-analysis: Cui 2020 "The efficacy and safety of valproate medications for migraine in adults: a meta-analysis"

Definition of migraine: "physician-confirmed diagnosis of migraine"

Inclusion criteria:
Parallel-group RCTs
Physician-confirmed diagnosis of migraine
Valproate vs placebo or other drugs in the prophylactic treatment of migraine
treatment efficacy defined as a ≥ 50% reduction in headache frequency

Search strategy: PubMed, Wiley, ScienceDirect, Web of Science, and Cochrane Library databases were searched up to December 2018

Assessment of quality of included trials: yes; Jadad score

Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result

Cui 2020 Design: SR Search date: December 2018	Valproate vs placebo	N= 3 n= 278 (Jensen 1994, Sarchielli 2014, Sadeghian 2015)	≥ 50% reduction in headache frequency	Valproate vs placebo **OR 5.07 (2.75 to 9.36)** **SS in favour of valproate** I^2 = 42%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Cui 2020)
Jensen 1994(248) RCT Crossover	43	age between 18 and 70 years migraine without aura 2 to 10 days with migraine per month Exclusion of daily headache; more than 6 attacks per year with aura, including daily ergotamine or large amounts of plain analgesics	12 weeks (with 4-week washout period)	Valproate 1500, 1000 mg/d vs placebo	Jadad score 3
Sarchielli 2014(249)	130	**medication-overuse headache patients** with a history of migraine without aura	3 months	Valproate 800 mg/d vs placebo	RCT does not meet our inclusion criteria (population)
Sadeghian 2015(250) RCT PG	85* *erroneously reported as	≥ 12 years of age migraine, according to the 2nd edition of International Classification of Headache Disorders (ICHD-II)	6 months	Valproate 500 mg/d vs Placebo vs Levetiracetam 500 mg/d	RCT does not meet our inclusion criteria (sample size)

	105 in SR Cui 2020	criteria of International Headache Society (IHS) ≥ 4 attacks per month			

13.4.5 Valproate v topiramate

Ref	Comparison	N/n	Outcomes	Result
Cui 2020 Design: SR Search date: December 2018	Valproate vs topiramate	N= 3 n= 245 (Afshari, Bartolini, Krymchantowski)	≥ 50% reduction in headache frequency	OR 0.74 (0.39 to 1.40) NS I^2 = 0%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Cui 2020)
Afshari 2012(251) RCT PG	76	18-65 years Diagnosis of migraine (with or without aura) according to the IHS criteria	12 weeks	Valproate 400 mg/d vs Topiramate 50 mg/d	RCT does not meet our inclusion criteria (sample size)

		4-10 migraine attacks per month Exclusion: Overused acute migraine treatments (>8 treatment days per month of ergots, NSAIDs, or triptans)			
Bartolini 2005(252) RCT PG	49	**chronic migraine** and a history consistent with a diagnosis of episodic migraine without aura fulfilling the diagnostic criteria for migraine of the IHS Classification of Head and Facial Pain	3 months	Valproate 750 mg/d vs Topiramate 75 mg/d	RCT does not meet our inclusion criteria (population)
Krymchantowski 2011(253)	120	ages 18 to 68 migraine less than 15 headache days/month	12 months	**Divalproex** 250 mg/d, 500 mgd/d vs Topiramate 25 mg/d, 150 mg/d	RCT does not meet our inclusion criteria (intervention)

Remarks: only outcome "≥ 50% reduction in headache frequency" reported

Author's conclusions: "Three vital perspectives were obtained from this study. Firstly, valproate medications were more effective than placebo in migraine prevention, with statistically significant differences. Secondly, both valproate and the other active comparators were well tolerated, and no significant difference was noted in the efficacy for the prophylaxis of migraine. Thirdly, several mechanisms for the protective effects of valproate for migraine have been proposed. The findings from these observational studies should be confirmed in future research, such as in more prospective cohort studies or RCTs providing the highest level of evidence."

13.4.6 Valproate vs magnesium

Study details	n/Population	Comparison	Outcomes	Methodological
	n= 260 (randomized)		Efficacy	RANDO:

RCT Khani(254) Design: RCT DB PG Duration of follow-up: 12 weeks	Mean age: 34 -37y (across groups) Definition of migraine diagnosis according to the latest International Headache Society criteria, with or without aura Additional medication: concurrent administration of acute abortive treatment was allowed <u>Inclusion</u> Age 18-65 y Migraine At least 4 monthly attacks <u>Exclusion</u> Overuse of analgesics (>8 days/month)	Valproate 200 mg 2x/day + placebo 2x/day Vs Valproate 200 mg 2x/day + magnesium 250 mg 2x/day Vs magnesium 250 mg 2x/day+ placebo 2x/day	Migraine frequency (PO) Month 3	valproate vs valproate + magnesium MD 0.20 (-0.17 to 0.45) NS valproate vs magnesium **MD -2.31 (-2.62 to -2.01)** **SS in favour of valproate** Valproate + magnesium vs magnesium **MD -2.51 (-2.77 to -2.14)** **SS in favour of valproate + magnesium**	Adequate ALLOCATION CONC: Unclear (containers were marked as A, B or C) BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Drop-out and Exclusions: 14.6% (38 patients) • Described: yes • Balanced across groups: unclear: 16 drop-outs in combination group and magnesium group compared to 6 in valproate group ITT: No; drop-outs were excluded from analysis SELECTIVE REPORTING: high risk; safety endpoints not reported, not all quantitative data reported Other important methodological remarks:
			Migraine severity Month 3	valproate vs valproate + magnesium MD 0.45 (-0.13 to 0.75) NS valproate vs magnesium **MD -0.70 (-1.00 to -0.39)** **SS in favour of valproate** Valproate + magnesium vs magnesium **MD -1.15 (-1.46 to -0.82)** **SS in favour of valproate + magnesium**	
			Duration of attacks (hours)	valproate vs valproate + magnesium **MD 0.98 (0.17 to 1.77)**	

	Total number of headache days per month >15 History of renal, liver, and chronic diseases Other comorbidities		Month 3	**SS in favour of valproate + magnesium** valproate vs magnesium **MD -1.09 (-1.90 to -0.29)** **SS in favour of valproate** Valproate + magnesium vs magnesium **MD -2.07 (-2.90 to -1.23)** **SS in favour of valproate + magnesium**	The assessment of adverse effects was not completely carried out due to faulty reports: no analysis of adverse effects Sponsor: The authors declared no funding
			Number of painkillers used per month Month 3	valproate vs valproate + magnesium **MD 0.46 (0.20 to 0.71)** **SS in favour of valproate + magnesium** valproate vs magnesium **MD -0.65 (-0.89 to -0.39)** **SS in favour of valproate** Valproate + magnesium vs magnesium **MD -1.11 (-1.36 to 0.84)** **SS in favour of valproate + magnesium**	
			MIDAS score (migraine-related disabilities)	valproate vs valproate + magnesium **p=0.023** **SS in favour of valproate + magnesium** valproate vs magnesium **p<0.001** **SS in favour of valproate**	

				Valproate + magnesium vs magnesium **p<0.001** **SS in favour of valproate + magnesium**	
			HIT-6 score (36-78) (severity of headache impact on daily life)	valproate vs valproate + magnesium p=0.999 NS valproate vs magnesium **p<0.001** **SS in favour of valproate** Valproate + magnesium vs magnesium **p<0.001** **SS in favour of valproate + magnesium**	
			Safety		
			No safety data		

13.4.7 Valproate vs riboflavin

Study details	n/Population	Comparison	Outcomes		Methodological
Rahimdel(255) Design: RCT SB PG Duration of follow-up: 12 weeks	n= 90 Mean age: 30.2 -32.9 (NS difference between groups) Definition of migraine not described Additional medication: not described whether medication for acute migraine attack was permitted <u>Inclusion</u> Ages 15-55 Migraine headaches with or without aura	Vitamin B2 (riboflavin) 400 mg/day Vs Valproate 500 mg/day	Efficacy		RANDO: Unclear (using random number table) ALLOCATION CONC: Unclear (no information) BLINDING : Participants: yes Personnel: no (type of treatment decided by the physician) Assessors: unclear (“The follow-up data sampling and recording was done by the researcher, who was unaware of the medicine that was administered to each patient.”) FOLLOW-UP: Drop-out and Exclusions:5.5% (5/90 patients) • Described: unclear “removed from the study either because they were no present at the scheduled times or because they
			Frequency of headaches (Times/month)	riboflavin: decreased from 9.2 (SD 6.2) to 2.4 (SD 1.6) valproate: decreased from 6.5 (SD 3.1) to 2.1 (SD 1.0) between-group difference NS	
			Duration of headaches (hours)	riboflavin: decreased from 15.1 (SD 7.1) to 4.2 (SD 2.6) valproate: decreased from 16.2 (SD 10.6) to 8.2 (SD 4.7) between-group difference NS	
			Severity of headaches (% of patients with reduction of severity)	riboflavin: 71.8% valproate: 76.2% between-group difference NS p=0.9	

	2 or more headache attacks over the last 3 months <u>Exclusion</u> Systemic and underlying diseases		Safety		developed serious complications related to the medication" Not described in which group SAE occurred • Balanced across groups: unclear (see above; occurrence of SAEs) ITT: Unclear (not described) SELECTIVE REPORTING: unclear (limited information reported) Sponsor: self-funded research
			Adverse events	9 patients in total developed adverse events (including weight gain, dizziness and gastrointestinal problems) **SS more adverse events in valproate group** **P=0.005**	

13.5 Antidepressants

13.5.1 Amitriptyline vs placebo

Meta-analysis: Xu 2017(315) “Tricyclic antidepressants for preventing migraine in adults”

Definition of migraine: criteria as described in the Ad Hoc Committee on the Classification of Headache or the International Headache Society, or based on the distinctive features of migraine

Inclusion criteria:
RCTs
Adults (>18 years) with a primary diagnosis of migraine
Tricyclic antidepressants versus placebo
Amitriptyline versus other antidepressants

Search strategy: PubMed, Embase, Cochrane, and Web of Science databases were searched from inception to July 2016. Conference abstracts and reference
lists of all identified related publications were also searched.

Assessment of quality of included trials: yes

Other methodological remarks: pooled outcome most probably includes results at 4 and 8 weeks treatment. We reported a subanalysis at 24 weeks treatment separately.

Ref	Comparison	N/n	Outcomes	Result

Xu 2017(315) Design: SR Search date: July 2016	amitriptyline vs placebo	N= 4 n= 238 (Couch 1976, Gomersall 1973, Mathew 1981, Ziegler 1987)	Migraine frequency	**Std. MD -0.86 (-1.23 to -0.48)** **SS in favour of amitriptyline** **I^2 = 48%**
		N= 2 n= 100 (Gomersall 1973, Ziegler 1987)	Migraine frequency At 24 weeks	**Std. MD -0.77 (-1.34 to -0.20)** **SS in favour of amitriptyline** **I^2 = 47%**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Xu 2017)
Couch 1976(316) RCT Parallel group	73	Migraine (criteria not reported)	4 weeks	Amitriptyline 100 mg/d vs Placebo	RCT did not meet our inclusion criteria (duration)
Gomersall 1973(258) RCT crossover	26	Ad Hoc Committee of the National Institute migraine criteria	26 weeks	Amitriptyline 10-60 mg/d vs Placebo	RCT did not meet our inclusion criteria (sample size)

Mathew 1981(259) RCT Parallel group	87	Migraine (criteria not reported)	6 months	Amitriptyline 25-75 mg/d vs Placebo	RANDO: unclear risk ALLOCATION CONC: unclear risk BLINDING Participants/personnel: Low risk BLINDING Assessors : unclear risk INCOMPLETE OUTCOME DATA: unclear risk SELECTIVE REPORTING: unclear risk OTHER BIAS unclear risk
Ziegler 1987(260) RCT crossover	30	Migraine (criteria not reported)	8 weeks	Amitriptyline 50-150 mg/d vs Placebo	RCT did not meet our inclusion criteria (duration and sample size)

Remarks:
This SR found one cross-over RCT comparing amitriptyline to venlafaxine. However, it did not meet our inclusion criteria for sample size.

