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Comité voor de evalutie van de medische praktijk inzake geneesmiddelen

The rational use of non-opioid analgesics for chronic pain

Literature review: full report

Consensus conference
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1 Abbreviations

AE: adverse events
ARR: absolute risk reduction
BOCF: baseline observation carried forward
BPI: Brief pain inventory
CI: confidence interval
CO: crossover RCT
DB: double blind
EQ-5D: EuroQol 5 dimensions
HR: hazard ratio
HRQoL: Health Related Quality of Life
ITT: intention-to-treat analysis
LBP: low back pain
LOCF: last observation carried forward
LSM: least square means
LSMD: least square mean difference
MA: meta-analysis
MCID: minimally clinically important difference
MD: mean difference
n: number of patients
N: number of studies
NNH: number needed to harm
NNT: number needed to treat
NR: not reported
NRS: Numeric rating scale
NS: not statistically significant
NT: no statistical test
OA: osteoarthritis
OL: open label
PDN: painful diabetic neuropathy
PG: parallel group
PGIC: Patient Global Impression of Change
PHN: postherpetic neuralgia
PO: primary outcome
QoL: Quality of life
RMDQ: Roland Morris Disability Questionnaire
SAE: severe adverse event
SB: single blind
SD: standard deviation
SF-36: short form health survey (36 items)
SO: secondary outcome
SS: statistically significant

TEAE: treatment-emergent AE
VAS: Visual Analogue Scale
WOMAC: Western Ontario and McMaster Universities Arthritis Index

2 Methodology

2.1 Introduction

This systematic literature review was conducted in preparation of the consensus conference "The rational use of non-opioid analgesics for the treatment of chronic pain", which will take place on the 5th of december 2019.

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. Wat is de definitie van chronische pijn ? *(zie vorige consensusvergadering – korte samenvatting)*
1. Quelle est la définition de la douleur chronique ? (cf. réunion de consensus précédente – résumé succinct)

2. Wat is de plaats van een behandeling door middel van paracetamol en paracetamol-bevattende associaties in de multimodale behandeling van chronische pijn en verschilt deze doeltreffendheid naargelang het type van chronische pijn dat behandeld moet worden?
2. Quelle place occupent un traitement au paracétamol et les associations à base de paracétamol dans le traitement multimodal de la douleur chronique ? L'efficacité réelle diffère-t-elle selon le type de douleur chronique à traiter ?

2a. Wat is de correcte dosering bij de behandeling van chronische pijn en behoeven sommige pijntypes specifieke toedieningsschema's?
2a. Quelle est la posologie correcte pour le traitement de la douleur chronique et certains types de douleur nécessitent-ils des schémas d'administration spécifiques ?

2b. Wat zijn de ongewenste effecten van paracetamol bij chronische pijn, zowel op korte termijn als op lange termijn?
2b. Quels sont les effets indésirables du paracétamol dans le traitement de la douleur chronique, tant à court terme qu'à long terme ?

3. Wat is de plaats van de verschillende ontstekingsremmers (selectieve en niet-selectieve NSAID's en acetylsalicylzuur) in de multimodale behandeling van chronische pijn en verschilt deze doeltreffendheid naargelang het type van chronische pijn dat behandeld moet worden?
3. Quelle place occupent les différents anti-inflammatoires (AINS sélectifs et non sélectifs et acide acétylsalicylique) dans le traitement multimodal de la douleur chronique ? L'efficacité réelle diffère-t-elle selon le type de douleur chronique à traiter ?

3a. Wat is het belang van de gebruikte galenische vorm?
3a. Quelle est l'importance de la forme galénique utilisée ?

3b. Wat is het belang van een correcte dosering voor het klinisch effect en het veiligheidsprofiel?

3b. Quelle est l'importance d'une posologie correcte pour l'effet clinique et le profil de sécurité ?

4. Wat is het profiel van de ongewenste effecten van de verschillende selectieve en niet-selectieve NSAID's bij de behandeling van chronische pijn?
4. Quel est le profil des effets indésirables des différents AINS sélectifs et non sélectifs dans le traitement de la douleur chronique ?

4a. Wat is het belang van de gebruikte galenische vorm?
4a. Quelle est l'importance de la forme galénique utilisée ?

4b. Wat is het risico van een chronisch off-label gebruik?
4b. Quel est le risque d'une utilisation chronique « off-label » ?

5. Wat is de plaats van adjuvantia in de multimodale behandeling van chronische pijn?
5. Quelle place occupent les adjuvants dans le traitement multimodal de la douleur chronique ?

5a. Zijn de doeltreffendheid en ongewenste effecten afhankelijk van het te behandelen pijntype?
5a. L'efficacité réelle et les effets indésirables dépendent-ils du type de douleur à traiter ?

6. Noodzaken sommige patiëntenpopulaties (patiënten met leverinsufficiëntie, nierinsufficiëntie of met cardiale insufficiëntie, adolescenten, zwangeren, ouderen, patiënten met psychiatrische comorbiditeit) een bijzondere aandacht bij het gebruik van paracetamol, NSAID's en adjuvantia?
6. Certaines populations de patients (patients avec insuffisance hépatique, rénale ou cardiaque, adolescents, femmes enceintes, personnes âgées, patients avec comorbidité psychiatrique) nécessitent-elles une attention particulière pour l'utilisation de paracétamol, d'AINS et d'adjuvants ?

6a. Bestaan er specifieke contra-indicaties?
6a. Y a-t-il des contre-indications spécifiques ?

6b. Moeten bepaalde beschermingsmaatregelen in acht worden genomen (moment van inname, gebruik van PPI's,…)?
6b. Certaines mesures de protection doivent-elles être prises en compte (moment de prise, utilisation d'IPP, …) ?

7. Wat is de plaats van topicale toediening van analgetica in de multimodale behandeling van chronische pijnsyndromen?
7. Quelle est la place de l'administration topique d'analgésiques dans le traitement multimodal des syndromes douloureux chroniques ?

7a. Is de doeltreffendheid verschillend naargelang het te behandelen pijntype?
7a. L'efficacité réelle diffère-t-elle selon le type de douleur à traiter ?

7b. Wat is het veiligheidsprofiel van topicale behandelingen ten opzichte van systemische behandelingen?
7b. Quel est le profil de sécurité des traitements topiques par rapport aux traitements systémiques ?

8. Wat is de plaats van voedingssupplementen (curcumine, chondroïtine, hyaluronzuur e.a.) in de multimodale behandeling van chronische pijn?
8. Quelle place occupent les suppléments alimentaires (curcumine, chondroïtine, hyaluronate, etc.) dans le traitement multimodal de la douleur chronique ?

8a. Bestaat er evidentie rond een verschillende doeltreffendheid naargelang het pijntype?
8a. Existe-t-il des faits probants d'une efficacité réelle différente selon le type de douleur ?

8b. Wat zijn de ongewenste effecten bij langdurig gebruik in het kader van chronische pijn?
8b. Quels sont les effets indésirables en cas d'utilisation prolongée dans le cadre de la douleur chronique ?+

9a. Is er een plaats voor paracetamol en NSAID's in de vrije verkoop?
9a. Y-a-t-il une place en vente libre pour le paracétamol et les AINS ?

9b. Is er een plaats voor magistrale bereidingen?
9b. Y-a-t-il une place pour des préparations magistrales ?

9c. Is het actuele vergoedingssysteem voor niet-opioïde analgetica adequaat?
9c. Le système de remboursement actuel pour les analgésiques non opioïdes est-il adéquat ?

9d. Wat is de plaats van vaste of losse associaties van analgetica in de aanpak van chronische pijn?
9d. Quelle place occupent les associations fixes ou libres d'analgésiques dans le traitement de la douleur chronique ?

9e. Welk farmacologisch advies en opvolging moet door de apotheker verstrekt worden aan de patiënten bij aflevering?
9e. Quels avis et suivi pharmacologiques le pharmacien doit-il donner aux patients lors de la délivrance du médicament ?

Table 1

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** to provide an answer to certain research question.

See 2.3.2 for information on study type inclusion criteria and 2.3.3 for search details.

To search and report **observational studies** for selected safety endpoints.

See 2.3.2 for inclusion criteria for observational studies 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 2.3.2 for information on additional sources.

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 2014 onwards are to be selected.

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 (or observational studies for certain research questions)
- Reporting of clinically relevant outcomes (that match our selected outcomes)
- Only direct comparisons (no network meta-analyses)

If a meta-analysis does not match all the inclusion criteria for our Consensus Conference literature review (for example: it may include some studies with shorter study duration, 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
- Blinding: unblinded (open-label) studies will not be included
- Duration: Minimum duration of follow-up: 6 weeks.
- 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 (cohort) studies

- Observational studies will only be searched for pulmonary adverse events of paracetamol
- Prospective or retrospective **cohort** studies
- Minimum number of participants: 1000
- For other selected adverse events only **systematic reviews** of observational studies will be sought.

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(1) / Répertoire Commenté des Médicaments*
  - *Folia Pharmacotherapeutica*
- Martindale: The complete drug reference, 39th edition(2)

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 Populations

The following populations are to be discussed:

- Adults with chronic pain (≥ 3 months).

Exclusions:

- Acute pain (musculoskeletal, postoperative,…)
- Inflammatory diseases
- Headache, migraine
- Fibromyalgia
- Complex regional pain syndrome
- Palliative situations
- Children

The safety outcomes of following subgroups are of special interest (although no specific systematic search for subgroup analyses will be performed; information to be reported from guidelines):

- patients with liver disease

- patients with chronic kidney disease
- patients with cardiac disease
- elderly patients
- adolescents
- pregnant patients

2.3.3.2 Interventions

The following medications, available in Belgium, are to be reported from RCTs (or systematic reviews/meta-analyses of RCTs):

Paracetamol	Paracetamol
NSAID (oral)	Acetylsalicylic acid Diclofenac Dexketoprofen Ibuprofen Naproxen Celecoxib Etoricoxib Nabumetone
Antidepressive agents	**TCA** Amitriptyline Nortriptyline **SNRI** Duloxetine Venlafaxine
Anticonvulsants	Carbamazepine Gabapentin Pregabalin
Topical analgesics	Capsaicin Lidocaine Prilocaine Tetracaine DMSO (dimethyl sulfoxide) Diclofenac Indometacin Ibuprofen Ketoprofen Piroxicam Etofenamate Niflumic acid
Other In oral or topical form	Curcumin Glucosamine Chondroitin Hyaluronic acid

	Traumeel

Excluded from the literature review are

- Opioids
- Benzodiazepines
- Cannabinoids
- Baclofen
- Fixed-dose combinations
- Pharmaceutical formulations that are not available on the Belgian market.
- Any form of administration other than oral or topical

2.3.3.3 Comparisons

Paracetamol

- vs placebo
- vs NSAID (class)
- vs ibuprofen

NSAID

- acetylsalicylic acid vs placebo
- COX-selective NSAID (celecoxib and etoricoxib) vs placebo
- Non-COX-selective NSAID (group) vs placebo
- direct comparisons of a COX-selective NSAID and a non-COX-selective NSAID (individual products): celecoxib vs ibuprofen, naproxen, diclofenac, nabumetone, dexketoprofen

Antidepressive agents

- vs placebo
- direct comparisons of amitriptyline, duloxetine, venlafaxine, nortriptyline

Anticonvulsants

- vs placebo
- direct comparisons of carbamazepine, gabapentin, pregabalin

Topical medication

- vs placebo
- vs oral non-opioid analgesic medication

Other (curcumin, glucosamine, chondroitin, hyaluronic acid, Traumeel)

- vs placebo
- vs oral or topical non-opioid analgesic medication

2.3.3.4 Endpoints

The following endpoints are to be reported from RCTs or systematic reviews/meta-analyses of RCTs:

Efficacy
Functioning Pain Quality of life Opioid-sparing effect
Safety
Adverse events

The following safety endpoints are to be reported from systematic reviews of observational studies and individual cohort studies:

Respiratory endpoints (paracetamol only)

The following safety endpoints are to be reported from systematic reviews of observational studies:

For paracetamol:

- Hepatic adverse events

For NSAIDs:

- Gastrointestinal adverse events
- Renal adverse events
- Cardiovascular adverse events

Adverse events for topical vs oral NSAIDs

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 (and sometimes observational studies) that were published after the search date of our selected systematic reviews.

Guidelines were searched through the link "evidence-based guidelines" on the website of CEBAM (www.cebam.be). These contain links to the national and most frequently consulted international guidelines, as well as links to 'guideline search engines', like G-I-N.

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
Paracetamol	Saragiotto 2016(3)
NSAID	Moore 2015(4)
Antidepressants	Finnerup 2015(5)
Anticonvulsants	Wiffen 2013(6)
Capsaicin	Derry 2012(7)
Lidocaine	Derry 2014(8)
Curcumin	Perkins 2017(9)
Chondroitin	Singh 2015(10)
Glucosamine	Towheed 2005(11)
Nabumetone Dexketoprofen DMSO Topical NSAIDs Traumeel Hyaluronic acid	No adequate source document found, search without starting date

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 May 2019. If no source document could be found, a search of Medline without a starting date was performed.

2.4.3 Search strategy details

The full search strategies can be found in chapter 18.

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 chapter 1.1.2 with relevant populations, interventions, endpoints and study criteria.
The list of articles excluded after reading of the full text can be found in chapter 19.

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 RCT's 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 RCT's, 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.
Introduction

3 Critical reflections of the reading committee and the literature group

3.1 Remarks from the reading committee

The literature review shows that in the selected studies insufficient data are present to make proper considerations about the role of non-opioid analgesics in the multimodal treatment of chronic pain. There is little information in the guidelines about the multidisciplinary approach of chronic pain in a bio-psycho-social context, involving, among others, psychotherapists, occupational therapists, psychologists, …

The Reading Committee would therefore like the following remarks to be taken into consideration by the Jury.

> As the balance of advantage/ adverse effects is often undetermined at an individual level, **a patient-centered approach** is necessary, taking into account the patient's values and priorities, and considering function as much as pain. The risk of adverse effects could be acceptable if a treatment increases a patient's autonomy.
>
> The purpose of the treatment is thus not always to eliminate the pain, but to reduce it to an acceptable level, and **to allow the patient to achieve what is most important for him**.
>
> In prescribing pain medication it is important to evaluate pain attitudes, pain cognitions, emotional consequences of living with the pain, the meaning of these consequences, and the capacity the patient has to manage the pain and the consequences in his close and social relationships.
>
> Psychological factors, such as depression, anxiety and distress, are associated with pain intensity. Depression is highly prevalent in chronic pain. Psychological factors can be both a prognostic and maintaining factor of chronic pain.
>
> Furthermore, pain is often considered as a signal of something bad happening, which in turn makes patients anxious. In some cases, an explanation of what is happening may be enough make it tolerable.
>
> It is therefore important to **pay attention to the emotional state of the patient early on when prescribing analgesics** for pain. This could make a multimodal approach more acceptable to the patient and help to prevent pain from becoming a chronic condition.

3.2 Types of chronic pain

We searched for information on all types of chronic pain (with the exception of some excluded populations, see 'methodology'). Most of the studies that met our inclusion criteria were conducted in patients with **musculoskeletal pain** (i.e. osteoarthritis of the knee or hip and low back pain).

Neuropathic pain was mainly represented by painful diabetic neuropathy and postherpetic neuralgia.

For **cancer pain**, no trial met our inclusion criteria, mostly due to short trial duration.

3.3 Study duration

Many trials, even those in chronic pain, are of short duration. To assess the possible long-term use of analgesics in a chronic pain situation we would need trials with long-term use.

The Organizing committee chose a minimal treatment duration of 6 weeks as an inclusion criterion for this literature review. One could argue that 6 weeks is still quite short to assess long-term treatment.

3.4 Population

In the trials, serious comorbidities are generally a cause for exclusion. The patients in the trials are, in general, healthier than patients with the same symptoms in a real-life population.

Most of the subgroups of interest, such as patients with hepatic or renal insufficiency, cardiac morbidity, adolescents, pregnant women, the very elderly, and patients with psychiatric comorbidity, are not included and often outright excluded from the clinical trials. Results from these trials can therefore not be extrapolated to these populations.

In our 'guidelines' section, we report age-specific guidance recommendations, as well as recommendations for patients with renal or hepatic insufficiency, for patients with risk factors for cardiovascular or gastro-intestinal adverse events, and for pregnant women.

3.5 Interventions

As the amount of possible non-opioid analgesics and types of chronic pain were substantial, certain drugs and comparisons were selected by the Organising committee (see chapter "Methodology"). It is possible certain relevant comparisons were not covered in this document.

3.6 Outcomes

3.6.1 Pain

There was quite a variability in reporting pain outcomes in the trials. Often a 0-100 mm VAS scale was used, but the way the results were presented was not consistent between trials, which makes it more difficult to interpret the results.

Some authors state that the mean change on a pain-scale is not an ideal way to report pain outcomes, because mean results usually do not describe the experience of a typical patient in a trial. The percentage of responders (patients who achieve a predefined reduction in pain score, e.g. 30% or 50 %) would be a more robust way of measuring efficacy of analgesics.

Placebo-response can be quite high in trials that evaluate analgesic drugs.

3.6.2 Function and quality of life

Functional outcomes and quality of life outcomes were reported less frequently than pain outcomes.

There are many different instruments for measuring disability, functioning and quality of life, which are usually divided into different subdomains. This makes it more difficult to interpret the results. Meta-analyses sometimes try to standardize the results.

In some questionnaires, both function and quality of life are assessed throughout the different subdomains.

For example, the SF-36 (36- item Short form health survey) assesses quality of life in different physical and mental dimensions, for which summarized scores can be made, for example a physical component score and a mental component score. Some authors report the scores on the physical components under ‘functional outcomes’, others report these as ‘quality of life’ outcomes.

The lack of consistency of this important outcome variable restricts the interpretation of the results of these studies in a context the of multimodal approach of chronic pain.

3.6.3 Adverse events

It is difficult to draw conclusions from adverse events reported in RCTs, since they are usually set up in a way to minimize adverse events.

Some adverse events are rare occurrences. The less common they are, the longer and/or larger the studies need to be to identify a difference between active and control group.

To assess rare adverse events, we included observational studies (cohort studies). An observational study cannot prove a causal link, it can merely establish an association between the treatment and a specific outcome. The quality of evidence in the GRADE approach for observational studies is LOW by default, although upgrading or downgrading according to certain rules is possible.

Results from observational studies are very sensitive to hidden bias. Results are generally statistically adjusted to correct for confounders, but not all possible confounders are known or measured.

In the observational studies used to assess safety of analgesics, the indication for analgesic use was not always chronic pain. In some the indication was acute pain, fever, or even cancer prevention. In many large database studies the indication was not specified and all patients receiving a prescription for the analgesic at interest were included. It is not clear whether patients with chronic pain are at an additional risk of adverse events.

In chapter 11 "Additional safety information from other sources", we report information from BCFI/CBIP sources and from Martindale (39th) edition as an addition to the information that was reported in the observational studies included in our review.

3.7 Some methodological issues explained

3.7.1 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 (e.g. patients with different kinds of neuropathic pain), 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.

3.7.2 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. Some authors have tried to propose thresholds for clinical relevance.

The point estimate, as well as the upper and lower boundary of the confidence interval is then examined in relation to this threshold.

For pain outcomes, some authors in our included studies defined a minimal clinically relevant difference for pain as a change of 10 mm on a 100 mm VAS scale. For function, some defined this as a 5 point difference on a 100 point scale.

It will be up to the jury to consider the results of the trials in this report in the light of clinical relevance.

3.7.3 Primary endpoint – secondary endpoint

Studies are designed around a primary endpoint. Secondary endpoints can be considered as supportive evidence of the primary outcome, if the result of the primary outcome is statistically significant. When there is a large number of secondary outcomes, there is a higher risk that some secondary outcomes become false positive, due to chance. In a trial design, adjustments should be made for dealing with multiple comparisons (Bonferroni correction).

In most trials however, this was not the case.

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 the table below.

Abbreviation	Guideline
NHG 2018	De Jong L, Jansen P, Keizer D, Köke A, Schiere S, Van Bommel M, et al. NHG-Standaard Pijn. Huisarts en Wetenschap 2015 (herziening 2018): https://www.nhg.org/standaarden/volledig/nhg-standaard-pijn.(12)
WOREL 2017	Henrard G, Cordyn S, Chaspierre A, Kessels T, Mingels S, Vanhalewyn M. Aanpak van Chronische pijn in de eerste lijn. EBM Practice Net Werkgroep ontwikkeling richtlijnen eerste lijn 2017. (13) Henrard G, Cordyn S, Chaspierre A, et al. Prise en charge de la douleur chronique en première ligne de soins. EBM Practice Net groupe de travail réalisation de recommandations de première ligne 2017. (13)
NICE 2017	NICE National Institute for Health and Care Excellence. Neuropathic pain – pharmacological management. The pharmacological management of neuropathic pain in adults in non-specialist settings. NICE clinical guideline 173 2013 (updated 2017). (14)
ASCO 2016	Guideline on Chronic Pain Management in Adult Cancer Survivors. (15)
DOH_Ireland 2015	Pharmacological management of cancer pain in adults: national clinical guideline no 9. (16)

Table: 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 the tables below.

NHG 2018		
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	High	The true effect lies close to the estimated effect
	Moderate	The true effect probably lies close to the estimated effect, but the possibility exists that it differs substantially from it.
	Low	The true effect can differ substantially from the estimated effect.
	Very Low	The true effect probably differs substantially from the estimated effect.

Table: Grades of recommendation and Level of evidence of NHG 2018 guideline.

WOREL 2017		
Grades of recommendation:	Sterke aanbeveling (“1”)	Als artsen erg zeker zijn dat de voordelen de nadelen niet / wel waard zijn.
	Recommandation forte («1»)	Si les médecins sont tout-à-fait certains que l’application de la recommandation est davantage positive que négative
	Zwakke aanbeveling (“2”)	Als artsen geloven dat voordelen en nadelen (ongeveer) in balans zijn met elkaar, en er een redelijke onzekerheid bestaat over de grootte van de voor- en nadelen.

	Recommandation faible («2»)	Si les médecins estiment que les avantages et inconvénients sont (environ) en équilibre ou qu'il existe une incertitude quant à l'importance des avantages et des inconvénients.
	Advies van de richtlijnontwikkelingsgroep ("GPP")	geïnspireerd door de "GPP" ("Good Practice Points") van sommige Engelstalige richtlijnen, zoals SIGN, en die neerkomt op een aanbeveling op basis van de klinische ervaring van de ontwikkelingsgroep en/of als zodanig vermeld in onze geselecteerde richtlijnen.
	Recommandation du groupe de développement (« GPP »)	inspiré des « GPP » (« Good Practice Points ») de certains GPC anglophones dont SIGN, et qui équivaut à une recommandation basée sur l'expérience clinique du groupe de développement et / ou figurant comme tel dans nos GPC de référence.
Levels of evidence	Hoog (A)	verder onderzoek zal ons vertrouwen in de schatting van het effect zeer waarschijnlijk niet veranderen
	Élevée (A)	il est très improbable que des travaux de recherche futurs changent notre assurance dans l'estimation de l'effet
	Matig (B)	verder onderzoek zal waarschijnlijk een belangrijke invloed hebben op ons vertrouwen in de schatting van het effect en zou deze schatting kunnen veranderen
	Moyenne (B)	il est probable que des travaux de recherche futurs aient un impact sur notre confiance dans l'estimation de l'effet et changent l'estimation de l'effet

	Laag en zeer laag (C)	verder onderzoek zal zeer waarschijnlijk een belangrijke invloed hebben op ons vertrouwen in de schatting van het effect en zal waarschijnlijk deze schatting veranderen of eender welke schatting van het effect is zeer onzeker
	Faible et très faible (C)	il est très probable que des travaux de recherche futurs aient un impact important sur notre confiance dans l'estimation de l'effet et changent probablement l'estimation de cet effet, ou toute estimation de l'effet est très incertaine

Table: Grades of recommendation and Level of evidence of the WOREL 2017 guideline.