Author's conclusions:" : This research reveals that TCAs were more effective than placebo, but no more than SSRI or SNRI in ameliorating the headache burden in adults with migraine. However, TCAs appeared to be less tolerated than placebo and SSRIs or SNRIs for some side effects"

Study details	n/Population	Comparison	Outcomes		Methodological
Gonçalves 2016(261)	n= 196 (randomized) (59 amitriptyline, 59 placebo, 60 melatonin)	Amitriptyline 25 mg	Efficacy		RANDO: Adequate ALLOCATION CONC:
			Number of migraine headache days per	placebo: MD -1.1 amitriptyline: MD -2.2	

Design: RCT PG Duration of follow-up: 12 weeks	Mean age: 36.6 -37.2y (across groups) Definition of migraine: migraine with or without aura criteria according to the International Classification of Headache Disorders, third edition, β-version Additional medication: Use of acute migraine medication was permitted for breakthrough migraine attacks <u>Inclusion</u> Age 18-65y Migraine for at least 1 year at least 3 migraine headache attacks or 4	Vs Melatonin 3 mg Vs placebo	month comparing baseline with the past 4 weeks of treatment (PO) weeks 9-12	melatonin: MD -2.7 Amitriptyline vs placebo **MD -1.1 (95%CI -1.5 to -0.7)** **SS in favour of amitriptyline** Melatonin vs placebo **MD -1.6 (95%CI -2.4 to -0.9)** **SS in favour of melatonin** Amitriptyline vs melatonin NS (no quantitative analysis reported)	Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Drop-out and Exclusions: 9% (18 patients) • Described: no • Balanced across groups: yes ITT: Modified ITT: defined as randomized patients who received at least one dose of the study medication and provided at least one postbaseline efficacy assessment SELECTIVE REPORTING: no Other important methodological remarks
			Mean headache intensity (0-10) weeks 9-12	placebo: MD-1.8 amitriptyline: MD-3.5 melatonin: MD -3.5 Amitriptyline vs placebo **MD -1.3 (95%CI -1.7 to -0.9)** **SS in favour of amitriptyline** Melatonin vs placebo **MD -1.2 (95%CI -1.6 to -0.8)** **SS in favour of melatonin** Amitriptyline vs melatonin NR	
			Mean attack duration (hours)	placebo: MD -2.5 amitriptyline: MD -6.9	

	migraine headache days per month <15 headache days per month <u>Exclusion</u> a history of psychiatric disorder; ergotamine, triptan, opioid, or combination medication intake for >10 days per month, or simple analgesic intake for >15 days per month for >3 months; use of other preventive medications ; uncontrolled hypertension		weeks 9-12	melatonin: MD -7.2 Amitriptyline vs placebo **MD -4.4 (95%CI -5.1 to -3.9)** **SS in favour of amitriptyline** Melatonin vs placebo **MD -4.8 (95%CI -5.7 to -3.9)** **SS in favour of melatonin** Amitriptyline vs melatonin NR	*4-week run-in period to establish baseline measures and to determine eligibility for randomization *Missing data for the primary endpoint was analysed by treating all missing days as non-migraine headache days Sponsor: FAPESP, Fundação de Amparo a Pesquisa de São Paulo, a Brazilian governmental funding agency without any role in manuscript preparation
			number of analgesics used weeks 9-12	placebo: MD -0.6 amitriptyline: MD -1.4 melatonin: MD -1.6 Amitriptyline vs placebo **MD -1.0 (95%CI -1.5 to -0.5)** **SS in favour of amitriptyline** Melatonin vs placebo **MD -1.0 (95%CI -1.4 to -0.6)** **SS in favour of melatonin** Amitriptyline vs melatonin NR	
			percentages of patients with greater than 50%	placebo: 20.4% amitriptyline: 39.1% melatonin: 54.4%	

			reductions in migraine headache days	Amitriptyline vs placebo **SS in favour of amitriptyline** **P<0.01** Melatonin vs placebo **SS in favour of melatonin** **P<0.01** Amitriptyline vs melatonin **SS in favour of melatonin** **P<0.05**	
			Safety		
			Adverse events	Placebo: 17/59 Amitriptyline: 46/59 Melatonin: 16/60 Melatonin vs placebo NS Amitriptyline vs placebo **SS in favour of placebo** **p<0.03** (more adverse events with amitriptyline) Melatonin vs amitriptyline	

				SS in favour of melatonin **p<0.03** (more adverse events with amitriptyline)	
			Serious adverse events	None observed	

13.5.2 Amitriptyline vs melatonin

See RCT Gonçalves 2016(261) under "amitriptyline vs placebo"

13.5.3 Venlafaxine vs control

Meta-analysis: Wang 2020(262) "Serotonin–norepinephrine reuptake inhibitors for the prevention of migraine and vestibular migraine: a systematic review and meta-analysis"

Definition of migraine: migraine diagnosed based on the diagnostic criteria of the International Headache Society (IHS)

Inclusion criteria:
Study design: RCT, At least 8 weeks duration
Population: ≥16 years of age with migraine
Intervention: SNRI
Comparator: placebo or other active drugs

Search strategy: PubMed, Web of Science, and Cochrane Library databases were searched from inception to November 2019.

Assessment of quality of included trials: yes, Cochrane risk-of-bias tool

Other methodological remarks:

Remarks:

This SR found one RCT comparing venlafaxine to placebo (Ozyalcin 2005) It did not meet our inclusion criteria for sample size.
This SR found one RCT comparing venlafaxine to amitriptyline (Bulut 2004), one comparing venlafaxine to valproate (Liu 2017), one comparing venlafaxine to propranolol (Salviz 2015). None met our inclusion criteria for sample size.

Author's conclusions:

"SNRIs were clinically safe and effective for migraine and VM [=vestibular migraine] prophylaxis, were better than a placebo, and not inferior to other active drugs. SNRIs may be a preferable choice for patients with VM with psychiatric disorders"

13.6 Gepants

13.6.1 Rimegepant vs placebo

Meta-analysis: SR Dos Santos 2022(263)

Definition of migraine:

Inclusion criteria:
Study design: Phase 1/2/3 clincal trials
Population: Patients with migraine
Intervention: Atogepant, rimegepant and zavegepant for the preventive treatment of migraine

Search strategy: n Medline via PubMed, Embase, and Clinical trials were searched up to January 2022.

Assessment of quality of included trials: no

Remarks:
Dos Santos 2022(263) performed a systematic search for trials with rimegepant. One completed RCT (Croop 2021), comparing rimegepant to placebo, was found. As SR Dos Santos did not appraise this RCT, we will describe and appraise Croop 2021 below.
Rimegepant vs placebo in migraine prevention

Study details	n/Population	Comparison	Outcomes		Methodological
RCT Croop 2021(317) Design: Phase 2/3 RCT	n= 747 (randomized) 695 analyzed for efficacy 741 analyzed for AE Mean age: 41.2y Definition of migraine migraine with or	Rimegepant 75 mg every other day Vs placebo	Efficacy Change in the mean number of migraine days per month (PO) *change from the 4-week observation period in the mean number of*	Rimegepant: -4.3 (-4.8 to -3.9) Placebo: -3.5 (-4.0 to -3.0) **LS MD -0.8 (-1.5 to -0.2)** **SS in favour of rimegepant**	RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes

DB PG Duration of follow-up: 12 weeks + 52-week open label extension phase (not reported here)	without aura, or chronic migraine, as defined by the International Classification of Headache disorders, 3rd edition Additional medication: participants were allowed to take one **preventive migraine** drug, excluding CGRP receptor antagonists and CGRP monoclonal antibodies (stable dose) permitted **rescue medications** during the 12-week double-blind treatment phase included triptans, non-steroidal anti-inflammatory drugs, paracetamol up to 1000 mg/day for a maximum of 2		*migraine days per month in the last 4 weeks of the double-blind treatment phase (weeks 9–12)*		FOLLOW-UP: Drop-out and Exclusions: 7% • Described: yes • Balanced across groups: yes ITT: no : all randomised participants who received at least one dose of their assigned study medication (rimegepant or placebo) during the 12-week double-blind treatment phase and who had at least 14 days of electronic diary efficacy data from the 4-week observation period and for at least one 4-week interval during the 12-week double-blind treatment phase (747 randomized, 695 included for the analysis for efficacy) The safety analysis population included participants who received at least one dose of study drug. SELECTIVE REPORTING: no (
			achievement of at least a 50% reduction from the 4-week observation period in the mean number of moderate or severe migraine days (moderate or severe headache pain intensity) per month in the last 4 weeks of the double-blind treatment phase (weeks 9–12)	Rimegepant: 49% (44 to 54) Placebo: 41% (36 to 47) **LS MD 8% (0 to 15)** **p-value 0.044** **SS in favour of rimegepant**	
			change from the 4-week observation period in the mean number of migraine days per month across the double-blind treatment phase (weeks 1–12)	Rimegepant: -3.6 (-4.0 to -3.2) Placebo: -2.7 (-3.1 to -2.3) **LS MD -0.8 (-1.3 to -0.3)** **SS in favour of rimegepant**	
			mean number of rescue medication days per month in the last 4 weeks of the double-blind treatment phase (week 9–12)	Rimegepant: 3.7 (3.3 to 4.2) Placebo: 4.0 (3.5 to 4.4) LS MD -0.2 (-0.8 to 0.3) NS	

	consecutive days (including a fixed combination containing paracetamol 250 mg, aspirin 250 mg, and caffeine 65 mg), baclofen, antiemetics, and muscle relaxants. Rimegepant was not permitted as a rescue medication. <u>Inclusion</u> migraine at least 4 and not more than 18 migraine attacks per month				Other important methodological remarks: 4-week pretreatment observation period Investigators determined the severity of adverse events and the relation of adverse events to study treatment; no independent assessment was done. Sponsor: This clinical trial was supported by Biohaven Pharmaceuticals, developer of rimegepant. The funder had a role in study design, data collection, data analysis, data interpretation, and writing of the report
			change from baseline in MSQ role function (restrictive domain score) at week 12	Rimegepant: 18.0 (15.5 to 20.6) Placebo: 14.6 (12.1 to 17.1) **LS MD 3.5 (0.2 to 6.7)** **SS in favour of rimegepant**	
			Change from baseline in MIDAS total score at week 12	Rimegepant: -11.8 (-15.4 to -8.2) Placebo: -11.7 (-15.3 to -8.1) LS MD -0.1 (-4.7 to 4.5) NS	
			Safety		
			frequency of unique participants with: adverse events	Rimegepant: 133/370 (36%) Placebo: 133/371 (36%) No statistical testing	

	<u>Exclusion</u> >18 headache days/month History of non-response to more than two drug categories for preventive treatment of migraine history or current evidence of any medical condition that would expose them to undue risk of a significant adverse event or interfere with assessments of safety or efficacy; if they had an electrocardiogram or laboratory test finding that raised safety or tolerability concerns		frequency of unique participants with: serious adverse events	Rimegepant: 3/370 (1%) Placebo: 4/371 (1%) No statistical testing	

13.6.2 Atogepant vs placebo

Meta-analysis: SR Tao 2022 (264) "The efficacy and safety of atogepant for the prophylactic treatment of migraine: evidence from randomized controlled trials"

Definition of migraine:

Inclusion criteria:
Study design: RCT
Population: adults 18-80 y, diagnosed with migraine; 4-14 migraine days monthly
Intervention : atogepant
Comparison : placebo

Search strategy: MEDLINE, Embase, Cochrane Library and ClinicalTrials.gov were searched up until October 20, 2021. The reference lists and discussion sections of the identified studies and meta-analyses were searched for additional studies.