NICE 2017		
Grades of recommendation:	The NICE 2017 guideline does not explicitly attribute grades of recommendation. However, evidence statements are provided based on GRADE- tables. The grade of recommendation are expressed in the wording of the recommendation itself (i.e. using words as "offer" or "advise" in strong recommendations and "consider" in weaker recommendations).	
Levels of evidence	High	According to GRADE (assessment of risk of bias, directness, consistency and precision of the estimates)
	Moderate	
	Low	
	Very Low	

Table: Grades of recommendation and Level of evidence of NICE 2017 guideline.

ASCO 2016		
Grades of recommendation:	Strong	This indicates that all or almost all fully informed patients would choose the recommended course of action, and indicates to clinicians that the recommendation is appropriate for all or almost all individuals. Strong recommendations represent candidates for quality of care criteria or performance indicators.
	Weak	This indicates that the majority of informed patients would choose the suggested course of action, but an appreciable minority would not. With weak recommendations, clinicians should recognize that different choices will be appropriate for individual patients, and should assist

		patients to arrive at a decision consistent with their values and preferences. Weak recommendations should not be used as a basis for Standards of Practice (other than to mandate shared decision-making).
Levels of evidence	High	According to GRADE (assessment of risk of bias, indirectness, inconsistency, precision and publication bias)
	Moderate	
	Low	
	Very Low	

Table: Grades of recommendation and Level of evidence of ASCO 2016 guideline.

DOH_Ireland 2015		
Grades of recommendation:	A	Level 1 studies
	B	Level 2 or 3 studies
	C	Level 4 studies
	D	Level 5 studies or inconsistent or inconclusive studies of any level
Levels of evidence Based on the CEBM (Centre for Evidence Based Medicine) method of Oxford University	Level 1a	Meta analyses of randomised control trials (RCT)
	Level 1a	At least one RCT
	Level 2a	At least one well designed controlled study without randomisation or systematic review (SR) of cohort studies
	Level 2b	A well designed cohort study
	Level 3	Well designed experimental descriptive studies, such as case control or cross sectional studies
	Level 4	Case series
	Level 5	Expert Committee/Clinical experience

Table: Grades of recommendation and Level of evidence of DOH_Ireland 2015 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 the table below. 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
NHG 2018	7	4	5	5	6	7	6	3	**43**	**77%**
WOREL 2017	4	2	3	3	5	5	5	5	**32**	**57 %**
NICE 2017	7	6	6	6	6	6	6	7	**50**	**89%**
ASCO 2016	7	6	6	5	6	6	5	7	**48**	**86%**
DOH_Ireland 2015	5	4	6	6	6	6	7	7	**47**	**84%**

Table: 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.

NHG 2018	
Population	- Adults and children with acute pain - Adults with chronic pain, neuropathic pain - Adults with pain in the palliative setting
Interventions	- Medical treatment according to the WHO pain ladder - other treatments: physiotherapy, psychological interventions
Outcomes	Not specified

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

WOREL 2017	
Population	Deze richtlijn is van toepassing op patiënten met chronische pijn in de eerste lijn, met uitzondering van kinderen, kankerpatiënten of palliatieve patiënten. Deze richtlijn gaat niet in op chronischepijnsyndromen typisch voor een specifieke situatie (zoals postoperatieve pijn) of anatomische plaats (zoals hoofdpijn, chronische nekpijn of het begrip "complex regionaal pijnsyndroom).
	La population ciblée par ce GPC concerne les patients souffrant de douleur chronique. Sont exclus les patients pédiatriques, cancéreux ou suivis en soins palliatifs. Ce guide n'aborde pas spécifiquement des syndromes douloureux chroniques propres à une situation particulière (comme par exemple les douleurs post-opératoires) ou à une localisation anatomique particulière (comme par exemple les céphalées ou encore les cervicalgies chroniques ou de manière générale la notion de « syndrome régional douloureux complexe »).
Interventions	- Non-pharmaceutical interventions (physiotherapy, exercise, TENS, low level laser therapy (LLLT)) - Psychological interventions (pain education, relaxation, cognitive behavioral therapy, mindfulness) - Alternative treatment (acupuncture, diet therapy) - Pharmaceutical interventions: - Paracetamol - NSAIDs, topical NSAIDs

	- Weak opioids (codeine, tramadol) - Strong opioids - Anticonvulsants (gabapentin, pregabalin) - Anti-depressants (amitriptyline, duloxetine) - Multidisciplinary programs
Outcomes	Exact outcomes were not always clear since this guideline was based on three other selected guidelines and an additional search in the Cochrane library.

Table: Included population, intervention and main outcomes of the WOREL 2017 guideline.

NICE 2017	
Population	Adults with neuropathic pain in non-specialist settings The guideline decided to categorise neuropathic pain into 3 broad groups: central neuropathic pain, peripheral neuropathic pain, and trigeminal neuralgia. In addition, an overarching analysis was conducted for 'all pain'.
Interventions	- 43 different pharmacological treatment (including opioids) vs placebo - the comparison of the individual pharmacological treatments with each other - combination therapy vs monotherapy or other combination therapy
Outcomes	Critical outcomes: - Patient-reported global improvement - Patient-reported improvement in daily physical and emotional functioning, including sleep. - Major adverse effects (defined as leading to withdrawal from treatment) Important outcomes: - Patient-reported pain relief/intensity reduction - Individual adverse effects - Use of rescue medication

ASCO 2016	
Population	Any adult who has been diagnosed with cancer and is experiencing pain that lasts ≥ 3 months, irrespective of cause.
Interventions	- Nonpharmacological treatment - physical medicine and rehabilitation

	- integrative and neurostimulatory therapies - Psychological approaches - Pharmacological treatment - Adjuvant analgesics - Cannabinoids - Opioids - Risk assessment, mitigation, and universal precautions
Outcomes	Outcomes for which significant differences were found - Pain rating (intensity/relief) - QoI - Level of function - Opioid or additional analgesic consumption - Adverse events

DOH_Ireland 2015	
Population	Adults with cancer pain Patients with non-malignant or chronic non cancer pain and children were excluded.
Interventions	- for comparisons with opioids see the full guideline
DOH_Ireland 2015	
Population	Adult patients with pain directly due to cancer and with renal or hepatic failure
Interventions	- different routes of NSAID administration - NSAID vs NSAID + PPI - topical capsaicin vs control group/placebo - Lidocaine vs other analgesics/placebo - ketamine vs other analgesics/placebo - anticonvulsants vs control group/placebo - antidepressants vs control group/placebo - benzodiazepines vs placebo/alternative analgesics - management of cancer pain in patients with cancer and renal failure vs placebo/control group - management of cancer pain in patients with cancer and hepatic failure vs placebo/control group
Outcomes	Pain scores safety
Outcomes	Pain scores Safety Patient preference Dependency

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.

NHG 2018	
Development group	The guideline development group consisted of primary care physicians, a hospice physician, a palliative care physician, an anaesthesiologist/ pain specialist, a psychologist and a physiotherapist.
Target audience	Primary care

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

WOREL 2017	
Development group	This guideline was developed on behalf of the "Werkgroep Ontwikkeling Richtlijnen Eerste Lijn", funded by the "Riziv". The guideline was validated by the Belgian centre for evidence-based medicine (CEBAM).
Target audience	Care providers in primary care: for example primary care physicians, nurses, physiotherapists, pharmacists, and psychologists.

Table: Members of the development group and target audience of the WOREL 2017 guideline.

NICE 2017	
Development group	The guideline development group consisted of an expert group (a psychiatrist, general practitioners, neurologist, a nurse consultants, a pharmacist, etc.), patient and care members, an internal clinical guideline programme technical team (e.g. health economists)
Target audience	Non-specialist setting: i.e. primary and secondary care services that do not provide specialist pain services. Non-specialist settings include general practice, general community care and hospital care.

Table: Members of the development group and target audience of the NICE 2017 guideline.

ASCO 2016	
Development group	The ASCO Clinical Practice Guidelines Committee (CPGC) convened an Expert Panel with multidisciplinary representation in medical oncology, radiation oncology, cardiology, exercise physiology, family medicine, cancer prevention, cancer

	survivorship, patient/advocacy representation, and guideline implementation. The Expert Panel was led by two Co-Chairs who had primary responsibility for the development and timely completion of the guideline. For this guideline product, the Co-Chairs selected additional members from the Update Committee to form a Writing Group/Steering Committee to assist in the development and review of the guideline drafts.
Target audience	Health care practitioners who provide care to cancer survivors.

Table: Members of the development group and target audience of the ASCO 2016 guideline.

DOH_Ireland 2015	
Development group	The Guideline Development Group (GDG) comprised of core working members who carried out the work involved in developing the guideline. Additional members of the guideline development group, senior multidisciplinary service leads assembled by the National Clinical Programme for Palliative Care and known as the Guideline Steering Group, evaluated the quality of the development process and documentation at key stages of the process.
Target audience	The National Clinical Guideline applies to healthcare professionals involved in the management of cancer pain. This includes Palliative Care staff, Physicians, Surgeons, General Practitioners, Pharmacists and Nursing staff in hospital, hospice and community-based settings. The Guideline will also be of interest to patients with cancer pain and their carers. The National Clinical Guideline does not apply to cancer survivors, to patients who do not have a cancer diagnosis or to other forms of acute or chronic non-malignant pain. The National Clinical Guideline does not apply to children.

Table: Members of the development group and target audience of the DOH_Ireland 2015 guideline.

5 Recommendations from guidelines

Formal recommendations, that are supplied with grades of recommendations or levels of evidence, are written in bold.

Although the NHG 2018 guideline uses the GRADE methodology, it does not explicitly categorizes recommendations in strong and weak recommendations. However, the strength of the recommendations is expressed in the wording of the recommendation. In this document, the recommendations including the supplemental information of the NHG 2018 guideline are shown in plain text.

Similarly, the NICE 2017 guideline uses the GRADE methodology but it does not explicitly categorizes recommendations in strong and weak recommendations. The strength of the recommendations are expressed in the wording of the recommendation. However, concise recommendations were provided and were therefore shown in bold. Supplemental information are shown in plain text.

Overview of the selected guidelines

The 5 guidelines that were selected for this evidence report on chronic pain all have a different focus. The WOREL 2017 guideline focuses on chronic non-cancer pain. The NHG 2018 guideline focuses on chronic pain in general not excluding cancer pain. The NICE 2017 guideline focuses solely on the treatment of neuropathic pain.
Two guidelines specifically focus on patients with cancer. The ASCO 2016 guideline focuses on chronic pain in patients with cancer irrespective of cause and the DOH_Ireland 2015 guideline focuses on cancer-related pain.

5.1 Paracetamol

5.1.1 Summary

The NHG 2018 guideline recommends paracetamol as first choice for mild to moderate pain. Paracetamol or topical NSAID are preferred for chronic pain due to osteoarthritis of the knee and hand. Paracetamol is not effective in neuropathic pain.
The recommended maximum daily dosage is 4g for adults when used for less than one month or for malignant disease, and 2.5g when used for more than one month.

The Worel 2017 guideline recommends to consider paracetamol alone or in combination with NSAID for pain due to osteoarthritis. A maximum daily dosage of 3g is mentioned.

The NICE 2017 guideline for neuropathic pain did not include paracetamol in its recommendations.

The ASCO 2016 guideline includes paracetamol as one of the recommended drugs to relieve chronic pain and/or improve function in cancer survivors without contraindications.

The DOH_Ireland 2015 guideline recommends paracetamol for mild to moderate cancer pain in accordance with the WHO analgesic ladder. The addition of paracetamol to high doses of step 3 opioids is not recommended.

5.1.2 NHG 2018

Kernboodschappen

- Eerstekeuspijnstiller bij lichte tot matige pijn is paracetamol in adequate dosering.
- Geef bij acute spier- en gewrichtspijn en chronische pijn als gevolg van knie- en handartrose paracetamol of een dermaal NSAID (minder bijwerkingen dan orale NSAID's).

Acute en chronische nociceptieve pijn
De huisarts volgt bij de medicamenteuze behandeling van zowel acute als chronische pijn een stapsgewijze aanpak, gebaseerd op de pijnladder van de WHO. Medicamenteuze behandeling wordt ingezet als onderdeel van een multidimensioneel (biopsychosociaal) behandelplan. Dit geldt in het bijzonder voor patiënten met chronische en neuropathische pijn. Combinaties van geneesmiddelen kunnen worden toegepast.
Stap 1: paracetamol
Stap 2: NSAID

Note from consensus authors: For step 2 see "5.2 NSAID". Step 3 to step 5 concerns the use of opioids and have been discussed in the previous consensus "the rational use of opioids for chronic pain".

Stap 1: paracetamol
Algemeen
Bij acute en chronische pijn is paracetamol voor patiënten van alle leeftijden eerste keus, omdat dit middel van de beschikbare pijnstillers het breedste veiligheidsprofiel heeft en er zeer ruime ervaring mee is opgedaan. Dit geldt in het bijzonder voor ouderen, omdat zij gevoeliger zijn voor bijwerkingen van andere analgetica zoals NSAID's. Leg uit dat paracetamol in adequate dosering de pijnstiller van voorkeur is doordat de kans op ernstige bijwerkingen aanzienlijk kleiner is dan bij gebruik van andere pijnstillers.

Praktische adviezen zijn:

- Start bij voorkeur met orale behandeling: voor een volwassene 3 tot 4 dd 1 tot 2 tabletten van 500 mg en laat de patiënt contact opnemen bij onvoldoende pijnstilling. Adviseer dan indien mogelijk de dosering te verhogen of door te gaan met een volgende stap van het stappenplan.
- Maximale dagdosering is 4 g voor volwassenen bij gebruik < 1 maand en bij maligne aandoeningen.
- Maximale dagdosering bij gebruik > 1 maand is 2,5 g.

- Rectale toediening van paracetamol geeft een onvoorspelbaar wisselende, vertraagde absorptie. In de praktijk kan bij volwassenen 3 tot 4 dd 1000 mg aangehouden worden en kan kortdurend (2 tot 3 dagen) een hogere rectale dosering van 2 tot 3 dd 30 mg/kg lichaamsgewicht nodig zijn om adequate pijnstilling te bereiken.

Tabel 1 Medicamenteuze behandeling acute en chronische nociceptieve pijn

Geneesmiddel	Oraal of dermaal	Rectaal	Opmerkingen
Stap 1			
Paracetamol	3-4 dd 500-1000 mg (1-2 tablet) max 4 g/dag bij gebruik < 1 maand en bij afwezigheid van risicofactoren bij gebruik > 1 maand max. 2,5 g/dag kinderen 4 dd 15 mg/kg	3-4 dd 1000 mg zetpil kinderen 2-3 dd 20 mg/kg	

Noot 25: Paracetamol

Conclusie

In het weinige onderzoek over paracetamol versus placebo komt naar voren dat paracetamol (in hoge dosering) effectief is in het verminderen van pijn op de korte termijn. Paracetamol geeft mogelijk een verhoogd risico op cardiovasculaire en gastro-intestinale bijwerkingen, maar de kwaliteit van het bewijs is zeer laag.

Overweging

Er is alleen kortetermijnonderzoek met paracetamol gevonden. Ook is er geen goed onderzoek naar mogelijke bijwerkingen van paracetamol. De werkgroep is van mening dat het beschikbare bewijs over mogelijke bijwerkingen geen reden is om het gebruik van paracetamol af te raden. Een meta-analyse die is verschenen na de sluitingsdatum van de NHG-search concludeerde dat paracetamol bij lagerugpijn en nekpijn op de korte termijn geen significante pijnverbetering geeft ten opzichte van placebo. De resultaten in deze meta-analyse over het effect van paracetamol bij artrose komen overeen met die genoemd in de Cochrane-review van Towheed (zie hierboven) [Machado 2015]. Op grond van zeer ruime klinische ervaring en het brede veiligheidsprofiel, en in aansluiting op de pijnladder, is paracetamol de pijnstiller van eerste keus bij niet-ernstige tot matige pijn.

Neuropathische pijn

Paracetamol en NSAID's zijn in de regel niet werkzaam bij neuropathische pijn.

5.1.3 WOREL 2017

Overweeg paracetamol alleen of in combinatie met NSAID's voor de behandeling van pijn bij patiënten met artrose. (GRADE 2B)

Toelichting

Paracetamol wordt voorwaardelijk terugbetaald voor chronische pijn. Een geraadpleegde expert (zie methodologie) beveelt aan om de 3000 mg per dag niet te overschrijden om zo het risico van overdosering te beperken. Anderzijds mag de dosis van 3000 mg/24 u nooit overschreden worden in geval van alcoholverslaving, chronisch leverfalen of chronische ondervoeding. Bij zeer magere volwassenen (< 50 kg) mag men de dagelijkse dosis de 2000 mg niet overschrijden.

5.1.4 NICE 2017

No specific recommendations were provided. Paracetamol was not included as one of the studied treatments in this guideline.

5.1.5 ASCO 2016

Clinicians may prescribe the following systemic nonopioid analgesics and adjuvant analgesics to relieve chronic pain and/or improve function in cancer survivors in whom no contraindications including serious drug–drug interactions exist:

- **Acetaminophen (paracetamol)**
- **…**

(Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

Clinicians should assess the risks of adverse effects of pharmacologic therapies, including nonopioids, adjuvant analgesics, and other agents used for pain management. (Evidence-based and informal consensus; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

…Nabal et al considered the addition of paracetamol to step 3 opioid treatment and found only marginal effectiveness reported in one of five trials included in their review.

5.1.6 DOH_Ireland 2015

Paracetamol should be considered for patients with mild to moderate cancer pain, in accordance with the WHO Cancer Pain Relief guidance. (evidence category A)

Paracetamol is well established as an effective and well tolerated agent in the management of mild to moderate pain. When used alone, paracetamol has been shown to be more efficacious than placebo in the management of cancer pain. In addition, as an integral component of the WHO analgesic ladder, paracetamol is routinely used in cancer pain in combination with more potent analgesics. For example, codeine/paracetamol combinations have been identified as a useful option in the second step of the WHO analgesic ladder.

There is insufficient evidence to support the addition of paracetamol for analgesic purposes in patients taking high doses of step 3 opioid medication in a cancer setting. (evidence category A)

5.2 NSAID

5.2.1 Summary

- Every guideline covering the NSAID warns for the associated risk of gastro-intestinal, cardiovascular, renal adverse events, and possible interactions with many known drugs. The selection of NSAID should be based on patient characteristics.

- The **lowest effective NSAID dose** should be used for the **shortest period** to control symptoms (NHG 2018, Worel 2017, DOH_Ireland 2015).

- The NHG 2018 guideline recommends the use of oral NSAID when paracetamol are ineffective.
- Topical NSAID are recommended over oral NSAID considering the adverse effects.
- For oral NSAID select naproxen, ibuprofen, diclofenac according patient characteristics
    - Naproxen: lowest cardiovascular risk and highest gastro-intestinal risk
    - Diclofenac: lowest gastro-intestinal risk and highest cardiovascular risk
- COX-2 selective NSAIDs are not recommended due to the increased cardiovascular risk.
- In general, NSAID are not recommended for vulnerable patients with an increased risk for gastro-intestinal, cardiovascular, or renal side effects.
- NSAID are not effective for neuropathic pain.

- The Worel 2017 guideline recommends NSAID for the treatment of chronic **low back pain**.

- The ASCO 2016 guideline mentions NSAID as one of the drugs that may be prescribed to relieve chronic pain and/or improve function in **cancer survivors**.

- The DOH_Ireland 2015 guideline recommends to consider NSAID for **cancer pain**, both as single agents and in combination with step 3 opioids according to the WHO analgesic ladder.
-The guideline refers to the possibility of a reduction of opioid use when combining NSAID to step 3 opioids.
- An increased cardiovascular risk is associated with all users of NSAID, especially with chronic use of high doses NSAID. This risk is associated with COX-2-selective inhibitors, high dose diclofenac and high dose ibuprofen (>1200mg per day).
- Naproxen is possibly not associated with such a cardiovascular risk.
- COX-2 selective inhibitors have a lower gastro-intestinal risk than traditional NSAID. However this advantage is diminished by the co-administration of low dose aspirin**.**
- Low dose ibuprofen (<1200mg per day) has the lowest gastro-intestinal risk compared to other traditional NSAIDs such as diclofenac and naproxen.

5.2.2 NHG 2018

Kernboodschappen

- Geef bij acute spier- en gewrichtspijn en chronische pijn als gevolg van knie- en handartrose paracetamol of een dermaal NSAID (minder bijwerkingen dan orale NSAID's).
- Kies het NSAID op grond van patiëntkenmerken: naproxen heeft het laagste cardiovasculaire en hoogste gastro-intestinale risico, diclofenac heeft het laagste gastro-intestinale en hoogste cardiovasculaire risico. Combineer ibuprofen niet met acetylsalicylzuur.
- COX-2-selectieve NSAID's worden niet aanbevolen.
- Geef in beginsel geen NSAID's aan kwetsbare patiënten met een verhoogd risico op gastro-intestinale, renale of cardiovasculaire bijwerkingen.

Acute en chronische nociceptieve pijn

- Stap 1: paracetamol
- Stap 2: NSAID
    - diclofenacgel 1 tot 3% of ibuprofengel 5% op de huid bij gelokaliseerde spier- of gewrichtspijn;
    - oraal (eventueel rectaal of intramusculair) naproxen, ibuprofen of diclofenac afhankelijk van patiëntkenmerken.

Comment from consensus authors: for topical NSAID see "5.11 Topical analgesics".

Oraal (en rectaal en intramusculair toegediende) NSAID's

Geef een NSAID (of voeg die toe) wanneer paracetamol onvoldoende effect heeft. Door de combinatie van paracetamol met een NSAID kan worden volstaan met een lagere dosering van het NSAID (met kleinere kans op bijwerkingen) bij gelijkblijvend pijnstillend effect.