Assessment of quality of included trials: y; with Cochrane Bias of risk tool
Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result
Tao 2022 (264) Design: SR Search date: October 2021	atogepant vs placebo	N= 2 n= 698 (Aliani 2021; Goadsby 2020) N= 2 n= 797	mean monthly migraine days (PO)	Atogepant 10 mg **Std MD -0.41 (-0.56 to -0.25)** **SS in favour of atogepant** **I^2 = 0%** Atogepant 30 mg **Std MD -0.41 (-0.55 to -0.27)**

		(Aliani 2021; Goadsby 2020) N= 2 n= 791 (Aliani 2021; Goadsby 2020)		**SS in favour of atogepant** **I^2 = 0%** Atogepant 60 mg **Std MD -0.42 (-0.73 to -0.11)** **SS in favour of atogepant** **I^2 = 79%**
		N= 2 n= 698 (Aliani 2021; Goadsby 2020) N= 2 n= 797 (Aliani 2021; Goadsby 2020) N= 2 n= 791 (Aliani 2021; Goadsby 2020)	monthly headache days	Atogepant 10 mg **Std MD -0.43 (-0.59 to -0.28)** **SS in favour of atogepant** **I^2 = 0%** Atogepant 30 mg **Std MD -0.42 (-0.60 to -0.24)** **SS in favour of atogepant** **I^2 = 38%** Atogepant 60 mg **Std MD -0.41 (-0.73 to -0.10)** **SS in favour of atogepant** **I^2 = 80%**

		n= 698 (Aliani 2021; Goadsby 2020) N= 2 n= 797 (Aliani 2021; Goadsby 2020) N= 2 n= 791 (Aliani 2021; Goadsby 2020)	acute medication use days per month	Atogepant 10 mg **Std MD -0.45 (-0.61 to -0.30)** **SS in favour of atogepant** **I^2 = 0%** Atogepant 30 mg **Std MD -0.49 (-0.63 to -0.35)** **SS in favour of atogepant** **I^2 = 0%** Atogepant 60 mg **Std MD -0.46 (-0.60 to -0.32)** **SS in favour of atogepant** **I^2 = 80%**
		n= 698 (Aliani 2021; Goadsby 2020) N= 2 n= 797 (Aliani 2021; Goadsby 2020)	≥50% reduction in monthly migraine days	Atogepant 10 mg: 172/306 Placebo: 134/392 **RR 1.66 (1.23 to 2.23)** **SS in favour of atogepant** **I^2 = 65%** Atogepant 30 mg: 228/405 Placebo:134/392 **RR 1.63 (1.07 to 2.49)** **SS in favour of atogepant**

				I^2 = 85%
		N= 2 n= 791 (Aliani 2021; Goadsby 2020)		Atogepant 60 mg: 227/399 Placebo: 134/392 **RR 1.64 (1.01 to 2.66)** **SS in favour of atogepant** **I^2 = 89%**
		n= 722 (Aliani 2021; Goadsby 2020)	Total adverse events	Atogepant 10 mg: 178/314 Placebo: 218/408 RR 1.11 (0.78 to 1.56) NS I^2 = 85%
		N= 2 n= 819 (Aliani 2021; Goadsby 2020)		Atogepant 30 mg: 234/411 Placebo:218/408 RR 1.08 (0.79 to 1.48) NS I^2 = 85%
		N= 3 n= 1564 (Allergan 2021, Aliani 2021; Goadsby 2020)		Atogepant 60 mg: 454/960 Placebo: 316/604 RR 0.96 (0.79 to 1.17) NS I^2 = 73%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Tao 2022)
Allergan 2021	739	18-80 y Episodic migraine with or without aura History of 4 to 14 migraine days per month on average Exclusion: chronic migraine; ≥15 headache days per month; Usage of opioids or barbiturates > 2 days/month, triptans or ergots ≥ 10 days/month, or simple analgesics (e.g., aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen) ≥ 15 days/month; Any clinically significant hematologic, endocrine, pulmonary, renal, hepatic, gastrointestinal (GI), or neurologic disease; hypertension	52 weeks	atogepant 60 mg 1x/day vs placebo	RANDO: Low risk ALLOCATION CONC: Low risk BLINDING Participants/personnel: unclear risk BLINDING Assessors : unclear risk INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: unclear risk OTHER BIAS unclear risk
Aliani 2021	902	18 to 80 y Episodic migraine with or without aura, diagnosed as specified in the International Classification of Headache Disorders, 3rd edition (ICHD-3) exclusion: chronic migraine, 15 or more headache days per month; inadequate response to more than 4	12 weeks	atogepant 10 mg 1x/day Vs atogepant 30 mg 1x/day vs atogepant 60 mg 1x/day vs placebo	RANDO: Low risk ALLOCATION CONC: Low risk BLINDING Participants/personnel: Low risk BLINDING Assessors : unclear risk INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING:

		preventive medications; use of opioids or barbiturates on more than 2 days per month, triptans or ergots on 10 or more days per month, or simple analgesic agents (e.g., aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs], or acetaminophen) on 15 or more days per month			low risk OTHER BIAS Low risk
Goadsby 2020	825	18 to 75y episodic migraine with or without aura Use of acute migraine drugs for 14 days or fewer per 28-day period, including 10 days or fewer of triptan use per 28-day period self-reported mean of 4–14 migraine days per month exclusion: 15 or more headache days per month; a history of inadequate response to at least three medications prescribed for migraine prevention; use of opioids or barbiturates more than 2 days per month, triptans or ergots 10 days or more per month, or simple analgesics (eg, aspirin, non-steroidal anti-inflam matory drugs, acetaminophen) 15 days or more per month	12 weeks	atogepant 10 mg 1x/day Vs atogepant 30 mg 1x/day vs atogepant 60 mg 1x/day vs atogepant 30 mg 2x/day vs atogepant 60 mg 2x/day vs placebo	RANDO: Low risk ALLOCATION CONC: Low risk BLINDING Participants/personnel: Low risk BLINDING Assessors : unclear risk INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk OTHER BIAS Low risk

Remarks:

This SR also reported atogepant 30mg 2x/day and atogepant 60 mg 2x/day; we did not report this as this is not the recommended dose

Author's conclusions: "Atogepant has shown good efficacy and safety in the prophylactic treatment of migraine, and further studies are expected."

Study details	n/Population	Comparison	Outcomes	Methodological
Ref…	n= 910 (randomized)		Efficacy	RANDO:

Lipton 2022 Design: RCT DB PG Duration of follow-up: 12 weeks	873 (analyzed) (atogepant 10mg [n=214]; 30mg [n=223]; 60mg [n=222]; placebo [n=214]) Mean age: 41.7y Definition of migraine: migraine with or without aura consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) Additional medication (acute/prevention): Participants were allowed to take treatments for migraine attacks, which included triptans, ergot derivatives, opioids,	Atogepant 10 mg 1x/day Atogepant 30 mg 1x/day Atogepant 60 mg 1x/day Vs placebo	Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) RFR-domain Role Function–Preventive (RFP) domain measures the degree to which migraine interrupts or prevents the performance of daily social and work-related activities. (MID) for MSQRFR is 3.2 points higher scores indicate better daily functioning Change from baseline to week 12 (Prespecified secondary endpoint)	Atogepant 10 mg vs placebo **LSMD= 9.90 (5.45 to 14.36)** **SS in favour of atogepant** Atogepant 30 mg vs placebo **LSMD= 10.08 (5.71 to 14.46)** **SS in favour of atogepant** Atogepant 60 mg vs placebo **LSMD = 10.80 (6.42 to 15.18)** **SS in favour of atogepant**	Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Drop-out and Exclusions:105/910 (11.5%) • Described: yes • Balanced across groups: unclear (22,29,23 and 31 discontinuations for placebo, ato 10 mg, 30 mg and 60 mg respectively) ITT: No; “modified ITT” described as “The mITT population included all participants who received ≥1 dose of study drug, had an evaluable baseline period of eDiary data, and ≥1 evaluable postbaseline 4-week period of eDiary data during the double-blind treatment period.”

	analgesics, NSAIDs, and antiemetic agents. Participants were not allowed to take any preventive treatments for migraine 30 days before visit 1 and throughout the trial. <u>Inclusion</u> 18–80 years of age patients with 4-14 migraine days per month. <u>Exclusion</u> Chronic migraine ≥15 monthly headache days; Inadequate response to >4 preventive medications; Use of opioids >2 days/month, triptans or ergots ≥10 days/month, or simple				SELECTIVE REPORTING: no Other important methodological remarks Prespecified analysis of ADVANCE trial Sponsor: Allergan now AbbVie sponsored the study; contributed to the design; participated in the analysis, and interpretation of data; in writing, reviewing, and approval of the final version.

	analgesics (e.g., aspirin, nonsteroidal anti-inflammatory drugs, acetaminophen) ≥15 days/month or use of barbiturates >2 days/month				

13.7 Supplements

Meta-analysis: Okoli 2019(268) “Vitamins and Minerals for Migraine Prophylaxis: A Systematic Review and Meta-analysis”

Definition of migraine:

Inclusion criteria:
Study design: parallel and crossover RCTs
Population: adult and pediatric patients with a history of migraines
Intervention: vitamin A (retinol), vitamin B1 (thiamine), vitamin B2, (riboflavin), vitamin B3 (niacin), vitamin B6 (pyridoxine), vitamin B12 (cobalamin), vitamin C (ascorbic acid), vitamin D, (cholecalciferol), vitamin E (tocopherol), calcium, iron, magnesium, phosphate, selenium, zinc, and coenzyme Q10 (CoQ10 or Ubiquinone
Comparison: placebo or no treatment (exclusion of active agents)

Search strategy: MEDLINE (Ovid) , Embase (Ovid), Cochrane Central Register of Controlled Trials (Wiley), PsycINFO (ProQuest), and CINAHL with Full Text (EBSCO) were searched up to June 2017. . In order to identify ongoing or unpublished trials clincialtrials.gov,the World Health Organization International Clinical Trials Registry Platform (ICTRP), and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) website were searched as well.

Assessment of quality of included trials: yes, Cochrane risk of bias tool
Other methodological remarks:

13.7.1 Coenzyme Q10 vs placebo

Ref	Comparison	N/n	Outcomes	Result

Okoli 2019(268) Design: SR Search date: June 2017	Coenzyme Q10 vs placebo	N= 2 n= 97 (Khorvash 2016, Sandor 2005)	Migraine frequency	MD −0.44 (95% CI −2.14 to 1.26) NS I^2 = 53%
		N= 2 n= 97 (Khorvash 2016, Sandor 2005)	Migraine duration	MD −1.97 (95% CI −4.82 to 0.87) NS I^2 =0%
		N= 2 n= 97 (Khorvash 2016, Sandor 2005)	Migraine severity	RoM −0.05 (95% CI −0.20 to 0.11 NS I^2 = 0%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Khorvash 2016 Parallel RCT	54	16–52 y Patients with migraine (with or without aura) o	8 weeeks	30 mg Coenzyme Q10 2x/day vs. Placebo	RCT does not meet our inclusion criteria (sample size and duration)
Sandor 2005 Parallel RCT	43	18–65 y Migraine (with or without aura), two to eight attacks per month	12 weeks	100 mg coenzyme Q10 3x/day vs. Placebo	RCT does not meet our inclusion criteria (sample size)

Author's conclusions: "Based on the available but insufficient evidence, it is unknown if coenzyme Q10 and magnesium are effective for migraine prophylaxis in adults. It is important to note that the available evidence is of low to moderate strength and from trials with substantial risk of bias. High-quality, adequately powered RCTs are needed to fully evaluate the efficacy and safety of vitamins and minerals to be able to make clinical recommendations on their use for migraine prophylaxis."

13.7.2 Folic acid (vit B9) vs placebo

Meta-analysis: Liampas 2020b(275) "Pyridoxine, folate and cobalamin for migraine: A systematic review"

Inclusion criteria:
Study design: interventional or observational studies, controlled or uncontrolled
Population: migraine and other primary headache disorders
Intervention: vitamin B6, folic acid or vitamin B12 supplementation, alone or as adjunctive therapies

Search strategy: MEDLINE (through PubMed), EMBASE (through Elsevier) and CENTRAL (Cochrane Central Register of Controlled Trials, the Cochrane Library) databases were searched from inception to January 2020. The search strategy, additionally, included the following trial registries: World Health Organization (WHO)—International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov (CT.gov) and the European Union (EU) Clinical Trials Register (CTR), as well as both a structured and a manual search of Google Scholar (the manual search of Google Scholar involved all articles that cited the papers retrieved by the systematic literature search). Grey literature was investigated through the OpenGrey database, conference abstracts and abstracts (in English) from articles not published in English.

Assessment of quality of included trials: yes, Cochrane risk of bias tool for RCTs

SR Liampas 2020b searched for observational and interventional studies evaluating vitamin B6, folic acid (vitamin B9) or vitamin B12 in migraine and other primary headache disorders. None of the found studies met our inclusion criteria.

13.7.3 Magnesium vs placebo

Ref	Comparison	N/n	Outcomes	Result
Okoli 2019(268) Design: SR Search date: June 2017	Magnesium vs placebo	N= 4 n= 266 (Tarighat Esfanjani 2012, Mahdavi 2009, Koseoglu 2008, Peikert 1996)	Migraine frequency	**MD -2.57 (-4.2 to -0.94)** **SS in favour of magnesium** **I^2 = 88%*** *sensitivity analyses and examination of the trial characteristics did not resolve potential sources of heterogeneity.
		N= 1 n= 81 (Peikert 1996)	Migraine duration	MD -0.21 (-0.70 to 0.28) NS
		N= 3 n= 226 (Peikert 1996, Mahdavi 2009, Tarighat Esfanjani 2012)	Migraine severity	RoM −0.17 (95% CI −0.36 to 0.02) NS I^2 = 48%
		N= 3 n= 226 (Peikert 1996, Mahdavi 2009, Tarighat Esfanjani 2012)	Days with migraine	**MD -3.00 (-5.02 to -0.98)** **SS in favour of magnesium** **I^2 = 87%**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology

Tarighat Esfanjani 2012 Parallel RCT	139	18-55 y Migraine with at least two attacks per month	12 weeks	500 mg magnesium /day Vs Placebo	RANDO: unclear risk (method not described) ALLOCATION CONC: High risk ("In this clinical trial, 133 migrainous patients were randomly assigned into three intervention groups. The present study was a single-blind clinical trial in which subjects were assigned into one out of four groups) BLINDING Participants/personnel: unclear risk (no information) BLINDING Assessors : High risk (no information) INCOMPLETE OUTCOME DATA: low risk SELECTIVE REPORTING: low risk
Mahdavi 2009 Parallel RCT	95	18-65 y migraine	12 weeks	250 mg magnesium /day Vs Placebo	RANDO: unclear risk (" No reporting on sequence generation and the randomization process is questionable) ALLOCATION CONC: unclear risk (" No reporting on sequence generation and the randomization process is questionable) BLINDING Participants/personnel: High risk (no mention of blinding) BLINDING Assessors : high risk (no mention of blinding) INCOMPLETE OUTCOME DATA:

					High risk ("18 patients were excluded from the study (14 from Mg and 4 from control) due to not coming for the visits.") SELECTIVE REPORTING: low risk
Koseoglu 2008 Parallel RCT	40	20-55 y migraine(without aura	12 weeks	300 mg magnesium /day Vs Placebo	RCT does not meet our inclusion criteria (sample size)
Peikert 1996 Parallel RCT	81	18-65 y Migraine (with or without aura) patients with mean attack frequency of 3.6 per month	12 weeks	600 mg magnesium /day Vs Placebo	RANDO: unclear risk (method not described) ALLOCATION CONC: high risk (not described) BLINDING Participants/personnel: unclear risk (method not described) BLINDING Assessors : high risk (not described) INCOMPLETE OUTCOME DATA: unclear risk ("The evaluation was done according to the intention-to-treat principle. It includes all patients who submitted an at least 4-week long headache diary and who randomly received the study medication.") SELECTIVE REPORTING: low risk

Author's conclusions: "Based on the available but insufficient evidence, it is unknown if coenzyme Q10 and magnesium are effective for migraine prophylaxis in adults. It is important to note that the available evidence is of low to moderate strength and from trials with substantial risk of bias. High-

quality, adequately powered RCTs are needed to fully evaluate the efficacy and safety of vitamins and minerals to be able to make clinical recommendations on their use for migraine prophylaxis."

13.7.4 Melatonin vs control

Meta-analysis: Liampas 2020a(276)

Definition of migraine:

Inclusion criteria:
Study design: RCTs or non-randomized studies with at least 1 group of participants with migraine and receiving exogenous melatonin
Population: migraine
Intervention: exogenous melatonin for migraine prophylaxis

Search strategy: MEDLINE EMBASE, CENTRAL, PsycINFO, trial registries, Google Scholar, and OpenGrey were searched up until January 2020

Assessment of quality of included trials: yes, Cochrane risk of bias tool

Other methodological remarks: cohort studies were also searched in this SR for a different clinical question.

None of the RCTs comparing melatonin versus placebo met our inclusion criteria.
1 RCT comparing melatonin, valproate and placebo was found, but we did not report this study as it did not meet our inclusion criteria for sample size.
One RCT comparing amitriptyline to melatonin in adults was found; we reported the RCT individually (Gonçalves 2016); see "amitriptyline vs placebo"

13.7.5 Riboflavin vs placebo

SR Okoli 2019 found only one RCT in adults comparing riboflavin to placebo; however, it did not meet our inclusion criteria (sample size).

14 Appendix. Evidence tables. Acute treatment of migraine in children.

14.1 paracetamol versus placebo for children

Meta-analysis: Richer 2016(277), Drugs for the acute treatment of migraine in children and adolescents.

Definition of migraine: Migraine is defined by clinical symptoms and signs in the 3rd edition of the International Classification of Headache Disorders, beta version. ICHD-3 beta includes revised comments for the diagnosis of migraine in children and adolescents, including shorter duration of headache (2 to 72 hours), bilateral frontotemporal location, and the presence of photophobia and phonophobia as inferred from behaviour.
There have been two other versions of the International Classification of Headache Disorder and a proposed revision of the 1988 criteria in the context of children or adolescents. We included a study in this review if investigators used any version of the International Headache Society classification systems above or the proposed revision for pediatrics for the diagnosis of migraine with or without aura.

Inclusion criteria:
We included all prospective, placebo-controlled trials of pharmacological interventions for symptomatic or acute treatment of migraine in children and adolescents in the outpatient setting if allocation to treatment groups was randomized. We included studies regardless of design (i.e. parallel-group or cross-over), publication status, or language of publication. We included cross-over studies, as migraine is an episodic disorder, and we did not expect any carry-over or period effects.
We excluded non-placebo-controlled studies, concurrent cohort comparisons and other quasi- or non-experimental designs.

Population: We included studies involving pediatric participants 17 years of age or less with a diagnosis of migraine with or without aura. We excluded studies involving both pediatric and adult patients unless they reported results separately for the pediatric patients.

Intervention: We included studies allocating participants to receive a pharmacological intervention by any route of administration for symptomatic acute treatment of a migraine attack. Acceptable comparator groups included placebo or other active drug treatments.

Search strategy: We systematically searched the following databases:• Cochrane Central Register of Controlled Trials (CENTRAL) (1991 to 2013, Issue 3). • OvidSP MEDLINE (1946 to February 2016). • Ovid MEDLINE In-Process & Other Non-Indexed Citations (2012 to February 2016). • EMBASE (1980 to

February 2016). • Database of Abstracts and Reviews of EKects (1991 to April 2013). • International Pharmaceutical Abstracts (1970 to April 2013). • PsycINFO (1806 to April 2013). • EBSCOhost CINAHL (Cumulative Index of Nursing and Allied Health) (1937 to April 2013).
We conducted a gray literature search including reviewing the reference lists of included studies and handsearching meeting abstracts from the American Headache Society and International Headache Society Scientific meetings. The review authors attempted to contact primary authors, experts in the area, and drug manufacturers (GlaxoSmithKline, AstraZeneca, Ortho-McNeil, Merck, and Pfizer) for information on recent, ongoing, or unpublished trials. We searched ClinicalTrials.gov for new or ongoing studies and used Current Controlled Trials to search across multiple trial registries.

Assessment of quality of included trials: yes

Other methodological remarks:
We included studies allocating participants to receive a pharmacological intervention by any route of administration for symptomatic acute treatment of a migraine attack. Acceptable comparator groups included placebo or other active drug treatments.
We only analyzed the available data for all outcomes.

Ref	Comparison	N/n	Outcomes	Result
Richer 2016 Design: SR+MA Search date: February 2016	Paracetamol Vs Placebo	N = 1 n = 88 (Hämäläinen 1997)	Pain-free at 2h (PO)	RR 1.40, 95% CI 0.75 to 2.58 **NS**
		N = 1 n = 88 (Hämäläinen 1997)	Headache relief at 2h (defined as a decrease in headache intensity from severe or moderate to mild or none at two hours prior to the use of rescue medication.)	No raw data provided **NS**
		N = 1 n = 88 (Hämäläinen 1997)	Rescue medication (% of participants taking rescue medication at two hours or earlier to a maximum of six hours after the test drug.)	No raw data provided **NS**

		N = 1 n = 88 (Hämäläinen 1997)	Headache recurrence (participants who were initially pain-free or achieved the study PO of headache relief within 2 hours without the use of rescue medication but who experienced recurrence of any headache from 2 to 48 hours.)	No raw data provided **NS**
		N = 1 n = 88 (Hämäläinen 1997)	Adverse events (any) (PO)	No raw data provided **NS**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Hämäläinen 1997 R, DB, placebo-controlled, 3-way CO trial	106	Children or adolescents 4-16 years with a diagnosis of migraine with or without aura meeting IHS 1988 criteria from 3 pediatric hospitals in the Greater Helsinki Area of Finland who found previous therapy for migraine unsatisfactory. Participants were required to have 2 migraine attacks per month lasting 2h or more. Headache relief at 2 h: defined as severe or moderate (a grade of ≥ 3) to at least 2 grades lower. Headache severity scale: Participants were allowed to choose between the 5-faces pain scale (5 severe, 4 to 3		Ibuprofen Vs Paracetamol Vs Placebo Each participant treated 1 of 3 migraine attacks with either oral paracetamol (15 mg/kg), oral ibuprofen (10 mg/kg), or placebo. The active drugs and matching placebo were supplied by the University Pharmacy of Helsinki in 3 mixtures containing peppermint water, black	As assessed in Richer 2016 ALLOCATION CONCEALMENT: Unclear risk; no information provided RANDOMIZATION: Unclear risk ; no information provided BLINDING: All outcomes: Low risk Quote: "[T]he active drugs and matching placebo were supplied by the University Pharmacy of Helsinki in three mixtures containing peppermint water, black currant syrup, sugar syrup, and either 30 mg/ml paracetamol or 20 mg/ml ibuprofen, or as placebo (cellulose). Each participant

		moderate, 2 mild, 1 no pain) or the 100 mm visual analogue scale (VAS). The VAS (0 to 100) data were transformed to a nominal scale: grade 1: 0 to U 12; grade 2: 12 to U 37; grade 3: 37 to U 62; grade 4: 62 to U 87; and grade 5: 87 to U 100. Completed: 88 F: 44 M: 44		currant syrup, sugar syrup, and either 30 mg/ml paracetamol or 20 mg/ml ibuprofen, or, as a placebo, cellulose. Each participant received a package of 3 identically numbered bottles and a plastic 10 ml syringe for exact weight-based dosing (0.5 ml/kg, maximum dose 30 ml).	received a package of three identically numbered bottles and a plastic 10 ml syringe for exact weight-based dosing (0.5 ml/kg; max 30 ml)." INCOMPLETE OUTCOME DATA: All outcomes: Low risk; outcome data balanced across intervention groups FOLLOW-UP: Randomized (N = 106); lost to follow-up (N = 2); medication not used (N = 16); 1 medication used (N = 5); 2 medications used (N = 8); withdrawn (N = 9) ITT: “All additional children and adolescents with any data on efficacy were included in the intention-to-treat analysis, which was performed without regard to pain intensity at the start of the attack.” SELECTIVE REPORTING: Low risk; all expected outcomes reported FUNDING: Not specified

Remarks:

- For the purposes of the review, authors defined children as under 12 years of age and adolescents as 12 to 17 years of age.
- In the one three-way cross-over study that evaluated paracetamol (Hämäläinen 1997), the participant age ranged from 4 to 15.8 years, but investigators did not report results for children and adolescents separately. However, the mean age of inclusion was 10.7 years, so authors of the MA deemed the study to be predominantly in children.
- All outcome measures were reported for the treatment of a single attack.