Praktische adviezen zijn:

- Houd vanwege de mogelijke (ernstige) bijwerkingen van NSAID's de dosering zo laag en de duur van het gebruik zo kort mogelijk. Zie voor doseringen (*tabel 3*).
- Geef geen NSAID's bij waterpokken of gordelroos; deze kunnen dan ernstige huidcomplicaties geven.
- Kies afhankelijk van specifieke patiëntkenmerken (comorbiditeit, voorgeschiedenis van cardiovasculaire of gastro-intestinale aandoeningen, respons op eerder voorgeschreven NSAID's, indicatie voor intramusculaire toediening) voor naproxen, ibuprofen of diclofenac. Naproxen heeft het laagste cardiovasculaire risico, diclofenac het hoogste (dosisafhankelijk). Van de klassieke NSAID's heeft diclofenac het laagste gastro-intestinale risico, naproxen het hoogste.
- NSAID's (waarschijnlijk met uitzondering van naproxen) verhogen het risico op het optreden van veneuze trombo-embolische gebeurtenissen. Dit risico is afhankelijk van de toegepaste dosering, ook bij kortdurend gebruik.
- COX-2-selectieve NSAID's worden niet aanbevolen vanwege een hoger risico op cardiovasculaire complicaties zonder aangetoonde voordelen ten opzichte van de klassieke NSAID's gecombineerd met een protonpompremmer. De COX-2-selectieve NSAID's geven minder gastro-intestinale complicaties dan de klassieke NSAID's, maar geven in ongeveer gelijke mate aspecifieke maagklachten (maagpijn).

- Alle NSAID's (inclusief COX-2-selectieve) beïnvloeden de nierfunctie in gelijke mate nadelig. Bij verminderde nierfunctie kan acute nierinsufficiëntie of water- en zoutretentie optreden, waardoor hartfalen en hypertensie kunnen ontstaan of verergeren.
- Diclofenac is het enige NSAID dat beschikbaar is in injectievorm en kan worden toegepast bij een indicatie voor parenterale toediening van een NSAID.
- Combineer een klassiek NSAID (ook na parenterale toediening) met een protonpompremmer in standaard-dosering als het gastro-intestinale risico is verhoogd (zie de NHG-Standaard Maagklachten, onderdeel Maagbescherming). Er is geen relatie tussen het optreden van aspecifieke maagklachten en het optreden van gastro-intestinale complicaties.
- Combineer geen verschillende NSAID's vanwege de grotere kans op bijwerkingen.
- Vermijd NSAID-gebruik als onderhoudsbehandeling bij jicht zonder contra-indicatie voor of bewezen ineffectiviteit van allopurinol.

Tabel 3 Doseringen van NSAID's (volwassenen)

Geneesmiddel	*Oraal*	*Rectaal*	*Parenteraal*
naproxen	2 dd 250-500 mg (tablet)	2 dd 1 zetpil 250-500 mg	-
ibuprofen	3-4 dd 400-600 mg (dragee, tablet)	-	-
diclofenac	2-3 dd 25-50 mg of 2 dd 75 mg (tablet) of zo nodig 2 dd 100 mg ged. max. 1-2 dg	2-3 dd 25-50 mg zetpil of zo nodig 2 dd 1 zetpil 100 mg ged. max 1-2 dg	injectievloeistof 25 mg/ml; ampul 3 ml

Overschrijd de geregistreerde maximale dagdosering niet: boven deze dosering is de kans op bijwerkingen sterk verhoogd terwijl er geen bewijs is voor extra pijnvermindering.

Patiëntkenmerken waarbij NSAID's afgeraden worden:

- Geef géén NSAID (of acetylsalicylzuur) aan patiënten die ooit een anafylactische reactie hebben gehad op een NSAID (kruisovergevoeligheid).
- Schrijf NSAID's bij voorkeur niet voor:
  - aan kwetsbare ouderen;
  - bij een verminderde nierfunctie (eGFR < 60 ml/min/1,73 m^2, absolute contra-indicatie bij eGFR < 30 ml/min/1,73 m^2: acute urineretentie mogelijk) of verminderde leverfunctie;
  - bij hypertensie, hartfalen of atherosclerotisch hart- en vaatlijden;
  - bij een verhoogd gastro-intestinaal risico;
  - bij inflammatoire darmziekten;
  - bij oorzaken die leiden tot dehydratie;
  - bij geneesmiddelen die de nierfunctie kunnen verminderen (bijvoorbeeld diuretica of RAS-remmers), vanwege het risico op acute nierinsufficiëntie.
- Geef aan patiënten die een lage dosering acetylsalicylzuur als trombocytenaggregatieremmer gebruiken bij voorkeur geen ibuprofen.
- Als een NSAID toch noodzakelijk is bij patiënten met myocardinfarct en CVA in de voorgeschiedenis, dan is naproxen de eerste keus vanwege het laagste cardiovasculaire risico; diclofenac is bij hen gecontra-indiceerd.
- Als een NSAID toch noodzakelijk is bij patiënten met een peptisch ulcus in de voorgeschiedenis, dan gaat de voorkeur uit naar diclofenac (vanwege het laagste risico op gastro-intestinale complicaties) of ibuprofen (beide met een protonpompremmer).

- Combineer geneesmiddelen die gecontra-indiceerd zijn bij een peptisch ulcus in de voorgeschiedenis (zoals clopidogrel, prasugrel of ticagrelor, systemisch werkende glucocorticoiden, SSRI's en spironolacton) bij voorkeur niet met een NSAID (zie de NHG-Standaard Maagklachten).
- Schrijf geen NSAID's voor aan patiënten die anticoagulantia (risico op bloedingen in combinatie met verlengde protrombinetijd met fatale afloop in het bijzonder bij ouderen), lithium (verhoging lithiumspiegels met risico op toxiciteit), ciclosporine en tacrolimus (verhoogde nefrotoxiciteit ciclosporine en tacrolimus) en methotrexaat (toename methotrexaat toxiciteit) gebruiken.

Controle bij NSAID's:

- NSAID's kunnen het effect van diuretica, RAS-remmers en bètablokkers verminderen doordat ze water- en zoutretentie veroorzaken.
- Controleer de nierfunctie voorafgaand aan en regelmatig tijdens chronisch gebruik van een NSAID (zie de LESA Rationeel aanvragen laboratoriumdiagnostiek).

Neem bij de keuze van de medicatie de stopcriteria in acht (zie de Multidisciplinaire Richtlijn Polyfarmacie bij ouderen):
voor NSAID's: matige tot ernstige hypertensie, hartfalen, chronische nierinsufficiëntie (eGFR < 50 ml/ min/1,73 m2), gebruik langer dan drie maanden voor symptoombestrijding van matige artrose, gebruik langer dan drie maanden als onderhoudsbehandeling bij jicht zonder contra-indicatie of bewezen ineffectiviteit voor allopurinol

Noot 31: Paracetamol plus NSAID
Overwegingen
Door een NSAID met paracetamol te combineren kan mogelijk bij een lagere dosering van het NSAID (en ook van paracetamol) een effectieve pijnbestrijding worden gekregen. Dit vermindert in theorie de kans op bijwerkingen.
Aanbeveling
Indien een anti-inflammatoir effect gewenst is, kan door de combinatie paracetamol met een NSAID worden volstaan met een lagere dosering van het NSAID bij gelijkblijvend pijnstillend effect.

Noot 32: Bijwerkingen van NSAID's
Aanbeveling
Bij het voorschrijven van een NSAID is in geval van een verhoogd cardiovasculair risico naproxen het middel van eerste keus. Er kan ook voor diclofenac of ibuprofen worden gekozen bij een verhoogd gastro-intestinaal risico in afwezigheid van cardiovasculaire comorbiditeit. Geef NSAID's in zo laag mogelijke dosering voor zo kort mogelijke duur. COX-2-selectieve NSAID's worden niet aanbevolen.

Neuropathische pijn
Paracetamol en NSAID's zijn in de regel niet werkzaam bij neuropathische pijn.

5.2.3 WOREL 2017

Overweeg NSAID's voor de behandeling van aspecifieke chronische lagerugpijn. (GRADE 2B)
Toelichting
Het risico op gastro-intestinale bijwerkingen van niet-steroïde anti-inflammatoire geneesmiddelen (NSAID's) is sinds vele jaren bewezen. Men dient rekening te houden met dit risico, evenals met de cardiovasculaire en renale risico's. Schrijf NSAID's voor aan de laagst mogelijke dosis en voor een korte periode. Anderzijds bestaat er een risico op farmacodynamische interacties met heel wat medicatie die het risico op bloedingen, gastro-intestinale bijwerkingen of functionele nierinsufficiëntie kan verhogen.

5.2.4 NICE 2017

No specific recommendations were provided. NSAID's were not included as one of the studied treatments in this guideline.

5.2.5 ASCO 2016

Clinicians may prescribe the following systemic nonopioid analgesics and adjuvant analgesics to relieve chronic pain and/or improve function in cancer survivors in whom no contraindications including serious drug–drug interactions exist:

- **Nonsteroidal anti-inflammatory drugs**
- **…**

(Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

Clinicians should assess the risks of adverse effects of pharmacologic therapies, including nonopioids, adjuvant analgesics, and other agents used for pain management. (Evidence-based and informal consensus; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

…A systematic review considering the addition of NSAIDS to opioids found improved analgesia and a reduction of opioid consumption in patients with cancer pain.

5.2.6 DOH_Ireland 2015

NSAIDs should be considered for the treatment of cancer pain, both as single agents and in combination with step 3 opioids. (evidence category A)

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely accepted as a treatment option for cancer pain. The WHO guidelines suggest an NSAID as a potential nonopioid for use at the first step of the WHO analgesic ladder, and throughout a patients escalating pain trajectory.

Although it is not feasible to recommend an optimal dose of NSAID based on the available evidence, advice from the Commission on Human Medicines (CHM) states that the lowest effective NSAID dose should be used for the shortest period to control symptoms, and the need for long term treatment should be reviewed regularly. From a pharmacoeconomic perspective, in one prospective randomised controlled study carried out in 156 consecutive advanced cancer patients with pain, it was demonstrated that the use of NSAIDs in addition to strong opioids had a negligible impact on cost and reduced the need for further opioid dose escalation allowing for lower opioid dosing.

Risk stratification and identification of the individual cardiovascular and gastrointestinal risk factors should inform the decision regarding choice of NSAID, and gastroprotective strategy. (evidence category D)

Cardiovascular risk with NSAID use

Recent evidence has linked NSAID use to cardiovascular risk.

• Kearney et al (2006), in a meta-analysis of randomised trials, showed that COX-2 selective inhibitors demonstrate an increased risk of thrombotic cardiovascular adverse reactions, particularly myocardial infarction (MI) and stroke.

• Following a comprehensive Europe-wide review of clinical trial and epidemiological data in 2006, the Commission on Human Medicines advised that non-selective NSAIDs may also be associated with a small increased risk of thrombotic events when used at high doses and for long term treatment. The findings from two more recent studies are consistent with, and hence validate, the earlier 2006 review. In addition, the newer studies reported an increased cardiovascular risk with all users of NSAIDs, irrespective of their baseline cardiovascular risk, and not only in chronic users. However, the greatest concern relates to chronic use of high doses. The risk is associated with COX-2-selective inhibitors, high dose diclofenac and high dose ibuprofen (>1200mg per day). Evidence indicates that naproxen is not associated with such a risk.

Renal toxicity with NSAID use

NSAIDs may provoke or worsen renal failure. They should be used with caution in patients who are at high risk of developing renal impairment or those who are on concurrent potentially nephrotoxic drugs. Doses should be maintained as low as possible and renal function monitored as appropriate.

Gastrointestinal risk with NSAID use

Gastrointestinal (GI) complications are widely recognised as a commonly associated adverse effect of NSAIDs. The risk of GI toxicity with NSAIDs is increased by a number of factors including increasing age (>65 years), previous peptic ulcer disease and concurrent use of other drugs that may increase the risk of ulceration or bleeding.

• COX-2 selective inhibitors are associated with a lower risk of GI toxicity than traditional NSAIDs, however this advantage is diminished by the co-administration of low dose aspirin.

• Low dose ibuprofen (<1200mg per day) is associated with the lowest risk of GI complications compared to other traditional NSAIDs such as diclofenac and naproxen.

Risk stratification and identification of the individual cardiovascular and GI risk factors should inform the decision regarding choice of NSAID and gastroprotective strategy.

Note from consensus authors: for more information on NSAID and gastroprotective strategy see “5.9 Specific patients group: gastro-intestinal risk”.

5.3 Adjuvantia

5.3.1 Summary

The NHG 2018 guideline recommends a tricyclic antidepressant (TCA) as first choice for neuropathic pain with amitriptyline as the most studied drug. Nortriptyline is preferred for elderly because of less central anticholinergic adverse effects. In case TCA are insufficient, adverse events, or cardiovascular contra-indications for TCA, consider the use of gabapentin. If this is still insufficient or in case of adverse events, consider pregabalin or duloxetine. A combination of drugs with a different mechanism of action can be considered in case of insufficient pain relief with monotherapy.

The Worel 2017 guideline recommends amitryptiline for neuropathic pain. Duloxetine is a possible selection for diabetic neuropathic pain. Gabapentine can be considered for neuropathic pain, pregabaline can be considered after failure of first choice pharmacological treatment.

The NICE 2017 guideline recommends the selection of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain. In case of lack of effectiveness or tolerance, the drugs can be switched with one and another. Nortriptyline is no longer recommended in the guideline.

The ASCO 2016 guideline recommends that selected antidepressants (e.g. duloxetine) and selected anticonvulsants (e.g. gabapentin and pregabalin) may be prescribed for neuropathic pain conditions or chronic widespread pain in cancer survivors.

The DOH_Ireland 2015 recommends considering anti-depressants (e.g. amitriptyline, venlafaxine, duloxetine) and anticonvulsants (e.g. gabapentin, pregabalin) for cancer-related neuropathic pain with careful monitoring of side effects.

Carbamazepine is recommended for trigeminal neuralgia (NHG 2018, NICE 2017).

5.3.2 NHG 2018

Kernboodschappen

- Geef bij neuropathische pijn als eerste keus een tricyclisch antidepressivum (behalve bij trigeminusneuralgie, dan carbamazepine).

Neuropathische pijn

Antidepressiva, anti-epileptica en opioïden (inclusief tramadol) zijn werkzaam bij neuropathische pijn, al zijn er grote interindividuele verschillen. De aard van de neuropathische pijn is geen leidraad voor de keuze van het middel met uitzondering van trigeminusneuralgie waarbij carbamazepine eerste keus is. De tricyclische antidepressiva (TCA's) (vooral amitriptyline) zijn het meest onderzocht bij diverse vormen van neuropathische pijn, tonen goede effectiviteit en hebben daarom de voorkeur. Bij ouderen heeft nortriptyline de voorkeur, omdat het minder centrale anticholinerge bijwerkingen heeft die het cognitief functioneren kunnen beïnvloeden. Van de anti-epileptica gaat de voorkeur uit naar gabapentine. Laat bij de keuze ook de prijsverschillen meewegen.

Als een middel enige maar onvoldoende pijnvermindering geeft, kan combinatie van neuropathische pijnmedicatie met een verschillend werkingsmechanisme worden overwogen.

Tabel 7 Doseringen geneesmiddelen bij neuropathische pijn (volwassenen)

Geneesmiddel	*Startdosering*	*Onderhoudsdosering*	*Maximale dagdosering*
Trigeminusneuralgie			
Carbamazepine (geregistreerd bij trigeminusneuralgie)	Volwassenen tot 60-70 jaar: 2 dd 100-200 mg; verhoog zn. wekelijks met 100 mg per gift. ouder dan 60-70 jaar: 2 dd 100 mg	3-4 dd 200 mg Houd de (onderhouds)dosering zo laag mogelijk. bij verminderde nierfunctie: eGFR < 30 ml/min/1,73 m^2 wees extra alert op optreden van bijwerkingen. Doseer eventueel op geleide van spiegel.	1200 mg

Overige neuropathische pijn (m.u.v. hiv-neuropathie)			
*Amitriptyline** (off-label)	Start vóór de nacht met 10-25 mg, verhoog zo nodig met 25 mg elke 1 tot 2 weken.		125 mg
*Nortriptyline**,† (off-label)	Start met 10-25 mg, verhoog zo nodig met 25 mg elke 1 tot 2 weken.		100 mg
Gabapentine (geregistreerd bij perifere neuropathische pijn zoals diabetische neuropathie en postherpetische neuralgie)	900 mg of 1200 mg per dag, opbouwend in 3 dagen. Dag 1: 1 dd 300 mg; dag 2: 2 dd 300 mg; dag 3: 3 dd 300 mg. Zo nodig om de 2-3 dagen in stappen van 300 mg verhogen tot max. 3 dd 1200 mg per dag. De opbouw van een dagdosis van 1800 mg kost minimaal 1 week, een dagdosis van 2400 mg minimaal 2 weken en de maximale dagdosis van 3600 mg minimaal 3 weken.	900-3600 mg per dag in 3 giften. Bij verminderde nierfunctie: 50-80 ml/min/1,73 m^2: 600-2400 mg/dag; 30-50 ml/min/1,73 m^2: 300-1200 mg/dag; 10-30 ml/min/1,73 m^2: 150-600 mg/dag (dosering van 150 mg kan als 300 mg elke 2 dagen worden ingenomen).	3600 mg
Pregabaline (geregistreerd bij perifere en centrale neuropathische pijn)	150 mg per dag in 2-3 giften, op geleide van individuele reactie en het kunnen verdragen, na 3-7 dagen verhogen tot 300 mg per dag. Na een extra week kan indien nodig worden verhoogd tot 600 mg per dag.	150-300 mg per dag in 2-3 giften. Bij verminderde nierfunctie: 30-50 ml/min/1,73 m^2: 50% van de normale dosering; 10-30 ml/min/1,73 m^2: 25% van de normale dosering.	600 mg
Duloxetine (alleen geregistreerd bij diabetische perifere neuropathie)	60 mg 1x/dag, max. 120 mg/dag in gelijk verdeelde giften	60 mg 1x/dag, max. 120 mg/dag in gelijk verdeelde giften.	120 mg

* start bij ouderen en bij ervaren bijwerkingen met een lage dosering en verhoog de dosering langzaam.
† in verband met mogelijke slapeloosheid liever niet vóór de nacht laten innemen.

Praktische adviezen bij orale medicatie

- Geef bij trigeminusneuralgie een proefbehandeling met carbamazepine. Verhoog de dosering geleidelijk op geleide van de pijn. Verlaag bij een goede respons de onderhoudsdosering geleidelijk tot het niveau van voldoende pijnstilling.
- Geef bij neuropathische pijn anders dan door trigeminusneuralgie of hiv-neuropathie (zie *Consultatie en verwijzing*) als eerste keus een TCA zoals amitriptyline of nortriptyline (bij ouderen).
- TCA's zijn gecontra-indiceerd na een recent hartinfarct, cardiale geleidingsstoornissen en bij dementie. Terughoudendheid is geboden bij (voorgeschiedenis van of verhoogd risico op) urineretentie, lever- of nier-functiestoornis, glaucoom, epilepsie, obstipatie, prostatisme en cardiovasculaire aandoeningen zoals hartfalen. Overweeg een ecg bij patiënten met een verhoogde gevoeligheid voor cardiovasculaire bijwerkingen voorafgaand aan de start met een TCA (zie de NHG-Standaarden Depressie en Angst).
- Controleer bij gebruik van TCA's bij keelpijn en koorts in de eerste tien behandelweken het bloedbeeld in verband met de zeldzaam voorkomende beenmergdepressie.
- Overweeg behandeling met gabapentine als een TCA onvoldoende effect heeft, bij ongewenste bijwerkingen of bij een cardiovasculaire contra-indicatie voor een TCA. Als dit ook niet effectief is of bijwerkingen geeft, overweeg dan over te stappen op een volgend middel (pregabaline of duloxetine).

Noot 62: Antidepressiva bij neuropathische pijn
Aanbeveling
TCA's zijn eerste keus bij de behandeling van neuropathische pijn. Overweeg behandeling met duloxetine (of pregabaline of gabapentine), eventueel naast een lage dosering TCA, als een TCA onvoldoende effect heeft, bij ongewenste bijwerkingen of bij een contra-indicatie voor een TCA.

Neem bij de keuze van de medicatie de stopcriteria in acht (zie de Multidisciplinaire Richtlijn Polyfarmacie bij ouderen):
Voor tricyclische antidepressiva: dementie, glaucoom, cardiale geleidingsstoornissen, obstipatie, prostatisme, voorgeschiedenis of verhoogd risico op urineretentie, combinatie met opioïden.

5.3.3 WOREL 2017

Anti-epileptica

Gabapentine (getitreerd tot ten minste 1200 mg per dag) kan worden overwogen voor de behandeling van neuropathische pijn. (GRADE 2A)

Pregabaline (getitreerd tot ten minste 300 mg per dag) kan worden overwogen voor de behandeling van neuropathische pijn bij falende medicamenteuze eerstelijnsbehandelingen en voor de behandeling van fibromyalgie. (GRADE 2A)

Antidepressiva

Tricyclische antidepressiva

Amitriptyline (25-125 mg/dag) wordt aanbevolen voor de behandeling van neuropathische pijn en fibromyalgie. (GRADE 1A)
Toelichting

Amitriptyline in een dosis van 25-125 mg/dag is geïndiceerd voor de behandeling van patiënten met fibromyalgie en neuropathische pijn, met uitzondering van pijn die gepaard gaat met hiv-ziekte (geen voordeel aangetoond). Amitryptilline heeft sederende eigenschappen en geeft aanleiding tot ongewenste anticholinergische effecten. Voorzichtigheid is geboden bij gebruik van amitriptyline in geval van urineretentie, geslotenhoekglaucoom, chronische obstipatie of prostaathypertrofie. Amitriptyline is gecontra-indiceerd in geval van significante hartritmestoornissen en stoornis van de cardiale geleiding.

SNRI's

Duloxetine (60 mg/dag) komt **in aanmerking** voor de behandeling van diabetische neuropathie en in mindere mate voor met fibromyalgie geassocieerde pijn. (**GRADE 1A)**

5.3.4 NICE 2017

<u>All neuropathic pain (except trigeminal neuralgia)</u>

Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia).

If the initial treatment is not effective or is not tolerated, offer one of the remaining 3 drugs, and consider switching again if the second and third drugs tried are also not effective or not tolerated.

Do not start the following to treat neuropathic pain in non-specialist settings, unless advised by a specialist to do so:
capsaicin patch, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, topiramate, venlafaxine.

Note from consensus authors: we only reported the adjuvantia here, for a full list see the full NICE guideline.

<u>Trigeminal neuralgia</u>
Offer carbamazepine as initial treatment for trigeminal neuralgia.

If initial treatment with carbamazepine is not effective, is not tolerated or is contraindicated, consider seeking expert advice from a specialist and consider early referral to a specialist pain service or a condition-specific service.

Is response to pharmacological treatment predicted more reliably by underlying aetiology or by symptom characteristics? There is little evidence about whether certain symptoms that present in healthcare settings, or whether different neuropathic pain conditions with different aetiologies, respond differently to different treatments. Current evidence is typically focused on particular conditions and is limited to particular drugs. Further research should be conducted …

5.3.5 ASCO 2016

Clinicians may prescribe the following systemic nonopioid analgesics and adjuvant analgesics to relieve chronic pain and/or improve function in cancer survivors in whom no contraindications including serious drug–drug interactions exist:

- **…**
- **Adjuvant analgesics, including selected antidepressants and selected anticonvulsants with evidence of analgesic efficacy (such as the antidepressant duloxetine and the anticonvulsants gabapentin and pregabalin) for neuropathic pain conditions or chronic widespread pain**

(Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

The panel acknowledges that many other systemic nonopioids, including many other antidepressants and anticonvulsants, drugs in many other classes … are taken by some cancer survivors with chronic pain and may benefit some of those who receive them. However, the efficacy of these agents and their longterm effectiveness have not been established.