Author's conclusions:

"Paracetamol was not shown to be effective in providing pain freedom in children, but we only found one small study."

14.2 Ibuprofen versus placebo in children

Meta-analysis: Richer 2016(277), Drugs for the acute treatment of migraine in children and adolescents.

Definition of migraine: Migraine is defined by clinical symptoms and signs in the 3rd edition of the International Classification of Headache Disorders, beta version. ICHD-3 beta includes revised comments for the diagnosis of migraine in children and adolescents, including shorter duration of headache (2 to 72 hours), bilateral frontotemporal location, and the presence of photophobia and phonophobia as inferred from behaviour.
There have been two other versions of the International Classification of Headache Disorder and a proposed revision of the 1988 criteria in the context of children or adolescents. We included a study in this review if investigators used any version of the International Headache Society classification systems above or the proposed revision for pediatrics for the diagnosis of migraine with or without aura.

Inclusion criteria:
We included all prospective, placebo-controlled trials of pharmacological interventions for symptomatic or acute treatment of migraine in children and adolescents in the outpatient setting if allocation to treatment groups was randomized. We included studies regardless of design (i.e. parallel-group or cross-over), publication status, or language of publication. We included cross-over studies, as migraine is an episodic disorder, and we did not expect any carry-over or period effects.
We excluded non-placebo-controlled studies, concurrent cohort comparisons and other quasi- or non-experimental designs.

Population: We included studies involving pediatric participants 17 years of age or less with a diagnosis of migraine with or without aura. We excluded studies involving both pediatric and adult patients unless they reported results separately for the pediatric patients.

Intervention: We included studies allocating participants to receive a pharmacological intervention by any route of administration for symptomatic acute treatment of a migraine attack. Acceptable comparator groups included placebo or other active drug treatments.

Search strategy: We systematically searched the following databases: • Cochrane Central Register of Controlled Trials (CENTRAL) (1991 to 2013, Issue 3). • OvidSP MEDLINE (1946 to February 2016). • Ovid MEDLINE In-Process & Other Non-Indexed Citations (2012 to February 2016). • EMBASE (1980 to February 2016). • Database of Abstracts and Reviews of EKects (1991 to April 2013). • International Pharmaceutical Abstracts (1970 to April 2013). • PsycINFO (1806 to April 2013). • EBSCOhost CINAHL (Cumulative Index of Nursing and Allied Health) (1937 to April 2013).
We conducted a gray literature search including reviewing the reference lists of included studies and handsearching meeting abstracts from the American Headache Society and International Headache Society Scientific meetings. The review authors attempted to contact primary authors, experts in the area, and drug manufacturers (GlaxoSmithKline, AstraZeneca, Ortho-McNeil, Merck, and Pfizer) for information on recent, ongoing, or unpublished trials. We searched ClinicalTrials.gov for new or ongoing studies and used Current Controlled Trials to search across multiple trial registries.

Assessment of quality of included trials: yes

Other methodological remarks:
We included studies allocating participants to receive a pharmacological intervention by any route of administration for symptomatic acute treatment of a migraine attack. Acceptable comparator groups included placebo or other active drug treatments.
We only analyzed the available data for all outcomes.

Ref	Comparison	N/n	Outcomes	Result
Richer 2016 Design: SR+MA Search date: February 2016	Ibuprofen Vs Placebo	N = 2 n = 125 (Hämäläinen 1997, Lewis 2002)	pain-free at 2h (PO)	Ibuprofen: 32/65 Placebo: 16/60 **RR : 1.87, 95% CI 1.15 to 3.04** p: 0.01 **SS in favour of ibuprofen** I^2: 0%
		N = 2 n = 125	Headache relief at 2h (typically defined as a decrease in headache intensity from severe or	Ibuprofen: 48/65 Placebo: 29/60 RR : 1.49, 95% CI 1.11 to 2.00 p: 0.008

		(Hämäläinen 1997, Lewis 2002)	moderate to mild or none at two hours prior to the use of rescue medication.)	**SS in favour of ibuprofen** I^2: 0%
		N = 2 n = 164 (Hämäläinen 1997, Lewis 2002)	Rescue medication (% of participants taking rescue medication at two hours or earlier to a maximum of six hours after the test drug.)	Ibuprofen: 5/85 Placebo: 24/79 **RR : 0.19, 95% CI 0.02 to 1.56** p: 0.12 **NS** I^2: 72%
		N = 1 n = 38 (Hämäläinen 1997)	Headache recurrence (participants who were initially pain-free or achieved the study PO of headache relief within 2 hours without the use of rescue medication but who experienced recurrence of any headache from 2 to 48 hours.)	**Not enough evidence** according to our methodology (n < 40/group)
		N = 1 n = 80 (Hämäläinen 1997)	Adverse events (any) (PO)	Ibuprofen: 4/40 Placebo: 4/40 RD: **0.00, 95% CI -0.13 to 0.13** p: 1.00 **NS**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Hämäläinen 1997	106	Children or adolescents 4-16 years with a diagnosis of migraine with or without aura meeting IHS 1988 criteria from 3 pediatric hospitals in the Greater	ND	Ibuprofen Vs Paracetamol Vs	As assessed in Richer 2016 ALLOCATION CONCEALMENT: Unclear risk; no information provided

R, DB, placebo-controlled, 3-way CO trial		Helsinki Area of Finland who found previous therapy for migraine unsatisfactory. Participants were required to have 2 migraine attacks per month lasting 2h or more. Headache relief at 2 h: defined as severe or moderate (a grade of ≥ 3) to at least 2 grades lower. Headache severity scale: Participants were allowed to choose between the 5-faces pain scale (5 severe, 4 to 3 moderate, 2 mild, 1 no pain) or the 100 mm visual analogue scale (VAS). The VAS (0 to 100) data were transformed to a nominal scale: grade 1: 0 to U 12; grade 2: 12 to U 37; grade 3: 37 to U 62; grade 4: 62 to U 87; and grade 5: 87 to U 100. Completed: 88 F: 44 M: 44		Placebo Each participant treated 1 of 3 migraine attacks with either oral paracetamol (15 mg/kg), oral ibuprofen(10 mg/kg), or placebo. The active drugs and matching placebo were supplied by the University Pharmacy of Helsinki in 3 mixtures containing peppermint water, black currant syrup, sugar syrup, and either 30 mg/ml paracetamol or 20 mg/ml ibuprofen, or, as a placebo, cellulose. Each participant received a package of 3 identically numbered bottles and a plastic 10 ml syringe for exact weight-based dosing (0.5 ml/kg, maximum dose 30 ml).	RANDOMIZATION: Unclear risk ; no information provided BLINDING: All outcomes: Low risk Quote: "[T]he active drugs and matching placebo were supplied by the University Pharmacy of Helsinki in three mixtures containing peppermint water, black currant syrup, sugar syrup, and either 30 mg/ml paracetamol or 20 mg/ml ibuprofen, or as placebo (cellulose). Each participant received a package of three identically numbered bottles and a plastic 10 ml syringe for exact weight-based dosing (0.5 ml/kg; max 30 ml)." INCOMPLETE OUTCOME DATA: All outcomes: Low risk; outcome data balanced across intervention groups FOLLOW-UP: Randomized (N = 106); lost to follow-up (N = 2); medication not used (N = 16); 1 medication used (N = 5); 2 medications used (N = 8); withdrawn (N = 9)

					ITT: “All additional children and adolescents with any data on efficacy were included in the intention-to-treat analysis, which was performed without regard to pain intensity at the start of the attack.” SELECTIVE REPORTING: Low risk; all expected outcomes reported FUNDING: Not specified
Lewis 2002 R, DB, placebo-controlled, PG trial	138	Participants were 6-12 years of age and met diagnostic criteria for migraine without aura per revised IHS 1988 criteria for children from multiple sites in the United States. Headache relief: defined as a reduction from moderate or severe to mild or no headache at 2 h. Headache severity scale: 4-point scale (none, mild, moderate, severe) Completed: 84 F: ND M: ND	ND	Ibuprofen Vs Placebo liquid ibuprofen suspension (7.5 mg/kg) or placebo	ALLOCATION CONCEALMENT: Unclear risk Quote: "Subjects were randomized to one of the following groups in a 1:1 ratio RANDOMIZATION: Unclear risk Quote: "Subjects were randomly assigned (stratified by gender) to the study medication in a double-blind fashion." BLINDING: All outcomes: Low risk Quote: "matching placebo suspension" Comment: no description of taste or color INCOMPLETE OUTCOME DATA: All outcomes, low risk

					Quote: "FiPy-four patients were randomized but were not evaluable. . . Six treated with study agent" Comment: missing outcome data balanced between intervention groups FOLLOW-UP: Enrolled (N = 138); treated/completed diary (N = 84) ITT: no reported SELECTIVE REPORTING: Low risk, all expected outcomes were reported FUNDING: Not specified

Remarks:

- For the purposes of the review, authors defined children as under 12 years of age and adolescents as 12 to 17 years of age.
- In the one three-way cross-over study (Hämäläinen 1997), the participant age ranged from 4 to 15.8 years, but investigators did not report results for children and adolescents separately. However, the mean age of inclusion was 10.7 years, so authors of the MA deemed the study to be predominantly in children.
- Lewis 2002 was a parallel group study that included only 6 to 12 year-olds with a mean age of 9 years.
- All outcome measures were reported for the treatment of a single attack.

Author's conclusions:

"Low quality evidence from two small trials shows that ibuprofen appears to improve pain freedom for the acute treatment of children with migraine. We have only limited information on adverse events associated with ibuprofen in the trials included in this review."

14.3 Ibuprofen versus placebo in adolescents

Meta-analysis: Richer 2016(277), Drugs for the acute treatment of migraine in children and adolescents.

Definition of migraine: Migraine is defined by clinical symptoms and signs in the 3rd edition of the International Classification of Headache Disorders, beta version. ICHD-3 beta includes revised comments for the diagnosis of migraine in children and adolescents, including shorter duration of headache (2 to 72 hours), bilateral frontotemporal location, and the presence of photophobia and phonophobia as inferred from behaviour.
There have been two other versions of the International Classification of Headache Disorder and a proposed revision of the 1988 criteria in the context of children or adolescents. We included a study in this review if investigators used any version of the International Headache Society classification systems above or the proposed revision for pediatrics for the diagnosis of migraine with or without aura.

Inclusion criteria:
We included all prospective, placebo-controlled trials of pharmacological interventions for symptomatic or acute treatment of migraine in children and adolescents in the outpatient setting if allocation to treatment groups was randomized. We included studies regardless of design (i.e. parallel-group or cross-over), publication status, or language of publication. We included cross-over studies, as migraine is an episodic disorder, and we did not expect any carry-over or period effects.
We excluded non-placebo-controlled studies, concurrent cohort comparisons and other quasi- or non-experimental designs.

Population: We included studies involving pediatric participants 17 years of age or less with a diagnosis of migraine with or without aura. We excluded studies involving both pediatric and adult patients unless they reported results separately for the pediatric patients.

Intervention: We included studies allocating participants to receive a pharmacological intervention by any route of administration for symptomatic acute treatment of a migraine attack. Acceptable comparator groups included placebo or other active drug treatments.

Search strategy: We systematically searched the following databases: • Cochrane Central Register of Controlled Trials (CENTRAL) (1991 to 2013, Issue 3). • OvidSP MEDLINE (1946 to February 2016). • Ovid MEDLINE In-Process & Other Non-Indexed Citations (2012 to February 2016). • EMBASE (1980 to February 2016). • Database of Abstracts and Reviews of EKects (1991 to April 2013). • International Pharmaceutical Abstracts (1970 to April 2013). • PsycINFO (1806 to April 2013). • EBSCOhost CINAHL (Cumulative Index of Nursing and Allied Health) (1937 to April 2013).
We conducted a gray literature search including reviewing the reference lists of included studies and handsearching meeting abstracts from the American Headache Society and International Headache Society Scientific meetings. The review authors attempted to contact primary authors, experts in the area, and drug manufacturers (GlaxoSmithKline, AstraZeneca, Ortho-McNeil, Merck, and Pfizer) for information on recent, ongoing, or unpublished trials. We searched ClinicalTrials.gov for new or ongoing studies and used Current Controlled Trials to search across multiple trial registries.

Assessment of quality of included trials: yes

Other methodological remarks:
We included studies allocating participants to receive a pharmacological intervention by any route of administration for symptomatic acute treatment of a migraine attack. Acceptable comparator groups included placebo or other active drug treatments.
We only analyzed the available data for all outcomes.

Only one study was included in the MA, evaluating Zolmitriptan (2.5 mg, PO) vs ibuprofen vs placebo in 32 children and adolescents. No raw data were reported and the study did not meet our inclusion criteria (sample size < 40 per group) and was therefore excluded from the present document.

Not enough evidence for all outcomes (pain-free at 2h, headache relief at 2h, rescue medication, headache recurrence, nausea and vomiting and adverse events).

14.4 Ibuprofen versus paracetamol for acute treatment of migraine attack in children and adolescents

Meta-analysis: Jeric 2018(280), Treatment of acute migraine attacks in children with analgesics on the World Health Organization Essential Medicines List: A systematic review and GRADE evidence synthesis

Definition of migraine: ND

Inclusion criteria: randomized controlled trials (RCTs) and SRs analyzing ibuprofen and/or paracetamol as a pharmacological intervention for the treatment of acute attacks of migraine in children<18 years.

Search strategy: Five databases were searched, including Embase and MEDLINE via OVID, Cochrane Database of Systematic Reviews (CDSR), Database of Reviews of Effects (DARE) and Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library. A search strategy for MEDLINE was designed first, using keywords for headache disorders, children, ibuprofen and acetaminophen and searches for the other databases were adapted accordingly. The last database search was conducted on 18 April 2017. There were no search limits. Studies published in any language were considered for inclusion.

Assessment of quality of included trials: yes

Other methodological remarks:
Random-effects meta-analysis was conducted.
The data in the cross-over trials were presented per treatment group, as if the trials had parallel group design. This approach ignores cross-over design, giving the same point estimate as if cross-over was taken into account, but resulting in larger confidence intervals. This also has influence on the overall meta-analysis estimates, again producing slightly more conservative estimates.

Ref	Comparison	N/n	Outcomes	Result
Jeric 2018 Design: SR+MA Search date: April 2017	Ibuprofen Vs Paracetamol	N = 1 n = 81 (Hämäläinen 1997)	Pain-free at 2 h (PO)	Ibuprofen: 24/40 Paracetamol: 16/41 OR: 2.34, 95% CI 0.96 to 5.71 p: 0.06 **NS**
		N = 1 n = 81 (Hämäläinen 1997)	Pain relief at 2 h (Reduction in severe or moderate headache (grades_3 on a scale of 1 to 6) by two grades)	Ibuprofen: 27/40 Paracetamol: 22/41 OR 1.79, 95% CI 0.73 to 4.42 p: 0.20 **NS**
		N = 1 n = 81 (Hämäläinen 1997)	Adverse events	No events **Not estimable**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Hämäläinen 1997	106	Children or adolescents 4-16 years with a diagnosis of migraine with or without aura meeting IHS 1988 criteria from 3		Ibuprofen Vs Paracetamol	As assessed in Jeric 2018

R, DB, placebo-controlled, 3-way CO trial		pediatric hospitals in the Greater Helsinki Area of Finland who found previous therapy for migraine unsatisfactory. Participants were required to have 2 migraine attacks per month lasting 2h or more. Headache relief at 2 h: defined as severe or moderate (a grade of ≥ 3) to at least 2 grades lower. Headache severity scale: Participants were allowed to choose between the 5-faces pain scale (5 severe, 4 to 3 moderate, 2 mild, 1 no pain) or the 100 mm visual analogue scale (VAS). The VAS (0 to 100) data were transformed to a nominal scale: grade 1: 0 to U 12; grade 2: 12 to U 37; grade 3: 37 to U 62; grade 4: 62 to U 87; and grade 5: 87 to U 100. Completed 88 F: 44 M: 44		Vs Placebo Each participant treated 1 of 3 migraine attacks with either oral paracetamol (15 mg/kg), oral ibuprofen (10 mg/kg), or placebo. The active drugs and matching placebo were supplied by the University Pharmacy of Helsinki in 3 mixtures containing peppermint water, black currant syrup, sugar syrup, and either 30 mg/ml paracetamol or 20 mg/ml ibuprofen, or, as a placebo, cellulose. Each participant received a package of 3 identically numbered bottles and a plastic 10 ml syringe for exact weight-based dosing (0.5 ml/kg, maximum dose 30 ml).	ALLOCATION CONCEALMENT: Unclear. Allocation concealment method not described RANDOMIZATION: Unclear risk. Random Sequence generation method not described BLINDING (participants and personel): Low. Double-blind study BLINDING (assessor) Unclear. Blinding of outcome assessment was not described INCOMPLETE OUTCOME DATA: Unclear. Overall attrition was 17%, but attrition per group was not described SELECTIVE REPORTING: Low. There is no study protocol published, but all outcomes mentioned in the methods were reported in results

Remarks:

- The age range of the children was somewhat different between the studies included in the MA: In Hämäläinen 1997 patients were 4-16 years. A limitation of this study is the inability to separate data from primary studies for prepubertal and pubertal children (children and adolescents) because two trials that included both age ranges did not provide separate data for those populations.
- In the study by Hamalainen at al., multiple deviations from the original protocol were described.

Author's conclusions:

"We need new trials on this topic to get high-quality direct evidence about efficacy and safety of ibuprofen and paracetamol for migraine in children."

15 Appendix. Evidence tables. Prophylactic treatment of migraine in children.

15.1 Riboflavin versus placebo in children and adolescents

Meta-analysis: Locher 2020(283), Efficacy, Safety, and Acceptability of Pharmacologic Treatments for Pediatric Migraine Prophylaxis A Systematic Review and Network Meta-analysis

Definition of migraine: episodic migraine (with or without aura) defined according to the International Headache Society criteria, or criteria for migraine diagnosis had to be in close agreement with the International Headache Society classification.

Inclusion criteria: We included randomized clinical trials (RCTs) of prophylactic pharmacologic treatments for children and adolescents younger than 18 years. Participants were required to have a diagnosis of episodic migraine (with or without aura). Eligible trial designs included RCTs that make head-to-head comparisons of at least 2 pharmacologic agents (ie, comparator trials) as well as RCTs that compare at least 1 pharmacologic agent with a placebo (ie, placebo-controlled trials). Studies had to report at least 1 clinical outcome related to migraine (eg, migraine frequency or number of migraine days).

Excluded: crossover studies except when the results of the first period were given separately, studies in which migraine was associated with other neurologic disorders as well as studies on menstrual migraine. We only considered studies including patients who experienced other headaches (eg, tension type headache) if separate results for migraine patients were presented.

Search strategy: We searched MEDLINE, Cochrane, Embase, and PsycINFO from inception until July 2, 2018. Further trials were identified from an existing systematic review of prophylactic treatments for migraine.

Assessment of quality of included trials: yes

Other methodological remarks:
Our primary efficacy outcomes are continuous data, and we calculated the effect size (ES) of the interventions using the standardized mean difference (SMD). The magnitude of ESs was interpreted as small, moderate, or large,with 0.20, 0.50, and 0.80 SD units, respectively. f no continuous data were available, we calculated odds ratios (ORs) as ES between groups and transformed the min to SMDs according to the recommendations in the Cochrane Handbook of Systematic Reviews.
For efficacy, safety, and acceptability outcomes, we chose to apply random-effects models rather than fixed-effects models because the studies we included were heterogeneous, and the number of studies was relatively small.

Ref	Comparison	N/n	Outcomes	Result
Locher 2020 Design: SR+NMA Search date: July 2018	Riboflavin Vs Placebo	N = 3 n = 107 (Bruin 2010, MacLennan 2008, Telebian 2018)	Efficacy	SMD (95% CI): 0.19 (–0.39 to 0.78) **NS**
		N = 3 n = 107 (Bruin 2010, MacLennan 2008, Telebian 2018)	Acceptability	RR (95% CI): 0.49 (0.12 to 1.97) **NS**
		N = 1 n = 27 (MacLennan 2008)	Adverse events	**Not enough evidence** according to our methodology (n < 40)

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Bruin 2010 CO-RCT	44	Children and adolescents with migraine with and without aura according to ICHD second edition Riboflavin: mean age:9.9 (1.89); %F: 40 Placebo: mean age: 9.5 (1.63), %F: 45.5	Treatment duration: **16 weeks**, 4 weeks washout, 16 weeks Reported outcomes: 2-4 months	Riboflavin Vs Placebo Riboflavin 50 mg/day Placebo: carotène capsule	RCT did not meet our inclusion criteria (sample size per group)

MacLennan 2008 PG-RCT	48	Children and adolescents with migraine with and without aura according to ICHD second edition Riboflavin: mean age:11.1 (2.1); %F: 44.44 Placebo: mean age: 11.5 (2.5), %F: 57.14	Treatment duration: **12 weeks** Reported outcomes: up to 2 months	Riboflavin Vs Placebo Riboflavin 200 mg/day	RCT did not meet our inclusion criteria (sample size per group)
Talebian 2018 PG-RCT	90	Children and adolescents with migraine with and without aura according to ICHD second edition Riboflavin100 mg/day: n = 30, mean age:8.47; %F: 43.3 Riboflavin 200 mg/day: n = 30, mean age: 8.97, %F: 43.3 Placebo: n = 30, mean age: 7.9, %, F: 50	Treatment duration: 12 weeks Tx Reported outcomes: 2-4 months	Riboflavin 100 mg/day Vs Riboflavin 200 mg/day Vs Placebo	RCT did not meet our inclusion criteria (sample size in placebo group)

Remarks:

- In this SR, a NMA was conducted. According to our methodology we only reported data from direct comparisons.
- It was asked in the search criteria of the MA to report studies having min 3 months follow up. In this SR, the following time windows applied were: 8 weeks or 2 months after randomization, 3 to 4 months after randomization, 5 to 6 months after randomization, and more than 6 months after randomization. To increase the comparability between studies, the main analysis focused on outcomes reported at 3 to 4 months after randomization. If no data were reported for that time window, outcomes at 8 weeks or 2 months after randomization were used by authors. Regarding studies on riboflavin, reported time point were 2-4 months for Bruin 2010, up to 2 months for MacLennan 2008 and 2-4 months for Telebian 2018.
- If a study contained multiple treatment groups that differed only in the dosage, values were pooled by authors. Telebian 2018 had 2 intervention groups for different riboflavin dosages (100mg and 200mg).

- For all outcomes: there was no evidence of *inconsistency* between the direct and indirect evidence, i.e., all p-values were above 5%. Studies showed no significant heterogeneity.

Author's conclusions:
"There were no significant differences between the different prophylactic treatments. Further, none of the investigated drugs demonstrated convincing evidence that it reduces the migraine frequency in the long run more than a placebo. According to our results, prophylactic pharmacologic treatments have little evidence supporting efficacy for pediatric migraine. We advise to carefully weigh the benefits of prophylactic medications against their potential harms."

15.2 Magnesium versus placebo in children and adolescents

Meta-analysis: Shamliyan 2013(281), Migraine in Children: Preventive Pharmacologic Treatments

Definition of migraine: defined according to criteria set by the International Headache Society. According to the International Classification of Headache Disorders, second edition (ICHDII), migraine is a common disabling primary headache disorder manifesting in attacks that last from 4 to 72 hours. Migraine headaches range from moderate to very severe and are sometimes debilitating. Migraine frequency is classified as either episodic or chronic according to the number of monthly migraine days, with episodic being <15 days, and chronic being ≥15 days. Migraine may also be described as chronic when attacks recur over long periods of time. We included trials that used previous definitions of chronic daily headache.