Clinicians should assess the risks of adverse effects of pharmacologic therapies, including nonopioids, adjuvant analgesics, and other agents used for pain management. (Evidence-based and informal consensus; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

5.3.6 DOH_Ireland 2015

In patients with cancer-related neuropathic pain, anti-epileptic and antidepressant medications should be considered, with careful monitoring of side effects. (evidence category A)

Key finding
-There is evidence that antidepressants and anti-epileptics may improve cancer-related neuropathic pain.
-There is evidence in the cancer setting to support the use of tricyclic antidepressants such as amitriptyline.
-There is evidence in the non-cancer setting (which may be extrapolated to the treatment of cancer related neuropathic pain cancer setting) to support the use of serotonin-noradrenaline reuptake inhibitors such as venlafaxine, duloxetine.
-There is insufficient evidence to support a recommendation on the use of selective serotonin reuptake inhibitors (SSRIs).
-There is evidence in the cancer setting to support the use of anti-epileptics, such as pregabalin and gabapentin.

5.4 Specific patient groups: Pregnancy

5.4.1 Summary

Paracetamol
No specific recommendations were provided in the selected guidelines.

NSAID
NHG 2018: Use NSAID only incidentally and only in the first trimester. Ibuprofen and diclofenac can be used during breastfeeding.

WOREL 2017: NSAID, including topical NSAID, are contra-indicated during pregnancy.

Adjuvantia
The NICE 2017 guideline made an update in 2018 and 2019 concerning valproate during pregnancy and the risk of malformations and developmental abnormalities in the baby.

No recommendations were provided in the other selected guidelines. However, many anticonvulsants are known for their risk of teratogenicity. For more information see the chapter on "Additional safety information from other sources"

5.4.2 NHG 2018

Adviezen bij zwangeren en borstvoeding:

- Geef NSAID's alleen incidenteel aan zwangeren en alleen in de eerste helft van de zwangerschap (zie www.lareb.nl/teratologie/naslagwerk). Ibuprofen en diclofenac kunnen tijdens borstvoeding worden gebruikt.

5.4.3 WOREL 2017

NSAID's, zelfs als topicum, zijn gecontra-indiceerd tijdens de zwangerschap.

5.4.4 NICE 2017

MHRA advice on valproate: In April 2018, we added warnings that valproate must not be used in pregnancy, and only used in girls and women when there is no alternative and a pregnancy prevention plan is in place. This is because of the risk of malformations and developmental abnormalities in the baby. See update information for details. In March 2019, we produced a summary of NICE guidance to support the safe use of valproate.

5.4.5 ASCO 2017

No specific recommendations were provided concerning the use of paracetamol, NSAID's, and adjuvantia in pregnant women.

5.4.6 DOH_Ireland 2015

No specific recommendations were provided concerning the use of paracetamol, NSAID's, and adjuvantia in pregnant women.

5.5 Specific patient groups: adolescents

5.5.1 Summary

The NHG 2018 guideline provides dosage recommendations for paracetamol in children, including children between 12-18 years.

The NHG 2018 guideline recommends ibuprofen when NSAID are indicated for children, including 12-18 year olds. A lower dose ibuprofen is recommended in children, including 12-18 year olds.

No other recommendations were provided in the other selected guidelines concerning the use of paracetamol, NSAID, and adjuvantia in adolescents.

5.5.2 NHG 2018

Paracetamol

Gewicht (en leeftijd)	*Oraal (tablet, oplostablet, kauwtablet, drank 24 mg/ml)*	*Rectaal (zetpil)*
op basis van gewicht	60 mg/kg/dag in 4 giften: 4 dd 15 mg/kg	60 mg/kg/dag in 3 giften: 2-3 dd 20 mg/kg
43-70 kg (12 tot 18 jaar)	4 dd 650-1000 mg	2-3 dd 1 zetpil 1000 mg
	incidenteel max. 90 mg/kg/dag in 4 giften: 4 dd 22,5 mg/kg ged. max. 3 dg	incidenteel max. 90 mg/kg/dag in 3 giften: 3 dd 30 mg/kg ged. max. 3 dg

Note from consensus authors: recommended dosages for more younger children are found in table 2 of the guideline.

Bij kinderen mag incidenteel kortdurend (2 tot 3 dagen) hoger dan de normale kinderdosering worden gedoseerd.

NSAID

Adviezen bij kinderen:

- Geef ibuprofen als een NSAID is geïndiceerd bij kinderen. Geef geen ibuprofen bij waterpokken of gordelroos, omdat dit ernstige huidcomplicaties kan geven.
- Acetylsalicylzuur wordt niet aanbevolen voor kinderen.

Note from consensus authors:

Recommended dosage from the NHG 2018 guideline:

- Ibuprofen (oral) for adults: 3-4 dd 400-600 mg (dragee, tablet)
- Ibuprofen (oral) for children between 12-18 years (43-70 kg): 2-3 dd 400 mg (tablet, dragee, capsule)
- Recommended dosages for more younger children are found in table 4 of the guideline.

Adjuvantia

No specific recommendations were provided.

5.6 Specific patient groups: renal risk

5.6.1 Summary

Paracetamol

Two guidelines mention that no dose adjustment is required in chronic kidney disease. (NHG 2018, DOH_Ireland 2015).

NSAID's

The NHG 2018 guideline mentions to avoid NSAID if:
- impaired kidney function (eGFR < 60 ml/min/1,73 m^2)
- concomitant drugs that could lower kidney function (e.g. diuretics or RAS-inhibitors)
- concomitant drugs that increase the risk of nephrotoxicity (ciclosporin and tacrolimus)

Severe renal insufficiency (eGFR < 30 ml/min/1,73 m^2) is an absolute contra-indication.

The WOREL 2017 guideline refers in general to the risk of interactions between NSAID and other drugs and the associated increased risk of adverse events including renal insufficiency.

The DOH_Ireland 2015 guideline states that NSAID may provoke or worsen renal failure. They should be used with caution in patients who are at high risk of developing renal impairment or those who are on concurrent potentially nephrotoxic drugs. Doses should be maintained as low as possible and renal function monitored as appropriate.

Two guidelines mention monitoring the kidney function if using NSAID (NHG 2018, DOH_Ireland 2015).

Adjuvantia

The NHG 2018 guideline provides dose adjustment recommendations in patients with renal insufficiency for carbamazepine, gabapentin, and pregabalin.

The Worel 2017 guideline warns to be cautious with gabapentin and pregabalin in patients with renal insufficiency.

The DOH_Ireland 2015 guideline mentions that adjuvant analgesics may require dose adjustment in patients with renal impairment without any further details.

5.6.2 NHG 2018

Paracetamol

Bij een verminderde nierfunctie is aanpassen van de dosering of het doseerinterval niet nodig.

NSAID

- Schrijf NSAID's bij voorkeur niet voor:
  - bij een verminderde nierfunctie (eGFR < 60 ml/min/1,73 m^2, absolute contra-indicatie bij eGFR < 30 ml/min/1,73 m^2: acute urineretentie mogelijk) of verminderde leverfunctie;
  - bij oorzaken die leiden tot dehydratie;
  - bij geneesmiddelen die de nierfunctie kunnen verminderen (bijvoorbeeld diuretica of RAS-remmers), vanwege het risico op acute nierinsufficiëntie.
- Schrijf geen NSAID's voor aan patiënten die …ciclosporine en tacrolimus (verhoogde nefrotoxiciteit ciclosporine en tacrolimus) en methotrexaat (toename methotrexaat toxiciteit) gebruiken.

Controle bij NSAID's:

- NSAID's kunnen het effect van diuretica, RAS-remmers en bètablokkers verminderen doordat ze water- en zoutretentie veroorzaken.
- Controleer de nierfunctie voorafgaand aan en regelmatig tijdens chronisch gebruik van een NSAID (zie de LESA Rationeel aanvragen laboratoriumdiagnostiek).

Adjuvantia

TCA's zijn gecontra-indiceerd na een recent hartinfarct, cardiale geleidingsstoornissen en bij dementie. Terughoudendheid is geboden bij (voorgeschiedenis van of verhoogd risico op) urineretentie, lever- of nier-functiestoornis, glaucoom, epilepsie, obstipatie, prostatisme en cardiovasculaire aandoeningen zoals hartfalen.

Note from consensus authors: for the recommended dosages of adjuvantia in patiens with renal insufficiency: see table 7 in "5.3 Adjuvantia".

5.6.3 WOREL 2017

Paracetamol

No specific recommendations were provided.

NSAID

Het risico op gastro-intestinale bijwerkingen van niet-steroïde anti-inflammatoire geneesmiddelen (NSAID's) is sinds vele jaren bewezen. Men dient rekening te houden met dit risico, evenals met de cardiovasculaire en renale risico's. Schrijf NSAID's voor aan de laagst mogelijke dosis en voor een korte periode. Anderzijds bestaat er een risico op farmacodynamische interacties met heel wat medicatie die het risico op bloedingen, gastro-intestinale bijwerkingen of functionele nierinsufficiëntie kan verhogen.

Adjuvantia

Toelichting

Zowel gabapentine als pregabaline hebben in gecontroleerde multicenterstudies hun doeltreffendheid bewezen bij neuropathische pijn. Excretie is vooral renaal; voorzichtigheid is dus geboden bij patiënten met nierinsufficiëntie.

5.6.4 NICE 2017

No specific recommendations were provided. NSAID were not included in this guideline.

5.6.5 ASCO 2017

No specific recommendations were provided.

5.6.6 DOH_Ireland 2015

Paracetamol

Paracetamol is metabolised by the liver with only 2-5% excreted unchanged in the urine and does not require dose adjustment in chronic kidney disease. It is considered the non-opioid analgesic of choice for mild-to-moderate pain in chronic kidney disease patients. It has been suggested that an increase in the dose interval of paracetamol from every six to every eight hours when eGFR < 10 ml/min/1.73m2 may be appropriate.

NSAID

Non-steroidal anti-inflammatory drugs (NSAIDs) can cause irreversible reduction in GFR, sodium and water retention aggravating hypertension, gastro-intestinal bleeding and hyperkalaemia. The Renal Drug Handbook states that the inhibition of renal prostaglandin synthesis by NSAIDs may interfere with renal function, especially in the presence of existing renal disease.

- For selected patients, the potential risk of precipitating renal failure should be weighed against the benefits of improved pain control through the use of NSAIDs. This may be of particular consideration where prognosis is expected to be short.
- If using an NSAID, the patient's urea, creatinine and electrolytes should be monitored.

NSAIDs may provoke or worsen renal failure. They should be used with caution in patients who are at high risk of developing renal impairment or those who are on concurrent potentially nephrotoxic drugs. Doses should be maintained as low as possible and renal function monitored as appropriate.

Adjuvantia

Adjuvant analgesics may also require dose adjustment in patients with renal impairment.

5.7 Specific patient groups: hepatic risk

5.7.1 Summary

Paracetamol

The NHG 2018 guideline mentions that the recommended dosage of paracetamol for patients with risk factors for liver damage is 2g (1.5g in case of multiple risk factors).

The WOREL 2017 guideline states not to exceed 3g/24h in patients with chronic liver failure.

The DOH_Ireland 2015 guideline states that paracetamol can be used safely at recommended doses in patients with liver disease and is a preferred (compared to NSAID) weak analgesic. A maximum adult dose of 2g is mentioned for this population.

NSAID

The NHG 2018 guideline mentions avoiding NSAID in patients with impaired liver function.

The DOH_Ireland 2015 guideline mentions that hepatotoxicity is considered a class characteristic of NSAID and that there is limited evidence for their use in hepatic impairment.

Adjuvantia

The NHG 2018 guideline mentions avoiding TCA in patients with impaired liver function.

5.7.2 NHG 2018

Paracetamol

De maximale dagdosering voor volwassenen met risicofactoren voor leverschade is 2 g (1,5 g indien meerdere risicofactoren tegelijk aanwezig zijn).
Risicofactoren voor leverschade zijn: bestaande leverziekte, hoge leeftijd (metabolisatiesnelheid daalt bij ouder worden), een genetisch bepaalde lage metabolisatiesnelheid, gebruik van carbamazepine, fenytoïne, fenobarbital, isoniazide, rifampicine (CY-P2E1-enzyminducerende middelen), lichaamsgewicht < 50 kg, vasten, slechte voedingstoestand (eiwitarm dieet), langdurig meer dan matig alcoholgebruik (> 2 alcoholconsumpties per dag), roken en gecombineerd gebruik van meerdere pijnstillers.

Noot 26: Leverschade door paracetamol
Bij overdosering (waarvan onder bijzondere omstandigheden ook al bij therapeutische doseringen sprake kan zijn) of bij een tekort aan glutathion kan levernecrose optreden. Deze kan ontstaan door acute intoxicatie (gemiddeld bij inname van meer dan 6 g in één keer). Hoewel zelden voorkomend is leverschade ook beschreven na chronisch gebruik van 3 tot 4 gram paracetamol per dag [KNMP 2015, Bolesta 2002]. Naar schatting moeten 2 op 100.000 gebruikers in het ziekenhuis worden opgenomen vanwege leverschade door paracetamol.

NSAID

Schrijf NSAID's bij voorkeur niet voor: …bij een verminderde leverfunctie

Adjuvantia
TCA's. Terughoudendheid is geboden bij … lever- of nier-functiestoornis.

5.7.3 WOREL 2017

Paracetamol
…Anderzijds mag de dosis van 3000 mg/24 u nooit overschreden worden in geval van alcoholverslaving, chronisch leverfalen of chronische ondervoeding. Bij zeer magere volwassenen (< 50 kg) mag men de dagelijkse dosis de 2000 mg niet overschrijden.

NSAID
No specific recommendations were provided.

Adjuvantia
No specific recommendations were provided.

5.7.4 NICE 2017
No specific recommendations were provided.

5.7.5 ASCO 2017
No specific recommendations were provided.

5.7.6 DOH_Ireland 2015

Paracetamol
There is very little information on paracetamol and its changes in metabolism in patients with chronic liver disease.
Benson et al (2005) discuss how paracetamol is often avoided in patients with chronic liver disease. The belief that paracetamol should be avoided in these patients came from the association between massive paracetamol overdose and hepatotoxicity. There is also a poor understanding of the metabolism of paracetamol in patients with liver disease. Studies of paracetamol in patients with chronic liver disease have shown that the half-life of paracetamol may be prolonged but the cytochrome P450 activity is not increased and glutathione stores are not depleted to critical levels in those taking recommended doses. Paracetamol has been studied in a variety of liver diseases without evidence of increased risk of hepatotoxicity at currently recommended doses. Therefore,
paracetamol can be used safely in patients with liver disease and is a preferred weak analgesic/antipyretic because of the absence of the platelet impairment, gastrointestinal toxicity and nephrotoxicity associated with non-steroidal anti-inflammatory drugs. Bosilkovska and colleagues (2012)

suggest that owing to the changes in the pharmacokinetics and the vulnerability of this population, it seems reasonable to limit the adult daily dose to 2g, half the suggested therapeutic dose.

NSAID

Hepatotoxicity is considered a class characteristic of NSAIDs and there is limited evidence regarding the use of NSAIDS in hepatic impairment. What evidence there is suggests that the pharmacokinetics and metabolism of ibuprofen and diclofenac in patients with hepatic impairment are similar those with normal liver function. Naproxen however has been shown to have reduced metabolism in hepatic impairment and dose reduction is recommended.

Adjuvantia

No specific recommendations were provided.

5.8 Specific patient groups: cardiovascular risk

5.8.1 Summary

Paracetamol

No specific recommendations are provided.

NSAID

The NHG 2018 guideline recommends avoiding NSAID in patients with increased cardiovascular risk (hypertension, heart failure, atherosclerosis). The risk of venous thromboembolic events is increased in a dose-dependent manner and with short term use as well. NSAID are not recommended in patients on anticoagulants. The combination ibuprofen and acetylsalicylic acid is not recommended.

The WOREL 2017 guideline refers to the increased cardiovascular risk (myocard infarction, coronary artery disease) and mentions that all NSAID are associated with an increased risk for heart failure.

The DOH_Ireland 2015 guideline refers to an increased cardiovascular risk with all users of NSAID, irrespective of the baseline cardiovascular risk, especially with chronic use of high doses NSAID. Naproxen is possibly not associated with such a cardiovascular risk.

For more information on the selection of NSAID with the lowest cardiovascular risk, see “5.2 NSAID”.

Adjuvantia

NHG 2018 states that tricyclic antidepressants are contra-indicated in patients with a recent myocardial infarction and arrhythmias. Avoid these drugs in patients with cardiovascular disease (e.g. heart failure). The guideline states to consider a ECG in patients with an increased risk for cardiovascular side effects prior to the start of treatment with these drugs.

The WOREL 2017 guideline also mentions significant arrhythmias and cardiac conduction disorders as an contra-indication for amitriptyline.

5.8.2 NHG 2018

Paracetamol

No specific recommendations were provided.

NSAID

Kernbooschappen

- Kies het NSAID op grond van patiëntkenmerken: naproxen heeft het laagste cardiovasculaire en hoogste gastro-intestinale risico, diclofenac heeft het laagste gastro-intestinale en hoogste cardiovasculaire risico. Combineer ibuprofen niet met acetylsalicylzuur.
- COX-2-selectieve NSAID's worden niet aanbevolen.
- Geef in beginsel geen NSAID's aan kwetsbare patiënten met een verhoogd risico op gastro-intestinale, renale of cardiovasculaire bijwerkingen.

Praktische adviezen zijn:

- Houd vanwege de mogelijke (ernstige) bijwerkingen van NSAID's de dosering zo laag en de duur van het gebruik zo kort mogelijk. Zie voor doseringen (*tabel 3*).
- NSAID's (waarschijnlijk met uitzondering van naproxen) verhogen het risico op het optreden van veneuze trombo-embolische gebeurtenissen. Dit risico is afhankelijk van de toegepaste dosering, ook bij kortdurend gebruik.
- COX-2-selectieve NSAID's worden niet aanbevolen vanwege een hoger risico op cardiovasculaire complicaties zonder aangetoonde voordelen ten opzichte van de klassieke NSAID's gecombineerd met een protonpompremmer.
- Alle NSAID's (inclusief COX-2-selectieve) beïnvloeden de nierfunctie in gelijke mate nadelig. Bij verminderde nierfunctie kan acute nierinsufficiëntie of water- en zoutretentie optreden, waardoor hartfalen en hypertensie kunnen ontstaan of verergeren.

Patiëntkenmerken waarbij NSAID's afgeraden worden:

- Schrijf NSAID's bij voorkeur niet voor:
  - bij hypertensie, hartfalen of atherosclerotisch hart- en vaatlijden;
  - bij oorzaken die leiden tot dehydratie;
- Geef aan patiënten die een lage dosering acetylsalicylzuur als trombocytenaggregatieremmer gebruiken bij voorkeur geen ibuprofen.
- Als een NSAID toch noodzakelijk is bij patiënten met myocardinfarct en CVA in de voorgeschiedenis, dan is naproxen de eerste keus vanwege het laagste cardiovasculaire risico; diclofenac is bij hen gecontra-indiceerd.
- Schrijf geen NSAID's voor aan patiënten die anticoagulantia (risico op bloedingen in combinatie met verlengde protrombinetijd met fatale afloop in het bijzonder bij ouderen),… gebruiken.

Adjuvantia

- TCA’s zijn gecontra-indiceerd na een recent hartinfarct, cardiale geleidingsstoornissen en bij dementie. Terughoudendheid is geboden bij (voorgeschiedenis van of verhoogd risico op) urineretentie, lever- of nier-functiestoornis, glaucoom, epilepsie, obstipatie, prostatisme en cardiovasculaire aandoeningen zoals hartfalen. Overweeg een ecg bij patiënten met een verhoogde gevoeligheid voor cardiovasculaire bijwerkingen voorafgaand aan de start met een TCA (zie de NHG-Standaarden Depressie en Angst).
- Overweeg behandeling met gabapentine als een TCA onvoldoende effect heeft, bij ongewenste bijwerkingen of bij een cardiovasculaire contra-indicatie voor een TCA. …

5.8.3 WOREL 2017

Paracetamol
No specific recommendations were provided.

NSAID
… Daarnaast blijkt uit meta-analyses van 280 RCT's (n=124 513) die verschillende regelmatig en op lange termijn genomen NSAID’s vergeleken met placebo, dat men moet rekening houden met het cardiovasculaire risico (myocardinfarct en coronaire hartziekte). Alle NSAID's werden daarnaast geassocieerd met een verhoogd risico op hartfalen. De Canadese richtlijn uit 2012 beveelt, op basis van twee reeds oude artikels (een niet-systematische review en een consensusvergadering, dus met zeer laag niveau van bewijskracht) aan om NSAID’s te beperken, en ze slechts aan lage dosis en voor korte duur te gebruiken bij musculoskeletale aandoeningen.

Adjuvantia
Amitriptyline is gecontra-indiceerd in geval van significante hartritmestoornissen en stoornis van de cardiale geleiding.

5.8.4 NICE 2017
No specific recommendations were provided.

5.8.5 ASCO 2017
No specific recommendations were provided.

5.8.6 DOH_Ireland 2015

Paracetamol
No specific recommendations were provided.

NSAID
Cardiovascular risk with NSAID use

Recent evidence has linked NSAID use to cardiovascular risk.
• Kearney et al (2006), in a meta-analysis of randomised trials, showed that COX-2 selective inhibitors demonstrate an increased risk of thrombotic cardiovascular adverse reactions, particularly myocardial infarction (MI) and stroke.
• Following a comprehensive Europe-wide review of clinical trial and epidemiological data in 2006, the Commission on Human Medicines advised that non-selective NSAIDs may also be associated with a small increased risk of thrombotic events when used at high doses and for long term treatment. The findings from two more recent studies are consistent with, and hence validate, the earlier 2006 review. In addition, the newer studies reported an increased cardiovascular risk with all users of NSAIDs, irrespective of their baseline cardiovascular risk, and not only in chronic users. However, the greatest concern relates to chronic use of high doses. The risk is associated with COX-2-selective inhibitors, high dose diclofenac and high dose ibuprofen (>1200mg per day). Evidence indicates that naproxen is not associated with such a risk.

Adjuvantia
No specific recommendations were provided.

5.9 Specific patient groups: gastro-intestinal risk

5.9.1 Summary

Paracetamol

No specific recommendations are provided.

NSAID

The NHG 2018 guideline recommends avoiding NSAID in patients with an increased gastro-intestinal risk. NSAID are not recommended in patients on anticoagulants. The combination ibuprofen and acetylsalicylic acid is not recommended.
COX-2 selective NSAID are not recommended. The addition of PPI to traditional NSAID is recommended in patients with an increased gastro-intestinal risk.
Avoid NSAID in combination with drugs that are contra-indicated in patients with peptic ulcer in their history (e.g. clopidogrel, prasugrel, ticagrelor, glucocorticoids, SSRI's, spironolactone). If NSAID are necessary in patients with a peptic ulcer in their history, select diclofenac or ibuprofen (both + PPI).