Inclusion criteria: Our inclusion criteria were:
1. Original epidemiologic studies that aimed to examine preventive pharmacologic treatments for migraine.
2. Publication in English.
3. Target population of community-dwelling children with episodic migraine, chronic daily headache, or chronic migraine defined according to International Headache Society criteria for chronic migraine.
4. Eligible intermediate and patient-centered outcomes

Exclusion:
1. Studies of treatments aimed at acute migraine attacks.
2. Studies that involved patients with migraine variants, such as basilar migraine, childhood periodic syndromes, retinal migraine, complicated migraines, and ophthalmoplegic migraine, hospitalized patients, or patients in emergency rooms. We also excluded hemiplegic migraine, a pathophysiologically distinct disorder with its own classification.

3. Studies of short-term prevention of migraine, including menstrual migraines.
4. Studies that included some pediatric patients with migraine but did not separately report those outcomes.
5. Studies that invlved surgical treatments for migraine.
6. Preclinical pharmacokinetic studies of eligible drugs; studies that examined the pathophysiology of migraine reporting instrumental measurements or biochemical outcomes.
7. Studies that did not test the associative hypotheses.
8. Studies that examined eligible drugs on populations with other diseases.
9. Studies evaluating the efficacy of nonpharmacologic treatments or economic outcomes were beyond the scope of this review.
10. Episodic or chronic migraine as defined by the Headache Classification Committee of the International Headache Society does not include migraine variants or migraine equivalents with atypical symptomatic pain in regions other than the head. Therefore, we exclude these studies.

Search strategy: We searched for published studies in several databases, including MEDLINE® (via Ovid and PubMed®), the Cochrane Library, and the SCIRUS bibliographic database. We searched the FDA Web site for medical and statistical reviews of the eligible drugs. We searched clinical trial registries including ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry to find ongoing, completed, and published trials of migraine prevention. o find relevant unpublished studies, we reviewed the reference lists of identified guidelines, textbooks, and systematic reviews. We searched for the studies published in English up to May 20, 2012. We did not contact the investigators of the primary studies for missing data or clarifications.

Assessment of quality of included trials: yes

Other methodological remarks:
Using Meta-Analyst and STATA® software, we calculated the relative risk and absolute risk difference from the abstracted events and the mean differences in continuous variables from the reported means and standard deviations. We evaluated statistical significance at a 95% confidence level. We tested consistency in the results by comparing the direction and strength of the association, and we assessed heterogeneity in results with Chi-square and I-square tests. We explored heterogeneity with meta-regression and sensitivity analysis, reporting the results from random effects models only. Using the random effects model, we incorporated into the pooled
analysis any differences between trials in patient populations, baseline rates of the outcomes, dosage of drugs, and other factors.

Ref	Comparison	N/n	Outcomes	Result
Shamliyan 2013	Magnesium Vs	N = 1 n = 118 (Wang 2003)	Migraine frequency	No raw data provided **NS**

Design: SR+MA Search date: May 2012	Placebo	N = 1 n = 118 (Wang 2003)	Severity of migraine attack	No raw data provided **SS in favour of magnesium**
		N = 1 n = 118 (Wang 2003)	Diarrhea	Magnesium: 11/58 Placebo: 4/60 RR 95% CI: 2.8 (1.0 to 8.4) **NS**
		N = 1 n = 118 (Wang 2003)	Treatment discontinuation	Magnesium: 16/58 Placebo: 16/60 RR 95% CI: 1.0 (0.6 to 1.9) **NS**
		N = 1 n = 118 (Wang 2003)	Treatment discontinuation because headache was resolved	Magnesium: 1/58 Placebo: 2/60 RR 95% CI: 0.5 (0.0 to 5.6) **NS**
		N = 1 n = 118 (Wang 2003)	Treatment discontinuation due to adverse events	Magnesium: 3/58 Placebo: 1/60 RR 95% CI: 3.1 (0.3 to 29.0) **NS**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Wang 2003 DB-RCT	118	Eligible age between 3 and 17 with history of at least weekly, moderate-to severe migraine during the previous 4 weeks and it must have been associated with	Follow up 16 weeks	Oral magnesium oxide Vs Placebo Magnesium : 9mg/kg/day	Global risk of bias: medium ALLOCATION CONCEALMENT: adequate RANDOMIZATION: Not adequate

		anorexia/nausea, vomiting, photophobia, sonophobia, a pulsatile or throbbing quality, or relief with sleep, but not with fever or evidence of infection. Presence of aurea not reported. Exclusion: Patients were excluded if they took any migraine prophylactic drug therapies (such as betablockers, valproic acid), mg, or fever medications within 4 weeks of potential study entrance. Mean age: 12.0 %F: 68.6			BLINDING: Double blinded ITT: yes FOLLOW UP: Randomized 118, analysed: 118 Loss of follow up: not reported Treatment discontinuation reported FUNDING: not reported

Author's conclusions:
A single RCT demonstrated no significant differences with magnesium oxide and placebo in migraine frequency. Magnesium oxide reduced severity of migraine attacks compared with placebo. No studies examined reducing monthly migraine attacks by ≥50 percent or other patient-centered outcomes.

16 Appendix. Evidence tables. Cardiovascular adverse events in older people with migraine

McKinley 2021(287)	
Design	retrospective cohort study using data from US adults >66 years of age between 2008-2017

n	n= 37,893 migraine patients (21,990 without a history of CVD and 15,903 with a history of CVD); matched to 87,960 patients without migraine nor history of CVD and 63,612 patients without migraine and with a history of CVD)	
Population	Older adults >66 years of age After stratification by history of CVD, patients with a history of migraine were matched 1:4 to those without a history of migraine	
Risk factor	Migraine vs No migraine	
Outcome	Risk for ischemic stroke Risk of coronary heart disease (CHD) events (defined as myocardial infarction hospitalization or coronary revascularization)	
Results		
Subpopulation: Migraine patients without a history of CVD taking a **triptan** vs participants without migraine (and without a history of CVD)	**Ischemic stroke** n=7905	Adj.* HR 0.86 (0.68, 1.08) NS
	CHD events n=7905	**Adj.* HR: 0.79 (95%CI 0.67 to 0.93)** **SS fewer CHD events among migraine patients without CVD and taking a triptan, versus patients without migraine**
Subpopulation: Migraine patient with CVD history and taking a **triptan** vs participants without migraine with CVD history	**Ischemic stroke** n=2,350	Adj.* HR 0.93 (0.74, 1.18) **NS**
	CHD events n=2,350	**Adj. HR 0.83 (95%CI, 0.72 to 0.95)** **SS fewer CHD events among migraine patients with CVD and taking a triptan, versus patients without migraine**
Subpopulation: Migraine patients without a history of CVD taking an **NSAID**	**Ischemic stroke** n=4,268	Adj.* HR 1.21 (0.95, 1.53) NS
	CHD events n=4,268	Adj.* HR 1.00 (0.85, 1.19) NS

vs participants without migraine (and without a history of CVD)		
Subpopulation: Migraine patient with CVD history and taking an **NSAID** vs participants without migraine with CVD history	**Ischemic stroke** n=3,045	**Adj.* HR 1.20 (1.01, 1.43)** **SS more ischemic strokes among migraine patients with CVD and taking an NSAID, versus patients without migraine**
	CHD events n=3,045	Adj.* HR 0.90 (0.80, 1.01) NS
Subpopulation: Migraine patients without a history of CVD taking a **migraine-preventive antiepileptic agent** vs participants without migraine (and without a history of CVD)	**Ischemic stroke** n=4,698	Adj.* HR 1.18 (0.93, 1.50) NS
	CHD events n=4,698	Adj.* HR 1.12 (0.96, 1.32) NS
Subpopulation: Migraine patient with CVD history and taking a **migraine-preventive antiepileptic agent** vs participants without migraine with CVD history	**Ischemic stroke** N=4,626	**Adj.* HR 1.17 (1.01, 1.36)** **SS more ischemic strokes among migraine patients with CVD and taking a migraine-preventive antiepileptic agent, versus patients without migraine**
	CHD events n=4626	Adj.* HR 1.01 (0.92, 1.11) NS

Subpopulation: Migraine patients without a history of CVD taking a **migraine-preventive antihypertensive agent** vs participants without migraine (and without a history of CVD)		
	Ischemic stroke 8,079	**Adj.* HR 1.21 (1.03, 1.43)** **SS more ischemic strokes among migraine patients without CVD and taking a migraine-preventive antihypertensive agent, versus patients without migraine**
	CHD events n=8079	Adj.* HR 1.01 (0.89, 1.14) NS
Subpopulation: Migraine patient with CVD history and taking a **migraine-preventive antihypertensive agent** vs participants without migraine with CVD history	N=8,527	**Adj.* HR 1.28 (1.15, 1.42)** **SS more ischemic strokes among migraine patients with CVD and taking a migraine-preventive antihypertensive agent, versus patients without migraine**
	CHD events n=8527	Adj.* HR 1.01 (0.95, 1.09) NS
Subpopulation: Migraine patients without a history of CVD taking a **migraine-preventive antidepressant** vs participants without migraine (and without a history of CVD)	**Ischemic stroke** n=6,394	Adj.* HR 1.19 (0.96, 1.48) NS
	CHD events n=6,394	Adj.* HR 1.00 (0.85, 1.16) NS

Subpopulation: Migraine patient with CVD history and taking a **migraine-preventive antidepressant** vs participants without migraine with CVD history	**Ischemic stroke** n=5,195	**Adj.* HR 1.34 (1.17, 1.54)** **SS more ischemic strokes among migraine patients with CVD and taking a migraine-preventive antidepressant, versus patients without migraine**
	CHD events n=5,195	Adj.* HR 0.96 (0.87, 1.05) NS
* adjusted for: age, sex, race/ethnicity, low income, area-level income, smoking, diabetes, hypertension, CKD, history of heart failure, dementia, depression, insomnia, cancer, epilepsy, hospitalization within the past year, use of antihypertensive medication, diabetes medication, barbiturates, benzodiazepines, antihistamine medication for insomnia, non-benzodiazepine medication for insomnia, sedative hypnotics, and sedative antidepressants, statins, non-statin lipid-lowering therapy, and hormone replacement therapy		

Li 2022(288)	
Design	retrospective observational cohort
n	Triptan-treated n=436642 Prescription NSAID-treated n=334152 Untreated migraine patients: 1168212
Population	adult patients aged ≥ 18 years Patients with migraine had at least one inpatient or outpatient diagnosis of migraine) or one prescription of a triptan during the study period.
Risk factor	triptan-treated vs prescription NSAID-treated migraine patients triptan-treated vs untreated migraine patients
Outcome	Occurrence of AMI
Results	

Subpopulation: Triptans vs untreated migraine Age ≥ 65 years	AMI	Adj* HR 0.95 (0.78 to 1.15) NS
Triptans vs NSAIDs Age ≥ 65 years	AMI	Adj* HR 0.97 (0.54 to 1.74) NS
* adjusted with propensity score analysis		

17 Appendix. Search strategy

17.1 Acute and preventive migraine treatments in adults and children

Search done on 05/01/2023 in MEDLINE via Pubmed.

(("Migraine Disorders"[Mesh] OR migraine*[TIAB])
AND
("Acetaminophen"[Mesh] OR acetaminophen[tiab] OR paracetamol[tiab] OR
"Aspirin"[Mesh] OR aspirin*[tiab] OR acetylsalicylic acid[tiab] OR

"Caffeine"[Mesh] OR caffein*[tiab] OR
"Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR
Cyclooxygenase[tiab] OR COX-2[tiab] OR coxib*[tiab] OR (Non-steroidal[tiab] OR nonsteroidal[tiab] AND anti-inflammatory[tiab]) OR NSAID*[tiab] OR
Diclofenac[tiab] OR Ibuprofen[tiab] OR Naproxen[tiab] OR "Diclofenac"[Mesh] OR "Ibuprofen"[Mesh] OR "Naproxen"[Mesh] OR
"Antiemetics"[Mesh] OR "Metoclopramide"[Mesh] OR "Domperidone"[Mesh] OR antiemetic*[tiab] OR nausea*[tiab] OR vomit*[tiab] OR metoclopramid*[tiab] OR domperidon*[tiab] OR alizaprid*[tiab] OR
"Serotonin 5-HT1 Receptor Agonists"[Mesh] OR "Sumatriptan"[Mesh] OR *triptan*[tiab] OR almotriptan[tiab] OR eletriptan[tiab] OR frovatriptan[tiab] OR naratriptan[tiab] OR rizatriptan[tiab] OR zolmitriptan[tiab] OR sumatriptan[tiab] OR
"Calcitonin Gene-Related Peptide Receptor Antagonists"[Mesh] OR rimegepant[tiab] OR ubrogepant[tiab] OR atogepant[tiab])

AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

AND
("2021/01/01"[Date - Publication] : "3000"[Date - Publication]))

OR

(("Migraine Disorders"[Mesh] OR migraine*[TIAB])
AND
("Adrenergic beta-Antagonists"[Mesh] OR "Propranolol"[Mesh] OR "Metoprolol"[Mesh] OR "Atenolol"[Mesh] OR "Timolol"[Mesh] OR "Bisoprolol"[Mesh] OR beta-antagonist*[tiab] OR beta blocker*[tiab] OR propranolol[tiab] OR metoprolol[tiab] OR atenolol[tiab] OR timolol[tiab] OR bisoprolol[tiab] OR

"Angiotensin II Type 1 Receptor Blockers"[Mesh] OR "Telmisartan"[Mesh] OR candesartan[tiab] OR telmisartan[tiab] OR
"Calcium Channel Blockers"[Mesh] OR "Verapamil"[Mesh] OR "Flunarizine"[Mesh] OR verapamil[tiab] OR flunarizin*[tiab] OR
"Anticonvulsants"[Mesh] OR "Valproic Acid"[Mesh] OR "Lamotrigine"[Mesh] OR "Topiramate"[Mesh] OR Antiepileptic*[tiab] OR Anticonvuls*[tiab] OR Valproic[tiab] OR Valproat*[tiab] OR Lamotrigine[tiab] OR Topiramate[tiab] OR
Antidepress*[tiab] OR TCA[tiab] OR (tricyclic[tiab] AND antidepress*[tiab]) OR Amitriptylin*[tiab] OR Venlafaxin*[tiab] OR "Antidepressive Agents"[Mesh] OR “Antidepressive Agents, Tricyclic"[Mesh] OR "Amitriptyline"[Mesh] OR "Venlafaxine Hydrochloride"[Mesh] OR "Serotonin and Noradrenaline Reuptake Inhibitors"[Mesh] OR
"Calcitonin Gene-Related Peptide Receptor Antagonists"[Mesh] OR rimegepant[tiab] OR ubrogepant[tiab] OR atogepant[tiab] OR
"Magnesium"[Mesh] OR "Melatonin"[Mesh] OR "Riboflavin"[Mesh] OR magnesium[tiab] OR coenzyme Q10[tiab] OR coenzyme Q 10[tiab] OR melatonin*[tiab] OR riboflavin*[tiab] OR vitamin B2[tiab] OR vitamin B 2[tiab] OR lactoflavin*[tiab] OR "Folic Acid"[Mesh] OR folic acid[tiab] OR vitamin B9[tiab] OR vitamin B 9[tiab])

AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

AND
("2012/04/01"[Date - Publication] : "3000"[Date - Publication]))
OR

((("Migraine Disorders"[Mesh] OR migraine*[TIAB]) AND ("Child"[Mesh] OR "Adolescent"[Mesh] OR child*[tiab] or adolescen*[tiab] or infant*[tiab] or juvenile*[tiab] or pediatric*[tiab] or paediatric*[tiab]))
AND
("Acetaminophen"[Mesh] OR acetaminophen[tiab] OR paracetamol[tiab] OR
"Aspirin"[Mesh] OR aspirin*[tiab] OR acetylsalicylic acid[tiab] OR
"Caffeine"[Mesh] OR caffein*[tiab] OR
"Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR
Cyclooxygenase[tiab] OR COX-2[tiab] OR coxib*[tiab] OR (Non-steroidal[tiab] OR nonsteroidal[tiab] AND anti-inflammatory[tiab]) OR NSAID*[tiab] OR
Diclofenac[tiab] OR Ibuprofen[tiab] OR Naproxen[tiab] OR "Diclofenac"[Mesh] OR "Ibuprofen"[Mesh] OR "Naproxen"[Mesh] OR"Antiemetics"[Mesh] OR "Metoclopramide"[Mesh] OR
"Domperidone"[Mesh] OR antiemetic*[tiab] OR nausea*[tiab] OR vomit*[tiab] OR metoclopramid*[tiab] OR domperidon*[tiab] OR
"Serotonin 5-HT1 Receptor Agonists"[Mesh] OR "Sumatriptan"[Mesh] OR sumatriptan*[tiab])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

AND

("2016/01/01"[Date - Publication] : "3000"[Date - Publication]))
OR

(((("Migraine Disorders"[Mesh] OR migraine*[TIAB]) AND ("Child"[Mesh] OR "Adolescent"[Mesh] OR child*[tiab] or adolescen*[tiab] or infant*[tiab] or juvenile*[tiab] or pediatric*[tiab] or paediatric*[tiab]))
AND
("Magnesium"[Mesh] OR "Riboflavin"[Mesh] OR magnesium[tiab] OR riboflavin*[tiab] OR vitamin B2[tiab] OR vitamin B 2[tiab] OR lactoflavin*[tiab])

AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

AND
("2018/06/01"[Date - Publication] : "3000"[Date - Publication]))

17.2 Specific searches

Specific searches for those treatments excluded by our source documents.

17.2.1 Caffeine

(("Migraine Disorders"[Mesh] OR migraine*[TIAB])
AND
("Caffeine"[Mesh] OR caffein*[tiab])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB]))

17.2.2 Flunarizine

(("Migraine Disorders"[Mesh] OR migraine*[TIAB])
AND
("Calcium Channel Blockers"[Mesh] OR "Flunarizine"[Mesh] OR flunarizin*[tiab])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB]))

17.2.3 Supplements

(("Migraine Disorders"[Mesh] OR migraine*[TIAB])
AND
("Magnesium"[Mesh] OR "Melatonin"[Mesh] OR "Riboflavin"[Mesh] OR magnesium[tiab] OR coenzyme Q10[tiab] OR coenzyme Q 10[tiab] OR melatonin*[tiab] OR riboflavin*[tiab] OR vitamin B2[tiab] OR vitamin B 2[tiab] OR lactoflavin*[tiab] OR "Folic Acid"[Mesh] OR folic acid[tiab] OR vitamin B9[tiab] OR vitamin B 9[tiab])

AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB]))

17.3 Cardiovascular adverse events in older people with migraine

(("Migraine Disorders"[Mesh] OR migraine*[TIAB]) AND ("Aged"[Mesh] OR elder*[tiab] OR old[tiab] OR olde*[tiab] OR geriatric[tiab] OR aged[tiab] OR late-life[tiab] OR later-life[tiab] OR 65[tiab] OR 80[tiab]))
AND
("Acetaminophen"[Mesh] OR acetaminophen[tiab] OR paracetamol[tiab] OR
"Aspirin"[Mesh] OR aspirin*[tiab] OR acetylsalicylic acid[tiab] OR
"Caffeine"[Mesh] OR caffein*[tiab] OR
"Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR
Cyclooxygenase[tiab] OR COX-2[tiab] OR coxib*[tiab] OR (Non-steroidal[tiab] OR nonsteroidal[tiab] AND anti-inflammatory[tiab]) OR NSAID*[tiab] OR
Diclofenac[tiab] OR Ibuprofen[tiab] OR Naproxen[tiab] OR "Diclofenac"[Mesh] OR "Ibuprofen"[Mesh] OR "Naproxen"[Mesh] OR
"Antiemetics"[Mesh] OR "Metoclopramide"[Mesh] OR "Domperidone"[Mesh] OR antiemetic*[tiab] OR nausea*[tiab] OR vomit*[tiab] OR metoclopramid*[tiab] OR domperidon*[tiab] OR alizaprid*[tiab] OR
"Serotonin 5-HT1 Receptor Agonists"[Mesh] OR "Sumatriptan"[Mesh] OR *triptan*[tiab] OR almotriptan[tiab] OR eletriptan[tiab] OR frovatriptan[tiab] OR naratriptan[tiab] OR rizatriptan[tiab] OR zolmitriptan[tiab] OR sumatriptan[tiab] OR
"Calcitonin Gene-Related Peptide Receptor Antagonists"[Mesh] OR rimegepant[tiab] OR ubrogepant[tiab] OR atogepant[tiab]
OR
"Adrenergic beta-Antagonists"[Mesh] OR "Propranolol"[Mesh] OR "Metoprolol"[Mesh] OR "Atenolol"[Mesh] OR "Timolol"[Mesh] OR "Bisoprolol"[Mesh] OR beta-antagonist*[tiab] OR beta blocker*[tiab] OR propranolol[tiab] OR metoprolol[tiab] OR atenolol[tiab] OR timolol[tiab] OR bisoprolol[tiab] OR
"Angiotensin II Type 1 Receptor Blockers"[Mesh] OR "Telmisartan"[Mesh] OR candesartan[tiab] OR telmisartan[tiab] OR

"Calcium Channel Blockers"[Mesh] OR "Verapamil"[Mesh] OR "Flunarizine"[Mesh] OR verapamil[tiab] OR flunarizin*[tiab] OR
"Anticonvulsants"[Mesh] OR "Valproic Acid"[Mesh] OR "Lamotrigine"[Mesh] OR "Topiramate"[Mesh] OR Antiepileptic*[tiab] OR Anticonvuls*[tiab] OR Valproic[tiab] OR Valproat*[tiab] OR Lamotrigine[tiab] OR Topiramate[tiab] OR
Antidepress*[tiab] OR TCA[tiab] OR (tricyclic[tiab] AND antidepress*[tiab]) OR Amitriptylin*[tiab] OR Venlafaxin*[tiab] OR "Antidepressive Agents"[Mesh] OR "Antidepressive Agents, Tricyclic"[Mesh] OR "Amitriptyline"[Mesh] OR "Venlafaxine Hydrochloride"[Mesh] OR "Serotonin and Noradrenaline Reuptake Inhibitors"[Mesh] OR
"Calcitonin Gene-Related Peptide Receptor Antagonists"[Mesh] OR rimegepant[tiab] OR ubrogepant[tiab] OR atogepant[tiab] OR
"Magnesium"[Mesh] OR "Melatonin"[Mesh] OR "Riboflavin"[Mesh] OR magnesium[tiab] OR coenzyme Q10[tiab] OR coenzyme Q 10[tiab] OR melatonin*[tiab] OR riboflavin*[tiab] OR vitamin B2[tiab] OR vitamin B 2[tiab] OR lactoflavin*[tiab] OR "Folic Acid"[Mesh] OR folic acid[tiab] OR vitamin B9[tiab] OR vitamin B 9[tiab])

AND
("Cardiovascular Diseases"[Mesh] OR "Stroke"[Mesh] OR "Myocardial Infarction"[Mesh] OR cardiovascular[tiab] OR heart disease*[tiab] OR stroke[tiab] OR Myocardial[tiab] OR cardiac*[tiab] OR coronary[tiab] OR angina[tiab] OR mortality[tiab] OR CVA[tiab] OR TIA[tiab] OR cerebrovascular[tiab])

AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB] OR "Epidemiologic Studies"[Mesh] OR "Observational Study" [Publication Type] OR "Comparative Study" [Publication Type] OR "Cohort Studies"[Mesh] OR Cohort*[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB] OR observational[TIAB])

18 Appendix. Excluded references

References that were excluded after consulting the full text.

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