The DOH_Ireland 2015 guideline recommends double dose H2-antagonists or a PPI in patients taking NSAIDs who are at high risk of gastrointestinal complications. Patients in this category could also be considered for a COX-2 inhibitor, depending on their cardiovascular risk factor profile.
Gastro-intestinal risk factors?
- Absent: traditional NSAID
- Present: traditional NSAID + PPI or COX-2 inhibitor

For more information on the selection of NSAID with the lowest gastro-intestinal risk, see "5.2 NSAID".

Adjuvantia

The WOREL 2017 mentions to be cautious with use of amitriptyline in patients with chronic constipation.

5.9.2 NHG 2018

Paracetamol

No specific recommendations were provided.

NSAID

Praktische adviezen zijn:

- Houd vanwege de mogelijke (ernstige) bijwerkingen van NSAID's de dosering zo laag en de duur van het gebruik zo kort mogelijk. Zie voor doseringen (*tabel 3*).
- Kies afhankelijk van specifieke patiëntkenmerken (comorbiditeit, voorgeschiedenis van cardiovasculaire of gastro-intestinale aandoeningen, respons op eerder voorgeschreven NSAID's, indicatie voor intramusculaire toediening) voor naproxen, ibuprofen of diclofenac. Naproxen heeft het laagste cardiovasculaire risico, diclofenac het hoogste (dosisafhankelijk). Van de klassieke NSAID's heeft diclofenac het laagste gastro-intestinale risico, naproxen het hoogste.
- COX-2-selectieve NSAID's worden niet aanbevolen vanwege een hoger risico op cardiovasculaire complicaties zonder aangetoonde voordelen ten opzichte van de klassieke NSAID's gecombineerd met een protonpompremmer. De COX-2-selectieve NSAID's geven minder gastro-intestinale complicaties dan de klassieke NSAID's, maar geven in ongeveer gelijke mate aspecifieke maagklachten (maagpijn).
- Combineer een klassiek NSAID (ook na parenterale toediening) met een protonpompremmer in standaard-dosering als het gastro-intestinale risico is verhoogd (zie de NHG-Standaard Maagklachten, onderdeel Maagbescherming). Er is geen relatie tussen het optreden van aspecifieke maagklachten en het optreden van gastro-intestinale complicaties.

Noot 34: COX-2-selectief NSAID versus klassiek NSAID met protonpompremmer

Conclusie

Als een NSAID noodzakelijk is bij patiënten met een verhoogd risico op ernstige maagcomplicaties, wordt een combinatie van een klassiek NSAID met een protonpompremmer aangeraden. Ook om het ontstaan van dyspeptische klachten te voorkomen heeft toevoeging van een protonpompremmer aan een klassiek NSAID de voorkeur boven vervanging door een COX-2-selectief NSAID [Van den Bemt 2007, Spiegel 2006].

Patiëntkenmerken waarbij NSAID's afgeraden worden:

- Schrijf NSAID's bij voorkeur niet voor:
  - bij een verhoogd gastro-intestinaal risico;
  - bij inflammatoire darmziekten;
- Als een NSAID toch noodzakelijk is bij patiënten met een peptisch ulcus in de voorgeschiedenis, dan gaat de voorkeur uit naar diclofenac (vanwege het laagste risico op gastro-intestinale complicaties) of ibuprofen (beide met een protonpompremmer).

- Combineer geneesmiddelen die gecontra-indiceerd zijn bij een peptisch ulcus in de voorgeschiedenis (zoals clopidogrel, prasugrel of ticagrelor, systemisch werkende glucocorticoiden, SSRI's en spironolacton) bij voorkeur niet met een NSAID (zie de NHG-Standaard Maagklachten).

Adjuvantia
No specific recommendations were provided.

5.9.3 WOREL 2017

Paracetamol
No specific recommendations were provided.

NSAID
Besides a general warning, no specific recommendations were provided.

Adjuvantia
Amitriptyline. Voorzichtigheid is geboden bij gebruik van amitriptyline in geval van urineretentie, geslotenhoekglaucoom, chronische obstipatie of prostaathypertrofie.

5.9.4 NICE 2017

No specific recommendations were provided.

5.9.5 ASCO 2017

No specific recommendations were provided.

5.9.6 DOH_Ireland 2015

Paracetamol
No specific recommendations were provided.

NSAID
Risk stratification and identification of the individual cardiovascular and GI risk factors should inform the decision regarding choice of NSAID and gastroprotective strategy. In the absence of any GI risk factors, patients may be managed with a traditional NSAID. In the presence of GI risk factors, the choice can be made between traditional NSAID and a PPI, or a COX-2 inhibitor.

Patients taking NSAIDs who are at high risk of gastrointestinal complications should be prescribed either double dose H2-antagonists or a proton pump inhibitor as pharmacological prophylaxis. Patients in this category could also be considered for a COX-2 inhibitor, depending on their cardiovascular risk factor profile. (evidence category C)

Adjuvantia
No specific recommendations were provided.

5.10 Specific patient groups: elderly

5.10.1 Summary

Paracetamol

The NHG 2018 guidelines recommends paracetamol as first choice for the treatment of chronic pain, especially in the elderly as they are at increased risk for side effects from other analgesics such as NSAID. The recommend dose for elderly is 2g (1.5g if multiple risk factors for liver damage are present).

NSAID

The NHG guideline does not recommend oral NSAID in elderly who are vulnerable. Due to their safer toxicity profile, topical NSAID can also be used in elderly with reduced kidney function or heart failure.

Adjuvantia
The NHG 2018 guideline recommends nortriptyline for neuropathic pain in the elderly because of less central anticholinergic adverse effects compared to amitriptyline (which is recommended in adults). Dose adjustments of the adjuvantia should be considered in the elderly.

5.10.2 NHG 2018

Paracetamol
Algemeen
Bij acute en chronische pijn is paracetamol voor patiënten van alle leeftijden eerste keus, omdat dit middel van de beschikbare pijnstillers het breedste veiligheidsprofiel heeft en er zeer ruime ervaring mee is opgedaan. Dit geldt in het bijzonder voor ouderen, omdat zij gevoeliger zijn voor bijwerkingen van andere analgetica zoals NSAID's.

Praktische adviezen zijn:

- De maximale dagdosering voor volwassenen met risicofactoren voor leverschade is 2 g (1,5 g indien meerdere risicofactoren tegelijk aanwezig zijn).
- Risicofactoren voor leverschade zijn: bestaande leverziekte, hoge leeftijd metabolisatiesnelheid daalt bij ouder worden), een genetisch bepaalde lage metabolisatiesnelheid, gebruik van carbamazepine, fenytoïne, fenobarbital, isoniazide, rifampicine (CY-P2E1-enzyminducerende middelen), lichaamsgewicht < 50 kg, vasten, slechte voedingstoestand (eiwitarm dieet), langdurig meer dan matig alcoholgebruik (> 2 alcoholconsumpties per dag), roken en gecombineerd gebruik van meerdere pijnstillers.

NSAID

Dermale NSAID's geven vergeleken met placebo vaker (doorgaans lichte en voorbijgaande) lokale bijwerkingen maar zijn minder sterk geassocieerd met systemische bijwerkingen en kunnen daardoor ook door ouderen met een verminderde nierfunctie of hartfalen gebruikt worden (mits de huid intact is).

Comment from consensus authors: see also "5.11 Topical analgesics".

Patiëntkenmerken waarbij NSAID's afgeraden worden:

- Schrijf NSAID's bij voorkeur niet voor:
  - aan kwetsbare ouderen; …

Noot 37: Kwetsbare ouderen en klassieke NSAID's en COX-2-selectieve NSAID's

Conclusie werkgroep

De werkgroep adviseert geen COX-2-selectieve NSAID's voor te schrijven aan kwetsbare ouderen, omdat zij juist een verhoogd risico op trombo-embolische complicaties hebben zodat COX-2-selectieve NSAID's bij hen gecontra-indiceerd zijn. Als een NSAID toch noodzakelijk is, adviseert de werkgroep het gebruik zo kort en de dosering zo laag mogelijk te houden en een klassiek NSAID met een protonpompremmer te geven. Kies het klassieke NSAID afhankelijk van de patiëntkenmerken (zie noot 31).

Adjuvantia

Neuropathische pijn

De tricyclische antidepressiva (TCA's) (vooral amitriptyline) zijn het meest onderzocht bij diverse vormen van neuropathische pijn, tonen goede effectiviteit en hebben daarom de voorkeur. Bij ouderen heeft nortriptyline de voorkeur, omdat het minder centrale anticholinerge bijwerkingen heeft die het cognitief functioneren kunnen beïnvloeden.

Note from consensus authors: for the recommended dosages of adjuvantia: see table 7 in "5.3 Adjuvantia". A lower dose (carabamazpine) or start low go slow principle (e.g. amitriptyline, nortriptyline) is recommended in the elderly.

5.10.3 WOREL 2017

No specific recommendations were provided.

5.10.4 NICE 2017

No specific recommendations were provided.

5.10.5 ASCO 2017

No specific recommendations were provided.

5.10.6 DOH_Ireland 2015

No specific recommendations were provided for the use of paracetamol, NSAID, or adjuvantia in the elderly.

5.11 Topical analgesics

5.11.1 Summary

Topical NSAID

The NHG 2018 guideline recommends paracetamol or topical NSAID for chronic pain due to **osteoarthritis** of the knee and hand. Topical NSAID are recommended over oral NSAID's considering the systemic adverse effects, especially in the elderly. Diclofenacgel 1%-3% or ibuprofengel 5% is recommended for **localised muscle or joint pain**. Topical NSAID are less associated with systemic adverse events. The combination of topical NSAID and paracetamol is an option.

The WOREL 2017 guideline recommends considering topical NSAID for chronic **musculoskeletal pain**, especially in patients who cannot tolerate oral NSAID. Photosensitivity reactions are possible, especially with ketoprofen. Compared to oral NSAID less gastro-intestinal side effects are observed.

The ASCO 2016 guideline recommends considering topical NSAID for the management of chronic pain.

Capsaicin

The NHG 2018 guideline does not recommend capsaicin for **neuropathic pain** in the first-line setting due to possible (severe) adverse events (painful skin reactions).

The NICE 2017 guideline recommends considering capsaicin **cream** for people with localised **neuropathic pain** who wish to avoid, or who cannot tolerate, oral treatments. The capsaicin **patch** is not recommended in the non-specialist setting.

The ASCO 2016 guideline summarizes the available evidence for topical capsaicin(8%) but does not provide any specific recommendation and also refers to the common localized skin reactions.

The DOH_Ireland 2015 guideline does not recommend topical capsaicin for the treatment of **cancer pain** due to the lack of available evidence for this indication. It may provide some degree of relief **in noncancer related neuropathic pain conditions** and could therefore be considered a worthwhile option as an adjunctive treatment.

Lidocaine

The NHG 2018 states that the use of lidocaine 5% can be considered for neuropathic pain, especially for **postherpetic neuralgia**.

The ASCO 2016 guideline recommends considering local anaesthetics for the management of chronic pain.

The DOH_Ireland 2015 guideline states that there is limited evidence to support the use of topical lidocaine plaster in **cancer pain.** There is some evidence in **post herpetic neuralgia and other benign neuropathic conditions**.

Other topical analgesics
Besides NSAID and local anaesthetics, the ASCO 2016 guideline recommends considering compounded creams/gels containing baclofen, amitriptyline, and ketamine for the management of chronic pain.

5.11.2 NHG 2018

Kernboodschappen

- Geef bij acute spier- en gewrichtspijn en chronische pijn als gevolg van knie- en handartrose paracetamol of een dermaal NSAID (minder bijwerkingen dan orale NSAID's).

Acute en chronische nociceptieve pijn
De huisarts volgt bij de medicamenteuze behandeling van zowel acute als chronische pijn een stapsgewijze aanpak, gebaseerd op de pijnladder van de WHO.

- Stap 1: paracetamol
- Stap 2: NSAID
    - diclofenacgel 1 tot 3% of ibuprofengel 5% op de huid bij gelokaliseerde spier- of gewrichtspijn;
    - oraal (eventueel rectaal of intramusculair) naproxen, ibuprofen of diclofenac afhankelijk van patiëntkenmerken.

Dermaal

Dermaal NSAID's zoals diclofenacgel 1 tot 3% of ibuprofengel 5% op de huid zijn effectief bij de behandeling van gelokaliseerde pijn en kunnen worden toegepast bij acute spier- en gewrichtspijn. Combinatie met paracetamol is mogelijk. Het effect van dermaal diclofenac op vermindering van pijn als gevolg van artrose van knie en hand is vergelijkbaar met dat van orale NSAID's. Dermale NSAID's geven vergeleken met placebo vaker (doorgaans lichte en voorbijgaande) lokale bijwerkingen maar zijn minder sterk geassocieerd met systemische bijwerkingen en kunnen daardoor ook door ouderen met een verminderde nierfunctie of hartfalen gebruikt worden (mits de huid intact is).

Praktische adviezen zijn:

- Diclofenacgel 1 tot 3% of ibuprofengel 5% 2 tot 4 dd zacht op pijnlijke plek inwrijven. Verwijder overtollige gel met een tissue en gooi deze weg bij het restafval. Probeer wegspoelen van gelresten via de douche- of gootsteenafvoer zoveel mogelijk te voorkomen.
- Er zijn geen gegevens bij gebruik langer dan 3 weken.

Neuropathische pijn

Praktische adviezen bij dermale medicatie

- Dermaal capsaïcine (als pleister of crème) in een concentratie van 8% is effectief bij de behandeling van neuropathische pijn, in het bijzonder van postherpetische neuralgie. Voorts is 8%-capsaïcinepleister effectief bij hiv-neuropathie. Er is onvoldoende bewijs voor de werkzaamheid van capsaïcine in een lagere dosering. Gezien het frequent optreden van soms ernstige bijwerkingen (pijnlijke, erythemateuze huidreacties), in het bijzonder bij onjuist gebruik van de pleister (voorbehandeling met een cutaan anestheticum is aangewezen), wordt gebruik van capsaïcine niet aanbevolen in de huisartsenpraktijk.
- Lidocaïne-5%-pleister is effectief en kan toegepast worden bij de behandeling van neuropathische pijn, in het bijzonder van postherpetische neuralgie. Gebruik daarvoor crème of zalf met lidocaïnebase (lidocaïnegel bevat in de regel lidocaïne in zoutvorm dat alleen geschikt is voor gebruik op slijmvliezen). Voorts geeft lidocaïne-prilocaïnecrème onder occlusie met een pleister pijnverlichting bij veneuze ulcera.

  Overwegingen

  Lidocaïne dient niet te worden voorgeschreven aan patiënten met ernstig leverfalen bij wie excessieve bloedconcentraties theoretisch denkbaar zijn.

5.11.3 WOREL 2017

Overweeg topische NSAID's voor de behandeling van patiënten met chronische musculoskeletale pijn, vooral bij die patiënten die geen orale NSAID's kunnen verdragen. (GRADE 1A)

Toelichting

Men dient wel rekening te houden met fotosensitiviteitsreacties, vooral met ketoprofen.

Basis voor de aanbeveling

…Topische NSAID’s bleken werkzamer dan placebo in het verminderen van pijn bij chronische musculoskeletale aandoeningen. De werkzaamheid van topische diclofenac was gelijkwaardig aan die van orale NSAID’s voor artose van de knie en van de hand. (Meestal lichte) huidreacties kwamen frequenter voor met topische NSAIDs dan met placebo of met orale NSAID’s, maar men zag wel een vermindering van de gastro-intestinale bijwerkingen in vergelijking met orale NSAIDs.

5.11.4 NICE 2017

Consider capsaicin cream for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments.

Do not start the following to treat neuropathic pain in non-specialist settings, unless advised by a specialist to do so:

capsaicin patch, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, topiramate, venlafaxine.

5.11.5 ASCO 2016

Clinicians may prescribe topical analgesics (such as commercially available nonsteroidal anti-inflammatory drugs; local anesthetics; or compounded creams/gels containing baclofen, amitriptyline, and ketamine), for the management of chronic pain.
(Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

A Cochrane review that included six studies and 2,073 patients found evidence that high-concentration (8%) topical capsaicin worked in only two types of neuropathic pain: pain
after shingles and nerve-injury pain resulting from HIV infection. Evidence of effectiveness in other types of neuropathy is limited. Localized skin reactions are common.

5.11.6 DOH_Ireland 2015

There is limited evidence to support the use of topical lidocaine plaster in cancer pain. (recommendation category D)

Key finding
While there is evidence to support the use of lidocaine 5% plasters in post herpetic neuralgia and other benign neuropathic conditions, further studies are needed to fully elucidate its benefit in cancer pain.

The lidocaine 5% plaster is a medicated adhesive plaster, indicated for the relief of neuropathic pain associated with post herpetic neuralgia (PHN). More recently, it is increasingly used for other painful neuropathic conditions. There is anecdotal evidence for use of lidocaine 5% plasters in cancer-induced bone pain, particularly vertebral metastases, which may have a neuropathic element. A maximum of three patches should be applied for 12 hours per day. Although there is minimal absorption, topical lidocaine should not be used in patients taking oral class I antiarrhythmic drugs.

Studies involving the use of the lidocaine plaster in a number of benign neuropathic conditions have shown it to be an effective and well tolerated topical analgesic. … To date, only one study has evaluated the lidocaine plaster in patients with cancer pain, and it failed to produce robust evidence in favour of its use.

Finnerup et al, (2015) conducted a systematic review and meta-analysis of randomised, double-blind studies of oral and topical pharmacotherapy for neuropathic pain, …
The authors conclude that lidocaine patches have a weak recommendation for use in neuropathic pain and are proposed as generally second line because of low effect sizes but high values or preferences and tolerability or safety. In some circumstances—eg, when there are concerns because of side-effects or safety of first-line treatments particularly in frail and elderly patients—lidocaine patches might be a first-line option.

To date, there has been extremely limited examination of use in the cancer setting…

There is insufficient evidence to recommend the use of topical capsaicin for the treatment of cancer pain. It may provide some degree of relief in noncancer related neuropathic pain conditions and could therefore be considered a worthwhile option as an adjunctive treatment.

Key finding
Limited available evidence suggests that capsaicin may be useful as an adjunctive treatment in the non-cancer setting. Studies are lacking in the cancer setting.

Topical creams containing capsaicin are used to treat a wide variety of conditions, including neuropathic pain. Following application to the skin, the capsaicin causes enhanced sensitivity to noxious stimuli, followed by a period of reduced sensitivity and, after repeated applications, persistent desensitisation.
• Derry et al (2009) undertook a systematic Cochrane review to determine the efficacy and tolerability of topically applied capsaicin in chronic neuropathic pain. …

- The evidence suggests that capsaicin, either as a repeated application of low dose 0.075% cream or a single application of a high dose 8% patch, may provide some degree of pain relief in a range of neuropathic conditions, over a period of 6 to 12 weeks.
- Capsaicin was found to be commonly associated with localised skin reactions, which were often mild and transient, but that could lead to withdrawal of the patch.
- The authors were unable to make robust estimates on the number of participants achieving clinically useful levels of pain relief, owing to limited data relating to different neuropathic conditions and inconsistent outcome definition.

• Finnerup et al, (2015) conducted a systematic review and meta-analysis of randomised, double-blind studies of oral and topical pharmacotherapy for neuropathic pain, …

- The results of five of seven studies (in patients with post-herpetic neuralgia or HIV-related painful polyneuropathy) showed sustained efficacy of a single application of high-concentration capsaicin patch (8%, better results for 60 min application in post-herpetic neuralgia and 30 min in HIV neuropathy) compared with a low-concentration patch (0.04%, to minimise the risk of unmasking related to the burning sensation of capsaicin).
- The authors concluded that the final quality of evidence was high but effect size was small. Combined NNT was 10.6 (95% CI 7.4–18.8). Results for the secondary outcomes were inconsistent.
- Therefore, the authors made a weak recommendation for use of capsaicin high- concentration patches as second line treatment for neuropathic pain.

The available evidence thus suggests that topical capsaicin may be useful as an add-on therapy for patients with painful neuropathic conditions with an inadequate response to, or intolerance of, other treatments. There is no evidence available examining the use of capsaicin in cancer pain

5.12 Alternative drugs and the role of Over The Counter (OTC) drugs

5.12.1 Summary

The NHG 2018 guideline points out that OTC NSAID are used frequently by patients who have an increased gastro-intestinal or cardiovascular risk or who are on anticoagulants. The guideline emphasizes the role of the primary care physician of being aware of this and informing these patients of the risks associated with NSAID.

The WOREL 2017 guideline does not include nutritional supplements in their recommendations for the treatment of chronic pain due to the lack of evidence.

The ASCO 2016 guideline states that the efficacy of varied neutraceuticals and botanicals marketed as complementary or alternative medicines and their longterm effectiveness for chronic pain have not been established.

5.12.2 NHG 2018

De huisarts dient alert te zijn op het feit dat de in Nederland vrij verkrijgbare pijnstillers van het NSAID-type dikwijls gebruikt worden door mensen met een reeds verhoogd risico op gastrointestinale of cardiovasculaire complicaties en door mensen die anticoagulantia gebruiken. De huisarts informeert de risicopatiënt over de gevaren hiervan, bijvoorbeeld door na een nieuwe
diagnose of gewijzigde medicatie de patiënt te wijzen op zijn gewijzigde risicoprofiel, en daarmee op de gevaren van NSAID's. In aansluiting op de gegeven mondelinge voorlichting kan de huisarts de patiënt verwijzen naar de informatie over pijn en pijnstillers op de NHGPubliekswebsite www.thuisarts.nl of de betreffende tekst (voorheen NHG-Patiëntenbrief) meegeven (via het HIS). Deze patiënteninformatie is gebaseerd op de NHG-Standaard.

Noot 20: Vrij verkrijgbare NSAID's en zelfmedicatie
Uit Nederlands cross-sectioneel onderzoek blijkt dat veel mensen de vrij verkrijgbare NSAID's (diclofenac, ibuprofen, naproxen) gebruiken. Bovendien wordt deze zelfmedicatie vaak toegepast door mensen met een verhoogde kans op ernstige complicaties. Bijna één op de drie mensen gebruikt een of meerdere NSAID's zonder recept en bijna één op de tien gebruikers neemt meer in dan de dagelijks aanbevolen maximumdosering. Omgerekend naar de gehele Nederlandse bevolking gaat het om ongeveer 333.000 mensen [Koffeman 2014].
Volgens de onderzoekers kan de huisarts een belangrijke rol spelen bij het bevorderen van veilig gebruik van de pijnstillers. Bijvoorbeeld door na een nieuwe diagnose of gewijzigde medicatie de patiënt te wijzen op zijn gewijzigde risicoprofiel, en daarmee op de gevaren van NSAID's.

5.12.3 WOREL 2017

Voedingstherapie

Er zijn weinig kwaliteitsvolle RCT's over het gebruik van voedingssupplementen in de behandeling van chronische pijn.
Voedingsinterventies bleken meestal werkzaam wanneer ze werden gecombineerd met ademhalingsoefeningen en acupunctuur. Het bewijs is nochtans beperkt. Daarom werd deze behandelingsvorm niet opgenomen in deze aanbeveling.

5.12.4 NICE 2017

No specific recommendations were provided.

5.12.5 ASCO 2016

The panel acknowledges that many other systemic nonopioids, including many other antidepressants and anticonvulsants, drugs in many other classes (such as the so-called muscle relaxants, benzodiazepines such as clonazepam, N-methyl-D-aspartate receptor blockers such as ketamine, and a-2 agonists such as tizanidine), and varied neutraceutical and botanicals marketed as complementary or alternative medicines, are taken by some cancer survivors with chronic pain and may benefit some of those who receive them. However, the efficacy of these agents and their longterm effectiveness have not been established.

5.12.6 DOH_Ireland 2015

No specific recommendations were provided.

6 Summary and conclusions from the literature review. Paracetamol

6.1 Paracetamol vs placebo for osteoarthritis

A Cochrane review by Towheed 2006 searched for all trials comparing paracetamol to placebo in osteoarthritis (any joint). The results can be found in the supplementary tables. Only trials in knee or hip osteoarthritis were found.

Since more up-to-date results for knee or hip osteoarthritis are included in a more recent Cochrane review by Leopoldino 2019, we will only report the summary of the results from Leopoldino 2019 (see below).

Paracetamol vs placebo for osteoarthritis of the knee or hip			
Bibliography: Cochrane Leopoldino 2019(17), containing: Altman 2007(18), Amadio 1983(19), Case 2003(20), Golden 2004(21), Herrero-Beaumont 2007(22), Miceli-Richard 2004(23), Pincus a 2004(24), Pincus b 2004(24), Prior 2014(25), Zoppi 1995(26)			
Outcomes	**N° of participants (studies)** **Follow up**	**Results**	**Quality of the evidence (GRADE)**
Mean change in pain (0-100 scale) Short term , where 0 = no pain	2355 (7 studies) 6w-6m	**MD -3.23 (-5.43 to -1.02)** **SS in favour of paracetamol**	⨁⨁⨁⨀ **MODERATE** Study quality: -1 unclear rando and allocation concealment in half the trials, some issues with incomplete outcome data Consistency: ok Directness: duration… Imprecision: ok
Physical function (WOMAC function 0- 100), 0 = better function	2354 (7 studies) 6w-6m	**MD -2.92 (-4.89 to -0.95)** **SS in favour of paracetamol**	⨁⨁⨁⨀ **MODERATE** Study quality: -1 unclear rando and allocation concealment in half the trials, some issues with incomplete outcome data Consistency: ok Directness: duration… Imprecision: ok
Total number of patients with adverse event	3252 (8 studies) 7d-12w	RR 1.01 (0.92 to 1.11) NS	⨁⨁⨁⨀ **MODERATE** Study quality: -1 unclear rando and allocation concealment in half the trials, some issues with incomplete outcome data Consistency: ok Directness: duration… Imprecision: ok
Withdrawals due to adverse events 24 weeks	3023 (7 studies) 7d-6m	RR 1.19 (0.91 to 1.55) NS	⨁⨁⨀⨀ **LOW** Study quality: -1 unclear rando and allocation concealment in half the trials, some issues with incomplete outcome data Consistency: ok Directness: ok Imprecision: -1 CI includes possible harm
Abnormal liver function tests	1237 (3 studies) 12 weeks – 6 months	**RR 3.79 (1.94 to 7.39)** **SS** **More abnormal liver test results with paracetamol**	⨁⨁⨁⨀ **MODERATE** Study quality: -1, issues with incomplete outcome data Consistency: ok Directness: ok Imprecision: ok

This Cochrane review by Leopoldino 2019 included all trials that compared paracetamol to placebo in patients with osteoarthtritis of the knee or hip. The dose of paracetamol used in the trials was 3 or 4 grams per day . Study duration for this comparison varied from 7 days to 6 months.

Our confidence in the results is limited by the following methodological problems: unclear randomization and allocation concealment in many trials and unclear or high risk of bias due to incomplete outcome data.

In patients with osteoarthritis of the knee or hip, treatment with paracetamol resulted in a **larger mean decrease in pain score** compared to treatment with placebo.
GRADE: MODERATE quality of evidence

In patients with osteoarthritis of the knee or hip, treatment with paracetamol resulted in a **larger decrease in the WOMAC physical function scale** compared to treatment with placebo.
GRADE: MODERATE quality of evidence

In patients with osteoarthritis of the knee or hip, **no difference in total number of patients with adverse events** was observed between treatment with paracetamol and treatment with placebo.
GRADE: MODERATE quality of evidence

In patients with osteoarthritis of the knee or hip, treatment with paracetamol did **not** result in a statistically significantly **higher withdrawal rate due to adverse events** compared to placebo.
GRADE: LOW quality of evidence

In patients with osteoarthritis of the knee or hip, treatment with paracetamol resulted in **more abnormal liver test results** compared to treatment with placebo.
GRADE: MODERATE quality of evidence

6.2 Paracetamol vs NSAID for osteoarthritis

NSAID (ibuprofen 2400 mg, diclofenac, arthrotec, celecoxib and naproxen **) versus paracetamol**			
Bibliography: Cochrane Towheed 2006(27), containing: Bradley 1991a(28), Bradley 1991b(28), Boureau 2004(29), Case 2003(20), Geba 2002a(30), Geba 2002b(30), Geba 2002 c(30), Golden 2004(21), Pincus 2001(31), Pincus a 2004(24), Pincus b 2004(24), Schnitzer 2005a(32), Shen 2004(33), Williams 1993(34)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Overall pain (multiple methods)	2358 (8 studies) 7d-6w	**SMD -0.25 [-0.33, -0.17]** **SS in favour of NSAID**	⊕⊕⊖⊖ **LOW** Study quality:-1 for quality problems Consistency:ok Directness:-1 short duration Imprecision:ok

WOMAC function	832 (2 studies) 6-12w	**SMD -0.25 [-0.40, -0.11]** **SS in favour of NSAID** But NS for some other function scores	⊕⊕⊖⊖ **LOW** Study quality:-1 quality problems Consistency: ok Directness:-1 low number of trials reported this outcome Imprecision: ok
Total number of patients with any adverse event	3168 (7 studies) 7d-6w	RR 1.01 [0.92, 1.11] NS	⊕⊕⊖⊖ **LOW** Study quality:-1 for quality problems Consistency:pk Directness: -1 short study duration Imprecision:ok
GI advserse events	4205 (13 studies) 7d-2y	traditional NSAID **RR 1.47 [1.08, 2.00]** **SS more GI adverse events with traditional NSAID** **NNH 12** Coxibs 0.98 [0.80, 1.20] NS	⊕⊕⊖⊖ **LOW** Study quality:-1 for quality problems Consistency: ok Directness:-1 study duration Imprecision:ok

This Cochrane review searched for all trials that compare paracetamol to NSAID in osteoarthritis (any joint). Only trials in knee or hip osteoarthritis were found. The NSAID included in this comparison are ibuprofen 2400 mg, diclofenac, arthrotec, celecoxib and naproxen. The dose of paracetamol used in the studies was usually 4 g per day. Study duration varied betweed 4 weeks to 2 years. The median duration was 6 weeks.

The quality assessment of the included trials judged the allocation concealment to be unclear in most of the included trials. The short study duration in some of the trials is also a limiting factor in interpreting the evidence.

In patients with osteoarthritis of the knee or hip, treatment with NSAID resulted in a **lower overall pain score** compared to treatment with paracetamol.
GRADE: LOW quality of evidence

In patients with osteoarthritis of the knee or hip, treatment with NSAID resulted in a **lower WOMAC function score** compared to treatment with paracetamol.
GRADE: LOW quality of evidence

In patients with osteoarthritis of the knee or hip, **no difference in total number of patients with adverse events** was observed between treatment with NSAID and treatment with paracetamol.

GRADE: LOW quality of evidence

In patients with osteoarthritis of the knee or hip, treatment with traditional NSAID resulted in a **higher rate of gastro-intestinal adverse events** compared to treatment with paracetamol. No difference in gastro-intestinal adverse events was observed for coxibs compared to paracetamol.
GRADE: LOW quality of evidence

6.3 Paracetamol vs ibuprofen for osteoarthritis

The Cochrane review by Towheed 2006(27) found 3 RCTs comparing paracetamol to ibuprofen in osteoarthritis. All three trials were shorter than 6 weeks and one was only published as an abstract.

1 systematic review and meta-analysis (Da Costa 2016 {da Costa, 2016 #26) found 2 RCTs for this comparison. 1 RCT did not meet our inclusion criteria, the other did not perform a statistical analysis for this comparison. More detail can be found in the supplementary tables.

6.4 Paracetamol vs placebo for low back pain

A Cochrane review by Saragiotto 2016 {Saragiotto, 2016 #28} found only 1 trial that compared paracetamol to placebo in chronic low back pain. This trial was later retracted, one of the authors 'not having consented to the submission and publication of the trial'. Therefore we could include no studies for this comparison.

6.5 Paracetamol vs ibuprofen for low back pain

A systematic review by Chou 2016 (35) found no RCTs comparing paracetamol to ibuprofen in low back pain.

6.6 Paracetamol for neuropathic pain

A Cochrane review by Wiffen 2016 (36) found no studies that met our inclusion criteria.

6.7 Paracetamol for cancer pain

A Cochrane review by Wiffen 2017 (37) found 3 trials studying paracetamol for cancer pain. None met our inclusion criteria, due to their short duration.

7 Summary and conclusions from the literature review. NSAID

7.1 Nonselective NSAID vs placebo in osteoarthritis

7.2 Diclofenac vs placebo in osteoarthritis

diclofenac vs placebo in osteoarthritis			
Bibliography: Systematic review Jevsevar 2018(38), containing: Gibofsky 2014(39), Sandelin 1997(40), Sangdee 2002(41), Simon 2009(42), Dickson 2001(43), McKenna 2001(44) Systematic review da Costa 2016(45), containing Bocanegra 1998(46), Yocum 2000(47)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain	758 (4 studies) 4-12 weeks	**ES -0.41 (-0.63 to -0.19)** **SS in favour of diclofenac** I^2= 27.9%	⨁⨁⨀⨀ **LOW** Study quality: -2 (2 RCTs short duration, 2 RCTs high attrition; unclear risk other) Consistency: ok Directness: ok Imprecision: ok
Function	911 (4 studies) 4-12 weeks	**ES -0.92 (-1.3 to -0.54)** **SS in favour of diclofenac** I^2= 29.3%	⨁⨁⨀⨀ **LOW** Study quality: -2 (1 RCT short duration, 2 RCTs unclear rando, 1 w unclear allocation concealment, 3 RCTs with high attrition, unclear risk other) Consistency: ok Directness: ok Imprecision: ok

This systematic review and meta-analysis sought RCTs evaluating treatments of interest in patients with knee osteoarthritis. Treatments of interest: intra-articular hyaluronic acid, IA corticosteroids, IA PRP, IA placebo, acetominophen, diclofenac, ibuprofen, naproxen, celecoxib and oral placebo.

Six RCTs were found that compared diclofenac with placebo. The duration of the trials varied between 4 and 12 weeks.

Two RCTs did not meet our inclusion criteria (duration). One RCT had unclear allocation concealment, two had unclear randomization, four had high attrition.

A different systematic review sought RCTs of NSAIDs in patients with knee or hip osteoarthritis. This was a network-meta-analysis that did not pool the results of the direct comparisons. Two additional RCTs, with durations ranging between 6 and 12 weeks were found. The results were comparable to those of the meta-analysis reported above.

Of the two RCTs, two had unclear allocation concealment, two had unclear blinding of investigators and one had a high risk of incomplete outcome data.

These methodological problems could lead to bias and limit our confidence in the results.

Treatment with diclofenac resulted in **more pain reduction** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Treatment with diclofenac resulted in **better physical function** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

7.3 Ibuprofen vs placebo in osteoarthritis

ibuprofen vs placebo in osteoarthritis			
Bibliography: Systematic review Jevsevar 2018(38), containing: Davies 1999(48), Puopolo 2007(49) Systematic review da Costa 2016(45) , containing: Day 2000(50), Hawkey 2000(51), Saag 2000(52), Wiesenhutter 2005(53) Additional RCT: Gordo 2017 (54)			
Outcomes	**N° of participants (studies)** **Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain	424 (2 studies) 4-12 weeks	**ES -0.43 (-0.66 to -0.21)** **SS in favour of ibuprofen** I^2= 0%	⨁⨁⊖⊖ **LOW** Study quality: -2 (1 RCT short duration, 1 RCT with high attrition, unclear risk other) Consistency: ok Directness: ok Imprecision: ok

Function	424 (2 studies) 4-12 weeks	**ES -0.78 (-1.38 to -0.18)** **SS in favour of ibuprofen** I^2= 0%	⊕⊕⊖⊖ **LOW** Study quality: -2 (1 RCT short duration, 1 RCT with high attrition, unclear risk other) Consistency: ok Directness: ok Imprecision: ok

This systematic review and meta-analysis sought RCTs evaluating treatments of interest in patients with knee osteoarthritis. Treatments of interest: intra-articular hyaluronic acid, IA corticosteroids, IA PRP, IA placebo, acetominophen, diclofenac, ibuprofen, naproxen, celecoxib and oral placebo.

Two RCTs were found that compared ibuprofen with placebo. The duration of the trials varied between 4 and 12 weeks.

One RCT did not meet our inclusion criteria (duration). The other RCT had high attrition.

A different systematic review sought RCTs of NSAIDs in patients with knee or hip osteoarthritis. This was a network-meta-analysis that did not pool the results of the direct comparisons. Four additional RCTs, with durations ranging between 6 and 24 weeks were found. The results were comparable to those of the meta-analysis reported above. The primary outcome of one of the RCTs was ulcers at 12 weeks; significantly more ulcers were detected with ibuprofen treatment compared to placebo.

Of the four RCTs, three had unclear allocation concealment and all four had a high risk of incomplete outcome data.

Finally, one additional RCT was found by our literature search. This 6-week trial did not find a statistically significant difference in pain reduction between ibuprofen and placebo. It had unclear allocation concealment and high attrition.

The methodological problems of these trials could lead to bias and limit our confidence in the results.

Treatment with ibuprofen resulted in **more pain reduction** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Treatment with ibuprofen resulted in **better physical function** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

7.4 Naproxen vs placebo in osteoarthritis

naproxen vs placebo in osteoarthritis			
Bibliography: Systematic review Jevsevar 2018(38), containing: Essex 2014(55), Hochberg 2011 a(56), Hochberg 2011 b(56), Schnitzer 2010(57), Schnitzer 2011(58), Svensson 2006(59) Systematic review da Costa 2016(45), containing Baerwald 2010(60), Bensen 1999(61), Essex 2012a(62), Lohmander 2005(63), Makarowski 2002(64), Reginster 2007(65), Schnitzer 2005(66)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain	2122 (6 studies) 6-53 weeks	**ES -0.38 (-0.47 to -0.30)** **SS in favour of naproxen** I^2= 3.9%	⨁⨁⨀⨀ **LOW** Study quality: -2 (2 RCTs w unclear rando and allocation concealment, 3 RCTs with high attrition, unclear risk other) Consistency: ok Directness: ok Imprecision: ok
Function	2122 (6 studies) 6-53 weeks	**S -1.27 (-1.51 to -1.03)** **SS in favour of naproxen** I^2= 0%	⨁⨁⨀⨀ **LOW** Study quality: -2 (2 RCTs w unclear rando and allocation concealment, 3 RCTs with high attrition, unclear risk other) Consistency: ok Directness: ok Imprecision: ok

This systematic review and meta-analysis sought RCTs evaluating treatments of interest in patients with knee osteoarthritis. Treatments of interest: intra-articular hyaluronic acid, IA corticosteroids, IA PRP, IA placebo, acetaminophen, diclofenac, ibuprofen, naproxen, celecoxib and oral placebo.

Two RCTs were found that compared naproxen with placebo. The duration of the trials varied between 6 and 53 weeks.

2 RCTs had unclear randomization and allocation concealment. Three RCTs had high attrition.

A different systematic review sought RCTs of NSAIDs in patients with knee or hip osteoarthritis. This was a network-meta-analysis that did not pool the results of the direct comparisons. Six additional RCTs,

with durations ranging between 6 and 15 weeks were found. The results were comparable to those of the meta-analysis reported above, although in two trials the improvement in pain with naproxen did not reach statistical significance in comparison to placebo.

Of the Six RCTs, all had unclear allocation concealment and four had a high risk of incomplete outcome data. In four it was unclear how the investigator was blinded to the intervention.

These methodological problems could lead to bias and limit our confidence in the results.

Treatment with naproxen resulted in **more pain reduction** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Treatment with naproxen resulted in **better physical function** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

7.5 Nabumetone vs placebo for osteoarthritis

Nabumetone vs placebo for osteoarthritis

We found four RCTs comparing nabumetone to placebo for osteoarthritis: Blechman 1987(67), Weaver 1995(68), Makarowski 1996(69), and Kivitz 2004(70).

All trials had a duration of 6 weeks.

3 trials evaluated nabumetone 1000 mg/day, and one trial evaluated nabumetone in a higher than recommended dose of 1500 mg/day.

Pain was assessed in different ways (patient's assessment of degree of pain due to OA, knee pain on weight bearing, knee pain when in motion) and most trials did not provide quantitative data for these results. This makes it challenging to summarize and to assess the clinical relevance of the results.

Unclear reporting of randomization and allocation concealment and problems with selective reporting could lead to bias, and further limit our confidence in the results.

In all trials but one; use of nabumetone led to a statistically significant **reduction of pain outcomes** at week 6.

There was **no statistically significant difference** in (all) adverse events between nabumetone 1000 mg/day and placebo.

There were **more adverse events** with nabumetone **1500 mg/day** than with placebo.

GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

7.6 COX-2-selective NSAID vs placebo in osteoarthritis

7.7 Celecoxib vs placebo

celecoxib vs placebo in osteoarthritis			
Bibliography: Cochrane Puljak 2017(71), containing: Asmus 2014 study 1(72), Asmus 2014 study 2(72), Bensen 1999(61), Bingham 2007 study 1(73), Bingham 2007 study 2(73), Birbara 2006 study 1(74), Birbara 2006 study 2(74), Boswell 2008 study a(75), Boswell 2008 study b(75), Clegg 2006(76), Conaghan 2013(77), DeLemos 2011(78), Essex 2012b(62), Essex 2014(55), Fleischmann 2005(79), Gibofsky 2003(80), Hochberg 2011 study 307(56), Hochberg 2011 study 309(56), Kivitz 2001(81), Lehmann 2005(82), McKenna 2001a(44), McKenna 2001b(44), Pincus 2004 PACES-a(24), Pincus 2004 PACES-b(24), Rother 2007(83), Schnitzer 2011(84), Sheldon 2005(85), Smugar 2006 study 1(86), Smugar 2006 study 2(86), Tannenbaum 2004(87), Williams 2000(88), Williams 2001(89) Additional RCTs: Essex 2016(90), RCT Gordo 2017 (54), Lee 2017(91)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain	1622 (4 studies) 6-24 weeks 357 (1 study) 6 weeks	I^2=0% **Std. MD -0.22 (-0.32 to -0.12)** **SS less pain with celecoxib** Celecoxib: -37.1 Placebo: -33.6	⊕⊕⊖⊖ **LOW** Study quality: -1 (1 RCT unclear rando and 2 w unclear allocation concealment, 4 RCTs high attrition, 1 RCT high risk of selective reporting) Consistency: -1 Directness: ok Imprecision: ok

		LSM -3.5 (-9.3 to 2.3) NS	
	362 (1 study) 6 weeks	Celecoxib: -5.7 Placebo: -2.6 **TD -3.1 (-5.1 to -1.2)** **SS in favour of celecoxib**	
	388 (1 study) 6 weeks	Per protocol population: Difference in LS means: -5.26 (-13.06 to 2.54) NS ***SS in mITT population:*** ***-9.41 (-16.34 to -2.52)*** ***P=0.0076***	
Physical function	1622 (4 studies) 6-24 weeks	I^2= 0% **Std. MD -0.17 (-0.27 to -0.07)** **SS in favour of celecoxib**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (2 RCTs high attrition, 1 RCT high risk of selective reporting) Consistency: ok Directness: ok Imprecision: ok
	362 (1 study) 6 weeks	Celecoxib: -5.7 Placebo: -2.6 **TD -3.1 (-5.1 to -1.2)** **SS in favour of celecoxib**	
Number withdrawn due to adverse events	12965 (28 studies) 6-24 weeks	Celecoxib: 428/ 7685 Placebo: 303/ 5280 I^2=22% Peto OR 0.99 (0.85 to 1.15) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (15 RCTs unclear rando, 23 w unclear allocation concealment, 20 RCTs with high and/or unbalanced attrition, 5 RCTs with high and 7 with unclear risk of selective reporting) Consistency: ok Directness: ok Imprecision: ok
Number experiencing any serious adverse events	13393 (28 studies) 6-24 weeks	Celecoxib: 71/7745 Placebo: 56/5648 I^2=12% Peto OR 0.95 (0.66 to 1.36) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (16 RCTs unclear rando, 23 w unclear allocation concealment, 21 RCTs with high and/or unbalanced attrition, 9 RCTs with high and 6 with

			unclear risk of selective reporting) Consistency: ok Directness: ok Imprecision: ok
Number experiencing gastro-intestinal events (perforation, ulcer, bleeds)	3263 (8 studies) 6-24 weeks	Celecoxib: 3/2010 Placebo: 1/1523 I^2= 24% Peto OR 1.91 (0.24 to 14.90) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 (5 RCTs unclear rando, 7 w unclear allocation concealment, 7 RCTs with high and/or unbalanced attrition, 6 RCTs with high risk of selective reporting) Consistency: ok Directness: ok Imprecision: -1 (95%CI contains both appreciable harm and benefit)
Number experiencing cardiovascular events (myocardial infarction, stroke)	2947 (5 studies)	Celecoxib: 6/1785 Placebo: 1/1162 I^2= 0% Peto OR 3.40 (0.73 to 15.88) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 (2 RCTs unclear rando, 3 w unclear allocation concealment, 4 RCTs with high and/or unbalanced attrition, 3 RCTs with high risk of selective reporting) Consistency: ok Directness: ok Imprecision: -1 (95%CI contains both appreciable harm and benefit)

This systematic review and meta-analysis sought RCTs comparing celecoxib 200 mg daily versus no intervention, placebo or other nonselective NSAID in knee and/or hip osteoarthritis.

The main analysis of this Cochrane review evaluated only RCTs with low risk of bias for randomization, allocation concealment and blinding.

Four RCTs were with low risk of bias for randomization, allocation concealment and blinding were found that compared COX-2-selective NSAID with placebo. The duration of the trials varied between 9 days and 16 weeks.

Some of these trials had high attrition and high risk of selective reporting. There were no differences with the analysis with all eligible studies for the comparison of celecoxib and placebo.

Safety outcomes included all eligible studies, of which many had unclear reporting of randomization and allocation concealment in addition to high attrition and unclear or high risk of selective reporting.

The author of the Cochrane systematic review expressed concern over the industry involvement in these studies and possible publication bias: “We are highly reserved about results due to pharmaceutical

industry involvement and limited data. We were unable to obtain data from three studies, which included 15,539 participants, and classified as awaiting assessment."

Three additional RCTs were found. 1 had unclear randomization, 2 had unclear allocation concealment and 2 had high or unbalanced attrition.

These methodological problems could lead to bias and limit our confidence in the results.

Treatment with celecoxib resulted in **more pain reduction** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Treatment with celecoxib resulted in **better physical function** compared to placebo treatment.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **the number of patients withdrawn due to adverse events** between celecoxib and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **the number of patients experiencing any serious adverse events** between celecoxib and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **the number of patients experiencing gastro-intestinal events** between celecoxib and placebo.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **the number of patients experiencing cardiovascular events** between celecoxib and placebo.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

7.8 Etoricoxib vs placebo

etoricoxib vs placebo in osteoarthritis
Bibliography:

Systematic review da Costa 2016(45), containing Gottesdiener 2002(92), Leung 2002(93), Puopolo 2007(49), Reginster 2007(65), Wiesenhutter 2005(53)

This systematic review sought RCTs of NSAIDs in patients with knee or hip osteoarthritis. This was a network-meta-analysis that did not pool the results of the direct comparisons.

It found five RCTs, with durations ranging between 12 and 14 weeks, that compared etoricoxib to placebo.

Two out of five RCTs had unclear allocation concealment and five had a high risk of incomplete outcome data.

These methodological problems could lead to bias and limit our confidence in the results.

Pain was assessed in all five RCTs and in all trials treatment with etoricoxib resulted in **more pain reduction** compared to placebo.

Physical function was assessed in four trials and in all these trials treatment with etoricoxib resulted in **better physical function** compared to placebo.

GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

7.9 COX-2-selective NSAID vs nonselective NSAID in osteoarthritis

COX-2-selective NSAID vs nonselective NSAID for osteoarthritis			
Bibliography: Cochrane Puljak 2017(71), containing: Bensen 1999(61), Dahlberg 2009(94), Emery 2008(95), Essex 2012a(96), Essex 2012b(62), Essex 2014(55), Kivitz 2001(81), McKenna 2001b(44), Sowers 2005(97)			
Outcomes	**N° of participants (studies)** **Follow up**	**Results**	**Quality of the evidence (GRADE)**

Pain	1180 (2 studies) 12- 52 weeks	I^2=65% MD -4.52 (-10.65 to 1.61) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (1 RCT with high attrition) Consistency: ok Directness: ok Imprecision: ok
Physical function	264 (1 study) 12 weeks	I^2=/ **MD -4.00 (-11.40 to -0.60)** **SS in favour of celecoxib**	⊕⊕⊖⊖ **LOW** Study quality: -1 (single study, unclear risk of incomplete outcome data) Consistency: -1 (no NS difference in all eligible studies) Directness: ok Imprecision: ok
Number withdrawn due to adverse events	3150 (8 studies) 6-52 weeks	Celecoxib: 114/1577 Nonselective NSAID: 117/1573 I^2= 34% Peto OR 0.97 (0.74 to 1.27) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (2 RCTs unclear rando, 6 w unclear allocation concealment, 8 RCTs with high and/or unbalanced attrition, 5 RCTs with high and 4 with 3 unclear risk of selective reporting) Consistency: ok Directness: ok Imprecision: ok
Number experiencing any serious adverse events	2404 (5 studies) 6-52 weeks	Celecoxib: 76/1204 Nonselective NSAID: 82/1200 I^2= 32% Peto OR 0.92 (0.66 to 1.28) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (1 RCT unclear rando, 3 w unclear allocation concealment, 5 RCTs with high and/or unbalanced attrition, 2 RCTs with high and 2 with unclear risk of selective reporting) Consistency: ok Directness: ok Imprecision: ok
Number experiencing gastro-intestinal events (perforation, ulcer, bleeds)	1755 (4 studies) 6-52 weeks	Celecoxib: 3/877 Nonselective NSAID: 5/878 I^2= 38% Peto OR 0.61 (0.15 to 2.43) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 (1 RCT unclear rando, 2 w unclear allocation concealment, 4 RCTs with high and/or unbalanced attrition, 1 RCT with high and 2 with unclear risk of selective reporting) Consistency: ok Directness: ok Imprecision: -1 (95%CI contains both appreciable harm and benefit)

Number experiencing cardiovascular events (myocardial infarction, stroke)	916 (1 study) 52 weeks	Celecoxib: 5/458 Nonselective NSAID: 11/458 I^2= / Peto OR 0.47 (0.17 to 1.25) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (single study with high attrition and unclear risk of selective reporting) Consistency: NA Directness: ok Imprecision: ok

This systematic review and meta-analysis sought RCTs comparing celecoxib 200 mg daily versus no intervention, placebo or other nonselective NSAID in knee and/or hip osteoarthritis.

The main analysis of this Cochrane review evaluated only RCTs with low risk of bias for randomization, allocation concealment and blinding.

Two RCTs with low risk of bias for randomization, allocation concealment and blinding were found that compared celecoxib to placebo. The duration of the trials varied between 6 and 52 weeks.

One of these trials had high attrition.

One outcome showed a difference between the low risk of bias analysis and the analysis of all eligible trials: physical function: 6% absolute improvement in low risk of bias, no difference in all eligible studies.

Safety outcomes included all eligible studies, of which many had unclear reporting of randomization and allocation concealment in addition to high attrition and unclear or high risk of selective reporting.

The author of the Cochrane systematic review expressed concern over the industry involvement in these studies and possible publication bias: “We are highly reserved about results due to pharmaceutical industry involvement and limited data. We were unable to obtain data from three studies, which included 15,539 participants, and classified as awaiting assessment.”

These methodological problems could lead to bias and limit our confidence in the results.

There was **no statistically significant difference** in **pain reduction** between celecoxib and nonselective NSAID.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

Treatment with celecoxib resulted in **better physical function** compared to nonselective NSAID treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **the number of patients withdrawn due to adverse events** between celecoxib and nonselective NSAID.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **the number of patients experiencing any serious adverse events** between celecoxib and nonselective NSAID.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **the number of patients experiencing gastro-intestinal events** between celecoxib and nonselective NSAID.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **the number of patients experiencing cardiovascular events** between celecoxib and nonselective NSAID.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

7.10 Celecoxib vs ibuprofen

Celecoxib vs ibuprofen for osteoarthritis			
Bibliography: RCT Gordo 2017 (54)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain VAS	388 (1 study) 6 weeks	*Per protocol population* Difference in LS means: 2.76 (-3.38 to 8.90) Celecoxib is non-inferior to ibuprofen (when lower bound defined as greater than -10) *Also NS in mITT population*	⨁⨁⨀⨀ **LOW** Study quality: -2 (single study with unclear description of drop-out and unclear allocation concealment) Consistency: NA Directness: ok Imprecision: ok
Upper gastrointestinal events *Defined as a moderate or severe instance of one or*	388 (1 study) 6 weeks	Celecoxib: 1.3% Ibuprofen: 5.1% Placebo: 2.5% NS between-group differences	⨁⨀⨀⨀ **VERY LOW** Study quality: -2 (single study with unclear description of drop-out and unclear allocation concealment) Consistency: NA Directness: ok Imprecision: -1 (no CI)

more of abdominal pain, dyspepsia, and/or nausea	

We found one RCT comparing celecoxib 200 mg to ibuprofen 800 mg 3x/day for osteoarthritis.

The trial had a duration of 6 weeks.

It had an unclear description of drop-out and exclusions and unclear allocation concealment.

These methodological problems could lead to bias and limit our confidence in the results.

There was **no statistically significant difference** in **pain reduction** between celecoxib and ibuprofen.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **upper gastrointestinal events** between celecoxib and ibuprofen.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

7.11 Celecoxib vs diclofenac

Celecoxib 200 mg vs diclofenac 100 mg for osteoarthritis			
Bibliography: Cochrane Puljak 2017(71), containing: Dahlberg 2009(94)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain	916 (1 study) 52 weeks	I^2= / MD -2.0 (-5.32 to 1.32) NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (single study with high attrition) Consistency: NA Directness: ok Imprecision: ok

Number withdrawn due to adverse events	916 (1 study) 52 weeks	Celecoxib: 27/458 Nonselective NSAID: 19/458 I^2= / Peto OR 1.44 (0.80 to 2.61) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (single study with high attrition and unclear risk of selective reporting of AE) Consistency: NA Directness: ok Imprecision: ok
Number experiencing any serious adverse events	916 (1 study) 52 weeks	Celecoxib: 62/458 Nonselective NSAID: 68/458 I^2= / Peto OR 0.90 (0.62 to 1.30) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (single study with high attrition and unclear risk of selective reporting of AE) Consistency: NA Directness: ok Imprecision: ok
Number experiencing gastro-intestinal events (perforation, ulcer, bleeds)	916 (1 study) 52 weeks	Celecoxib: 0/458 Nonselective NSAID: 2/458 I^2= / Peto OR 0.14 (0.01 to 2.16) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (single study with high attrition and unclear risk of selective reporting of AE) Consistency: NA Directness: ok Imprecision: -1 (95%CI contains both appreciable harm and benefit)
Number experiencing cardiovascular events (myocardial infarction, stroke)	916 (1 study) 52 weeks	Celecoxib: 5/458 Nonselective NSAID: 11/458 I^2= / Peto OR 0.47 (0.17 to 1.25) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (single study with high attrition and unclear risk of selective reporting of AE) Consistency: NA Directness: ok Imprecision: ok

celecoxib 200 mg vs diclofenac 150 mg for osteoarthritis			
Bibliography: Cochrane Puljak 2017(71), containing: Emery 2008(95), McKenna 2001b(44)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain	398 (1 study) 6 weeks	VAS I^2= / MD 1.90 (-3.68 to 7.48) NS WOMAC I^2= / MD 0.30 (-0.52 to 1.12) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (single study with high and unbalanced attrition) Consistency: ok Directness: ok Imprecision: ok

Physical function	398 (1 study) 6 weeks	WOMAC I^2= / MD 1.90 (-0.72 to 4.52) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (single study with high and unbalanced attrition) Consistency: NA Directness: ok Imprecision: ok
Number withdrawn due to adverse events	650 (2 studies) 6 -12 weeks	Celecoxib: 27/325 Nonselective NSAID: 34/325 I^2= 10% Peto OR 0.78 (0.46 to 1.32) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (high attrition and high risk of selective reporting of AE) Consistency: ok Directness: ok Imprecision: ok
Number experiencing any serious adverse events	647 (2 studies) 6 -12 weeks	Celecoxib: 4/325 Nonselective NSAID: 5/322 I^2= 82% Peto OR 0.79 (0.21 to 2.93) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 (high attrition and high risk of selective reporting of AE) Consistency: -1 (high heterogeneity) Directness: ok Imprecision: -1 (95%CI contains both appreciable harm and benefit)
Number experiencing gastro-intestinal events (perforation, ulcer, bleeds)	252 (1 study) 12 weeks	Celecoxib: 2/126 Nonselective NSAID: 0/126 I^2= / Peto OR 7.45 (0.46 to 119.74) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 (high attrition and high risk of selective reporting of AE) Consistency: NA Directness: ok Imprecision: -1 (95%CI contains both appreciable harm and benefit)

This systematic review and meta-analysis sought RCTs comparing celecoxib 200 mg daily versus no intervention, placebo or other nonselective NSAID in knee and/or hip osteoarthritis.

Three RCTs were found that compared celecoxib to diclofenac (100 or 150 mg/day). The duration of the trials varied between 6 and 52 weeks.

All trials had high attrition. Two had an unclear to high risk of selective reporting of safety outcomes.

These methodological problems could lead to bias and limit our confidence in the results.

There was **no statistically significant difference** in **pain reduction** between celecoxib and diclofenac 100 mg.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **number of patients withdrawn due to adverse events** between celecoxib and diclofenac 100 mg.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **number of patients experiencing any serious adverse events** between celecoxib and diclofenac 100 mg.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **number of patients experiencing gastro-intestinal events** between celecoxib and diclofenac 100 mg.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **the number of patients experiencing cardiovascular events** between celecoxib and and diclofenac 100 mg.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **pain reduction** between celecoxib and diclofenac 150 mg.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **physical function** between celecoxib and diclofenac 150 mg.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **number of patients withdrawn due to adverse events** between celecoxib and diclofenac 150 mg.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **number of patients experiencing any serious adverse events** between celecoxib and diclofenac 150 mg.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **number of patients experiencing gastro-intestinal events** between celecoxib and diclofenac 150 mg.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

7.12 Celecoxib vs naproxen

COX-2-selective NSAID vs naproxen for osteoarthritis			
Bibliography: Cochrane Puljak 2017(71), containing: Bensen 1999(61), Essex 2012a(96), Essex 2012b(62), Essex 2014(55), Kivitz 2001(81), Sowers 2005(97) Additional RCTs: Essex 2016(90)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain	1781 (6 studies) 6 weeks – 6 months	I^2=0% Std. MD -0.04 (-0.14 to 0.05) NS	⨁⨁⨀⨀ **LOW** Study quality: -2 (3 RCTs w unclear randomization and 6 w unclear allocation concealment, 7 RCTs with high attrition; 1 w unclear risk of selective reporting for outcome VAS pain) Consistency: ok Directness: ok Imprecision: ok
	357 (1 study) 6 weeks	VAS Celecoxib: -37.1 Naproxen: -37.5 Naproxen vs celecoxib LSM -0.4 (-5.2 to 4.5) NS	

Physical function	1817 (6 studies) 6 weeks – 6 months	I^2= 69% Std. MD -0.01 (-0.18 to 0.16) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (2 RCTs w unclear randomization and 5 w unclear allocation concealment, 6 RCTs with high attrition) Consistency: ok Directness: ok Imprecision: ok
Number withdrawn due to adverse events	2173 (6 studies) 6 weeks – 6 months	Celecoxib: 104/1090 Nonselective NSAID: 128/1083 I^2= 42% OR 0.81 (0.54 to 1.23) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (2 RCTs w unclear randomization and 5 w unclear allocation concealment, 6 RCTs with high attrition; 3 w high and 2 w unclear risk of selective reporting of safety outcomes) Consistency: ok Directness: ok Imprecision: ok
Number experiencing any serious adverse events	841 (2 studies) 6 weeks – 6 months	Celecoxib: 10/421 Nonselective NSAID: 9/420 I^2= 0% Peto OR 1.11 (0.45 to 2.75) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 (2 RCTs w unclear allocation concealment, 2 RCTs with high and/or unbalanced attrition, 1 RCT with high and 1 with unclear risk of selective reporting) Consistency: ok Directness: ok Imprecision: -1 (95%CI contains both appreciable harm and benefit)
Number experiencing gastro-intestinal events (perforation, ulcer, bleeds)	587 (2 studies) 6-12 weeks	Celecoxib: 1/293 Nonselective NSAID: 3/294 I^2= 0% Peto OR 0.37 (0.05 to 2.62) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 (1 RCT unclear rando, 2 w unclear allocation concealment, 2 RCTs with high and/or unbalanced attrition, 1 RCT with high risk of selective reporting) Consistency: ok Directness: ok Imprecision: -1 (95%CI contains both appreciable harm and benefit)

This systematic review and meta-analysis sought RCTs comparing celecoxib 200 mg daily versus no intervention, placebo or other nonselective NSAID in knee and/or hip osteoarthritis.

Six RCTs with were found that compared celecoxib to naproxen. The duration of the trials varied between 6 weeks and 6 months.

An additional RCT with 6 weeks follow-up was found.

3 RCTs had unclear randomization and 6 had unclear allocation concealment. All had high attrition. There was a risk of unclear reporting of safety outcomes.

These methodological problems could lead to bias and limit our confidence in the results.

There was **no statistically significant difference** in **pain reduction** between celecoxib and naproxen.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **physical function** between celecoxib and naproxen.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **the number of patients withdrawn due to adverse events** between celecoxib and naproxen.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **the number of patients experiencing any serious adverse events** between celecoxib and naproxen.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **the number of patients experiencing gastro-intestinal events** between celecoxib and naproxen.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

7.13 Acetylsalicylic acid vs placebo for chronic low back pain

A systematic review (Enthoven 2016(98)) sought RCTs of NSAIDs (including acetylsalicylic acid) for non-specific chronic low back pain, with exclusion of sciatica.

No RCTs were found that compared acetylsalicylic acid with placebo.

7.14 COX-2-selective NSAID vs placebo for chronic low back pain

COX2-selective NSAID vs placebo in chronic low back pain			
Bibliography: Cochrane Enthoven 2016(98), containing: Birbara 2003(99), Coats 2004(100)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain change in pain intensity from baseline on 100 mm VAS	507 (2 studies) 4-12 weeks	**MD -9.11 (-13.56 to -4.66)** **SS in favour of COX-2-selective NSAID** I^2= 0%	⨁⨁⨀⨀ **LOW** Study quality: -1 (1 RCT short duration, 1 RCT with high attrition and unclear risk of selective reporting) Consistency: ok Directness: -1 (1 nsaid not available in Belgium) Imprecision: ok
Proportion of patients experiencing adverse events	507 (2 studies) 4-12 weeks	COX-2-selective NSAID: 108/255 Placebo: 86/252 RR 1.25 (1.00 to 1.56) NS I^2= 18%	⨁⨁⨀⨀ **LOW** Study quality: -1 (1 RCT short duration, 1 RCT with high attrition and unclear risk of selective reporting) Directness: -1 (1 nsaid not available in Belgium) Imprecision: ok

This systematic review and meta-analysis sought RCTs of NSAIDs (including acetylsalicylic acid) for non-specific chronic low back pain, with exclusion of sciatica.

Two RCTs were found that compared COX-2-selective NSAID with placebo. The duration of the trials varied between 4 and 12 weeks. The evaluated NSAID were valdecoxib (not available in Belgium) and etoricoxib. One RCT did not meet our inclusion criteria (duration). One RCT had high attrition (33%) and an unclear risk of selective reporting.

These methodological problems could lead to bias and limit our confidence in the results.

Treatment with COX-2-selective NSAID resulted in **more pain reduction** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **the proportion of patients experiencing adverse events** between COX-2-selective NSAID and placebo.
GRADE: LOW quality of evidence

We have low confidence that the results of the studies reflect the true effect.

7.15 Nonselective NSAID vs placebo for chronic low back pain

Nonselective NSAID vs placebo in chronic low back pain			
Bibliography: Cochrane Enthoven 2016(98), containing: Allegrini 2009(101), Berry 1982(102), Katz 2011(103), Kivitz 2013(104)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain change in pain intensity from baseline on 100 mm VAS	847 (4 studies) 9 days – 16 weeks	**MD -5.96 (-10.96 to -0.96)** **SS in favour of nonselective NSAID** I^2= 55%	⨁⨁⨀⨀ **LOW** Study quality: -2 (1 RCT short duration, 1 RCT small sample size, 2 RCT unclear rando, allocation concealment, 2 RCT with high attrition) Consistency: ok Directness: ok Imprecision: ok
Proportion of patients experiencing adverse events	847 (4 studies) 9 days – 16 weeks	Nonselective NSAID: 219/480 Placebo: 168/367 RR 0.94 (0.82 to 1.08) NS I^2= 0%	⨁⨁⨀⨀ **LOW** Study quality: -2 (1 RCT short duration, 1 RCT small sample size, 2 RCT unclear rando, allocation concealment, 2 RCT with high attrition) Consistency: ok Directness: ok Imprecision: ok

This systematic review and meta-analysis sought RCTs of NSAIDs (including acetylsalicylic acid) for non-specific chronic low back pain, with exclusion of sciatica.

Four RCTs were found that compared nonselective NSAID with placebo. The duration of the trials varied between 9 days and 16 weeks. The evaluated NSAID were naproxen and piroxicam (patch and cream). Both remaining RCTs had unclear reporting of randomization and allocation concealment and high attrition (33%).

These methodological problems could lead to bias and limit our confidence in the results.

Treatment with nonselective NSAID resulted in **more pain reduction** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **the proportion of patients experiencing adverse events** between nonselective NSAID and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

7.16 COX-2-selective NSAID vs nonselective NSAID in chronic low back pain

A systematic review (Enthoven 2016(98)) sought RCTs of NSAIDs (including acetylsalicylic acid) for non-specific chronic low back pain, with exclusion of sciatica.

1 RCT was found comparing etoricoxib with diclofenac. It did not meet our inclusion criteria (duration).

7.17 NSAID for sciatica

A systematic review (Rasmussen-Barr 2017(105)): sought RCTs comparing NSAID (including acetylsalicylic acid) to placebo, to other NSAIDs, or to other medication for sciatica.

- No RCTs comparing acetylsalicylic acid vs placebo were found.
- No RCTs comparing COX-2-selective NSAID to placebo were found.
- Four RCTs comparing nonselective NSAID to placebo were found, but none met our inclusion criteria (duration).
- No RCTs comparing COX-2-selective NSAID to nonselective NSAID were found.

We did not find any additional RCTs evaluating NSAID in sciatica.

7.18 NSAID for neuropathic pain

A systematic review (Moore 2015(4)) sought RCTs comparing any oral NSAID with placebo or another active treatment in chronic neuropathic pain.

No RCTs that met our inclusion criteria were found.

We did not find any additional RCTs evaluating NSAID in neuropathic pain.

7.19 NSAID for cancer pain

A systematic review (Derry 2017(106)) sought RCTs comparing any oral NSAID alone with placebo or another NSAID, or a combination of NSAID plus opioid with the same dose of the opioid alone, for cancer pain of any pain intensity.

No RCT comparing NSAID with placebo was found.

One RCT comparing celecoxib to diclofenac was found, but it did not meet our inclusion criteria (sample size).

We did not find any additional RCTs evaluating NSAID in cancer pain.

8 Summary and conclusions from the literature review. Adjuvant analgesics.

8.1 Duloxetine vs placebo for osteoarthritis

Duloxetine vs placebo in osteoarthritis			
Bibliography: Osani 2019(107), containing: Chappel 2009(108), Chappel 2011(109), Frakes 2011(110), Uchio 2018(111) Wang 2017(112)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain	1713 (5 studies) 12-14 weeks	I^2= 5% **SMD -0.38 (-0.48 to -0.28)** **SS more improvement of pain with duloxetine**	⨁⨁⨀⨀ **LOW** Study quality: -2 (high attrition in 3 studies) Consistency: ok Directness: ok Imprecision: ok
Function	1695 (5 studies) 12-14 weeks	I^2= 23% **SMD -0.35 (-0.46 to -0.24)** **SS more functional improvement with duloxetine**	⨁⨁⨀⨀ **LOW** Study quality: -2 (high attrition in 3 studies) Consistency: ok Directness: ok Imprecision: ok
Quality of life	826 (3 studies) 13-14 weeks	I^2= 0% **SMD 0.40 (0.26 to 0.53)** **SS more QoL improvement with duloxetine**	⨁⨁⨀⨀ **LOW** Study quality: -2 (high attrition in 2 studies) Consistency: ok Directness: ok Imprecision: ok
Discontinuation due to adverse events	1772 (5 studies) 12-14 weeks	Duloxetine: 12.4% Placebo: 5.5% I^2= 0% **RR 2.17 (1.57 to 3.01)** **SS more discontinuation due to adverse events with duloxetine**	⨁⨁⨀⨀ **LOW** Study quality: -2 (high attrition in 3 studies) Consistency: ok Directness: ok Imprecision: ok

Treatment-emergent adverse events	1762 (5 studies) 12-14 weeks	Duloxetine: 55.1% Placebo: 37.4% I^2= 77% **RR 1.53 (1.21 to 1.92)** **SS more treatment-emergent adverse events with duloxetin**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (high attrition in 3 studies) Consistency: -1 (high heterogeneity) Directness: ok Imprecision: ok
Serious adverse events	1762 (5 studies) 12-14 weeks	Duloxetine: 1.1% Placebo: 1.2% I^2= 0% RR 1.03 (0.42 to 2.54) NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (high attrition in 3 studies) Consistency: ok Directness: ok Imprecision: -1 (95%CI contains both appreciable harm and benefit)

In this systematic review and meta-analysis, RCTs evaluating duloxetine vs placebo in osteoarthritis patients were sought.

Five RCTs were found. The follow-up varied from 12 to 14 weeks.

One RCT had unclear randomization and allocation concealment. High drop-out rates were reported in 3 RCTs.

These methodological problems could lead to bias and limit our confidence in the results.

Duloxetine treatment resulted in **more improvement of pain** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Duloxetine treatment resulted in **more functional improvement** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Duloxetine treatment resulted in **more QoL improvement** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Duloxetine treatment resulted in **more discontinuation due to adverse events** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Duloxetine treatment resulted in **more treatment-emergent adverse events** compared to placebo treatment.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **serious adverse events** between duloxetine and placebo.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

8.2 Amitriptyline vs placebo for musculoskeletal pain

Amitriptyline vs placebo in musculoskeletal disorders			
Bibliography: van den Driest 2017(113), containing: Goldman 2010(114)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain reduction	118 (1 study) 6 weeks	Amitriptyline: -0.7 Placebo: -0.4 Difference -0.3 (-0.19 to 0.10) NS	⨁⨁⨀⨀ **LOW** Study quality: -1 (single study, unclear risk of selective reporting) Consistency: NA Directness: -1 (specific indication) Imprecision: ok
Function (improvement)	118 (1 study) 6 weeks	Amitriptyline: -3.9 Placebo: -0.8 **Difference -3.1 (-5.67 to -0.44)** **SS in favour of amitriptyline**	⨁⨁⨀⨀ **LOW** Study quality: -1 (single study, unclear risk of selective reporting) Consistency: NA Directness: -1 (specific indication) Imprecision: ok
Adverse events	118 (1 study) 6 weeks	Amitriptyline: 31% Placebo: 22% P=0.30 NS	⨁⨁⨀⨀ **LOW** Study quality: -1 (single study, unclear risk of selective reporting) Consistency: NA Directness: -1 (specific indication) Imprecision: ok

In this systematic review and meta-analysis, RCTs evaluating amitriptyline compared to placebo, usual care or standard analgesic use for musculoskeletal disorders were sought.

7 RCTs were found; 4 studies evaluated amitriptyline in low back pain, 2 in rheumatoid arthritis and one in persistent arm pain due to repetitive use. Only one study (comparing amitriptyline to placebo for persistent arm pain) met our inclusion criteria. We only reported this study.

It had an unclear risk of selective reporting.

There was **no statistically significant difference** in **pain reduction** between amitriptyline and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Amitriptyline treatment resulted in **more improvement of function** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **adverse events** between amitriptyline and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

8.3 Antidepressants vs placebo for low back pain

Antidepressants vs placebo for non-specific back pain			
Bibliography: Uruqhart 2010(115) ,containing: Atkinson 1999a(116), Atkinson 1999b(116), Atkinson 2007a(117), Atkinson 2007b(117), Atkinson 2007c(117), Dickens 2000(118), Goodkin 1990(119), Jenkins 1976(120), Katz 2005(121)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**

Pain	376 (9 studies) 4-12 weeks	I^2= 0% Std. MD -0.04 (-0.25 to 0.17) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (8 studies small sample size, 1 study unclear outcomes data) Consistency: ok Directness: ok Imprecision: ok
Specific functional status	132 (2 studies) 6-8 weeks	I^2= 0% Std. MD -0.06 (-0.40 to 0.29) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (1 study small sample size, 1 study unclear risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok

In this systematic review and meta-analysis, RCTs were sought that compared antidepressants to placebo for non-specific low back pain in adults.

Nine RCTs were found that compared antidepressants with placebo. The duration of the trials varied between 4 and 12 weeks.

8 of the trials did not meet our inclusion criteria (sample size). The remaining RCT had an unclear risk of incomplete outcome data.

These methodological problems could lead to bias and limit our confidence in the results.

There was **no statistically significant difference** in **pain** between antidepressants and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **specific functional status** between antidepressants and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

8.4 TCA vs placebo for low back pain

Tricyclic antidepressants vs placebo for non-specific back pain

Bibliography: Uruqhart 2010(115) ,containing: Atkinson 1999a(116), Atkinson 2007a(117), Atkinson 2007b(117), Jenkins 1976(120)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain	148 (4 studies) 4-12 weeks	I^2= 32% Std. MD -0.10 (-0.51 to 0.31) NS	⨁⨁⨀⨀ **LOW** Study quality: -2 (4 studies small sample size) Consistency: ok Directness: ok Imprecision: ok

In this systematic review and meta-analysis, RCTs were sought that compared antidepressants to placebo for non-specific low back pain in adults.

Four RCTs were found that compared tricyclic antidepressants with placebo. The included studies evaluated maprotiline, desipramine and imipramine. The duration of the trials varied between 4 and 12 weeks.

None of the trials met our inclusion criteria (sample size).

This could lead to bias and limit our confidence in the results.

There was **no statistically significant difference** in **pain** between tricyclic antidepressants and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

8.5 SSRI vs placebo for low back pain

SSRI vs placebo for non-specific back pain			
Bibliography: Uruqhart 2010(115) ,containing: Atkinson 1999b(116), Atkinson 2007c(117), Dickens 2000(118)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**

Pain	199 (3 studies) 8-12 weeks	I^2= 0% Std. MD 0.11 (-0.17 to 0.39) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (2 studies small sample size, 1 study unclear outcomes data) Consistency: ok Directness: ok Imprecision: ok

In this systematic review and meta-analysis, RCTs were sought that compared antidepressants to placebo for non-specific low back pain in adults.

Three RCTs were found that compared SSRI with placebo. The included studies evaluated paroxetine and fluoxetine. The duration of the trials varied between 8 and 12 weeks.

2 of the trials did not meet our inclusion criteria (sample size). The remaining RCT had an unclear risk of incomplete outcome data.

These methodological problems could lead to bias and limit our confidence in the results.

There was **no statistically significant difference** in **pain** between SSRI and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

8.6 Duloxetine vs placebo for low back pain

Duloxetine vs placebo for low back pain			
Bibliography: SR Chou 2016(35), containing: Skljarevksi 2009(122), Skljarevksi 2010a(123), Skljarevksi 2010b(124) Additional RCT: Konno 2016(125)			
Outcomes	**N° of participants (studies)** **Follow up**	**Results**	**Quality of the evidence (GRADE)**

Pain BPI-S mean change from baseline	1041 (3 studies) 12-13 weeks	Duloxetine 60mg: -2.50 Placebo: -1.87 **Duloxetine 60 mg vs Placebo: p<0.05** **SS in favour of duloxetine 60 mg** **----------** Duloxetine 60mg: -2.25 Placebo: -1.65 **Duloxetine 60 mg vs Placebo: p=0.002** **SS in favour of duloxetine 60 mg** **----------** Duloxetine 60mg: -2.66 Placebo: -1.90 **Duloxetine 60 mg vs Placebo: p<0.05** **SS in favour of duloxetine 60 mg**	⊕⊕⊖⊖ **LOW** Study quality: -2 (2 studies unclear alloc concealment, randomization; 3 studies selective outcome reporting) Consistency: ok Directness: ok Imprecision: ok
	458 (1 study) 14 weeks	BPI average pain score (PO) Duloxetine: -2.43 Placebo: -1.96 **LS Mean changes** **p=0.0026** **SS in favour of duloxetine**	
Function BPI-I average mean change from baseline	1041 (3 studies) 12-13 weeks	Duloxetine 60mg: -2.40 Placebo: -1.61 **Duloxetine 60 mg vs Placebo: p<0.05** **SS in favour of duloxetine 60 mg** **----------** Duloxetine 60mg: -2.01	⊕⊕⊖⊖ **LOW** Study quality: -2 (2 studies unclear alloc concealment, randomization; 3 studies selective outcome reporting) Consistency: ok Directness: ok Imprecision: ok

		Placebo: -1.43 **Duloxetine 60 mg vs Placebo: p<0.001** **SS in favour of duloxetine 60 mg** --- Duloxetine 60mg: -1.92 Placebo: -1.18 **Duloxetine 60 mg vs Placebo: p<0.01** **SS in favour of duloxetine 60 mg**	
Quality of life mean change SF-36 subscales -Bodily pain	640 (2 studies) 13 weeks 458 (1 study) 14 weeks	Duloxetine 60mg: 1.95 Placebo: . 1.36 **Duloxetine 60 mg vs Placebo: p<0.05** **SS in favour of duloxetine 60 mg and** **---** **Duloxetine 60 mg vs Placebo: p=0.04** **SS in favour of duloxetine 60 mg** Duloxetine: 0.08 Placebo: 0.09 LS Mean changes p= 0.5237 NS	⊕⊕⊖⊖ **VERY LOW** Study quality: -2 (1 study unclear alloc concealment, randomization; 2 studies selective outcome reporting) Consistency: -1 Directness: ok Imprecision: ok
Withdrawal due to adverse events	1041 (3 studies) 12-13 weeks	**I^2= 0%** **OR 2.52 (1.58 to 4.03)** **SS more withdrawals due to adverse events with duloxetine**	⊕⊕⊖⊖ **LOW** Study quality: -2 (2 studies unclear alloc concealment, randomization; 4 studies selective outcome reporting) Consistency: ok Directness: ok Imprecision:ok

In this systematic review and meta-analysis, SRs and RCTs of pharmacological treatments and nonpharmacological treatments for nonradicular or radicular low back pain were sought.

Three RCTs were found that compared duloxetine with placebo. The duration of the trials varied between 12 and 13 weeks.

Two of the studies had unclear allocation concealment and method of randomization. Three studies had an unclear risk of selective reporting.

We found an additional RCT with 14 weeks follow-up. It had a high risk of selective reporting of safety outcomes.

These methodological problems could lead to bias and limit our confidence in the results.

Duloxetine treatment resulted in **more pain reduction** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Duloxetine treatment resulted in **better function** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Duloxetine treatment resulted in **better quality of life** compared to placebo treatment.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

Duloxetine treatment resulted in **more withdrawals due to adverse events** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

8.7 Pregabaline vs placebo for low back pain

Systematic review Shanthanna 2017(126) sought RCTs reporting use of gabapentin or pregabalin for the treatment of chronic low back pain (with or without leg pain) in adult patients.

No RCTs were found that compared pregabalin to placebo and that met our inclusion criteria.

8.8 Gabapentine vs placebo for low back pain

Gabapentin vs placebo low back pain			
Bibliography: Shanthanna 2017(126), containing: Atkinson 2016(127), McCleane 2000(128), McCleane 2001(129)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain relief mean differences	185 (3 studies) 6-12 weeks	I^2=0% Std. Mean Difference: -0.22 (-0.51 to 0.07) NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (2 studies small sample size) Consistency: ok Directness: ok Imprecision: ok
Pain relief Success	120 (2 studies) 8-12 weeks	Gabapentin: 20/60 Placebo:21/60 I^2=69% RR 0.95 (0.61 to 1.499) NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (1 study w small sample size) Consistency: ok Directness: ok Imprecision: ok

In this systematic review and meta-analysis, RCTs were sought that compared gabapentin or pregabalin for the treatment of chronic low back pain (with or without leg pain) in adult patients

Three RCTs were found, with follow-up ranging from 6 to 12 weeks.

Two of these RCTs had very small sample sizes and did not meet our inclusion criteria.

There was **no statistically significant difference** in **pain relief** between gabapentin and placebo.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **proportion of patients with adequate pain relief** between gabapentin and placebo.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

8.9 Carbamazepine vs placebo for low back pain

Systematic review Chou 2016(35) sought systematic reviews and RCTs of pharmacological treatments and nonpharmacological treatments for nonradicular or radicular low back pain.

No RCTs were found that evaluated carbamazepine for low back pain.

8.10 Amitriptyline vs placebo for chronic neck pain

Amitriptyline vs placebo in chronic neck pain			
Bibliography: RCT Maarrawi 2018(130)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain (VAS)	332 (1 study) 2 months	Amitriptyline: 3.34 Placebo: 6.12 **MD 2.78 (2.46 to 3.11)** **SS in favour of amitriptyline**	⨁⨁⨀⨀ **LOW** Study quality: -2 (single study, unclear allocation conc, high attrition, per protocol analysis, selective reporting) Consistency: NA Directness: ok Imprecision: ok

One RCT was found that compared amitriptyline to placebo in chronic neck pain. It had 2 months of follow-up.

It had unclear allocation concealment, high attrition, it had a per protocol analysis and high risk of selective reporting.

These methodological problems could lead to bias and limits our confidence in the results.

Amitriptyline treatment resulted in **more improvement of pain** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

8.11 Amitriptyline vs placebo for neuropathic pain

Amitriptyline vs placebo in neuropathic pain			
Bibliography: Cochrane Moore 2015(131), containing: Anon 2000 (132), Cardenas 2002(133), Kautio 2008(134), Leijon 1989 (135), Max 1988(136), Rintala 2007(137), Shlay 1998(138), Vrethem 1997(139) Additional RCT: Dinat 2015(140)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain Painful diabetic neuropathy	169 (1 study) 9 weeks	Efficacy Amitriptyline: 37/88 Placebo: 24/81 RR 1.42 (0.94 to 2.15) NS	⨁⨁⨀⨀ **LOW** Study quality: -2 (single study, risk of incomplete outcome data, unclear allocation concealment and randomization) Consistency: NA Directness: ok Imprecision: ok
Pain painful HIV-associated sensory neuropathy	124 (1 study) 6 weeks	Amitriptyline: 2.7 SD 3.2 Placebo: 2.4 SD 3.2 P=0.47 NS	⨁⨁⨀⨀ **LOW** Study quality: -1 (single study, per protocol analysis) Consistency: NA Directness: ok Imprecision: ok
At least one adverse event	519 (6 studies) 4- 9 weeks	Amitriptyline: 148/269 Placebo: 89/250 I^2= 89% **RR 1.54 (1.32 to 1.81)** **SS more participants with at least one adverse event with amitriptyline**	⨁⨁⨀⨀ **LOW** Study quality: -1 (short duration, small studies, unclear allocation concealment, risk of incomplete outcome data) Consistency: -1 (high heterogeneity) Directness: ok Imprecision: ok

Adverse event withdrawal	303 (3 studies) 6-9 weeks	Amitriptyline: 25/159 Placebo: 10/144 I^2= 0% **RR 2.23 (1.11 to 4.45)** **SS more withdrawals because of an adverse event with amitriptyline**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (small studies, unclear allocation concealment, risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok

In this systematic review and meta-analysis, RCTs were sought that compared amitriptyline to placebo or an active comparator, for neuropathic pain.

Seven RCTs were found that compared amitriptyline with placebo. The duration of the trials varied between 4 and 9 weeks. Four were cross-over trials. Five of the seven RCTs did not meet our inclusion criteria for sample size or duration. We did not report the meta-analyses of efficacy of amitriptyline in postherpetic neuralgia, mixed neuropathic pain, cancer-related neuropathic pain or post-stroke pain because of insufficient sample size of the pooled groups. We did not report the meta-analyses of efficacy of amitriptyline in HIV-related neuropathy because of insufficient duration of follow-up.

The remaining two RCTs had unclear allocation concealment and an unclear risk of incomplete outcome data. One RCT did not report the method of randomization.

We found one additional RCT comparing amitriptyline to placebo for painful HIV-associated sensory neuropathy. Only the per protocol population was analyzed for the primary outcome.

These methodological problems could lead to bias and limit our confidence in the results.

In patients with **painful diabetic neuropathy**, there was **no statistically significant difference** in **pain** between amitriptyline and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

In patients with **painful HIV-associated sensory neuropathy**, there was **no statistically significant difference** in **pain** between amitriptyline and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Amitriptyline treatment resulted in **more participants with at least one adverse event** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Amitriptyline treatment resulted in **more withdrawals because of an adverse event** compared to placebo treatment.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

8.12 Nortriptyline vs placebo for neuropathic pain

Cochrane Derry 2015(141) found 3 small cross-over RCTs comparing nortriptyline with placebo. None met our inclusion criteria (duration).

GRADE: insufficient evidence

8.13 Duloxetine vs placebo for neuropathic pain

Duloxetine vs placebo in neuropathic pain			
Bibliography: Cochrane Lunn 2014(142), containing: Arnold 2004(143), Arnold 2005(144), Arnold 2010(145), Arnold 2012(146), Brecht 2007(147), Chappell 2008(148), Gao 2010(149), Gaynor 2011a(150), Gaynor 2011b(151), Goldstein 2005(152), Raskin 2005(153), Rowbotham 2012(154), Russel 2008(155), Tesfaye 2013(156), Vranken 2011(157), Wernicke 2006(158), Yasuda 2010(159) Additional RCT: Gao 2015(160)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain Number of participants with ≥50% improvement of pain	1655 (5 studies) 8- 12 weeks	Duloxetine: 489/1059 Placebo: 180/596 I^2= 62% **RR 1.53 (1.21 to 1.92)** **SS in favour of duloxetine**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (high dropout in 2 studies; 1 study with unclear blinding) Consistency: ok Directness: ok Imprecision: ok
Pain Number of participants with ≥30% improvement	1220 (4 studies) 12 weeks	Duloxetine: 458/725 Placebo: 220/495 I^2= 60% **RR 1.45 (1.30 to 1.63)** **SS in favour of duloxetine**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (high dropout in 1 study; 1 study with unclear blinding) Consistency: ok Directness: ok Imprecision: ok

Pain Pain severity reduction (0-10)	405 (1 study) 12 weeks	Duloxetine: -2.40 Placebo: -1.97 **LS MD: -0.43 (-0.82 to -0.044)** **P=0.030** **SS in favour of duloxetine**	⊕⊕⊖⊖ **LOW** Study quality: -2 (single study, unclear alloc concealment and randomization) Consistency: NA Directness: ok Imprecision: ok
Function SF-36 Physical Subscore Duloxetin 20 mg daily	200 (1 study) 8 weeks	I^2= not applicable MD -0.27 (-2.42 to 1.88) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (single study with high dropout and unclear risk of selective reporting) Consistency: -NA Directness: ok Imprecision: ok
Function SF-36 Physical Subscore Duloxetin 60 mg daily	541 (3 studies) 8-12 weeks	I^2= 0% **MD 2.65 (1.38 to 3.92)** **SS in favour of duloxetine**	⊕⊕⊖⊖ **LOW** Study quality: -2 (high dropout in 2 studies) Consistency: ok Directness: ok Imprecision: ok
Function SF-36 Physical Subscore Duloxetin 120 mg daily	409 (2 studies) 8-12 weeks	I^2= 26% **MD 2.80 (1.04 to 4.55)** **SS in favour of duloxetine**	⊕⊕⊖⊖ **LOW** Study quality: -2 (high dropout in 2 studies) Consistency: ok Directness: ok Imprecision: ok
Adverse events	5258 (14 studies) 8- 26 weeks	Duloxetine: 2033/2796 Placebo: 1530/2462 I^2= 9% **RR 1.15 (1.11 to 1.20)** **SS more adverse events with duloxetine**	⊕⊕⊖⊖ **LOW** Study quality: -1 (dropout, unclear alloc concealment) Consistency: ok Directness: -1 (also includes patients with fibromyalgia and depression) Imprecision: ok
	405 (1 study) 12 weeks	Duloxetine: 94 (46.5%) Placebo: 72 (35.6%) **P= 0.034** **SS more patients with an adverse event with duloxetine**	

Adverse event withdrawal	6285 (17 studies) 8- 26 weeks	Duloxetine: 447/3540 Placebo:158/2745 I^2= 0% **RR 1.99 (1.67 to 2.37)** **SS more adverse events leading to cessation with duloxetine**	⊕⊕⊖⊖ **LOW** Study quality -1 (dropout, unclear alloc concealment) Consistency: ok Directness: -1 (also includes patients with fibromyalgia and depression) Imprecision: ok
	405 (1 study) 12 weeks	Duloxetine: 3 (1.5%) Placebo: 2 (1.0%) No statistical testing	
Serious adverse events	4976 (14 studies) 8- 26 weeks	Duloxetine: 42/2785 Placebo: 39/2191 I^2= 0% RR 0.81 (0.53 to 1.25) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 (dropout, unclear alloc concealment) Consistency: ok Directness: -1 (also includes patients with fibromyalgia and depression) Imprecision: ok
	405 (1 study) 12 weeks	Duloxetine: 17 (8.4%) Placebo: 8 (4.0%) P: 0.097 NS	

In this systematic review and meta-analysis, RCTs were sought that compared duloxetine to placebo or an active comparator, for neuropathic pain.

Six RCTs were found that compared duloxetine with placebo for painful diabetic neuropathy.

The duration of the trials varied between 8 and 12 weeks.

One trial had unclear randomization and 2 had unclear allocation concealment. 2 RCTs had over 20% drop-out. One trial had an unclear risk of selective reporting.

For the safety outcomes a number of trials that compared duloxetine with placebo for fibromyalgia, or for pain in patients with a primary diagnosis of major depressive disorder, were included in the meta-analysis. We did not report the efficacy results of these trials.

We found one additional RCT comparing duloxetine to placebo for diabetic peripheral neuropathic pain. It had unclear randomization and allocation concealment.

These methodological problems could lead to bias and limit our confidence in the results.

Duloxetine treatment resulted in **more participants with at least 50% improvement of pain** compared to placebo treatment.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

Duloxetine treatment resulted in **more participants with at least 30% improvement of pain** compared to placebo treatment.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

Duloxetine treatment resulted in **more reduction of pain severity** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **function** between duloxetine 20 mg and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Treatment with duloxetine 60 mg resulted in **better function** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Treatment with duloxetine 120 mg resulted in **better function** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Duloxetine treatment resulted in **more adverse events** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Duloxetine treatment resulted in **more adverse events leading to withdrawal** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **serious adverse events** between duloxetine and placebo.

GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

8.14 Venlafaxine vs placebo for neuropathic pain

Venlafaxine vs placebo in neuropathic pain			
Bibliography: Cochrane Gallagher 2015(161), containing RCT Rowbotham 2004(162)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain Pain intensity reductions VAS	244 (1 study) 6 weeks	Venlafaxine XR 75 mg: 22.4 mm Venlafaxine XR 150-225 mg: 33.8 mm Placebo : 18.7 mm Venlafaxine 75 vs placebo NS **Venlafaxine 150-225 vs placebo** **P<0.001** **SS in favour of venlafaxine 150-255**	⨁⨁⨀⨀ **LOW** Study quality: -2 (single study, unclear rando and alloc concealment, risk of selective reporting) Consistency: NA Directness: ok Imprecision: ok
Pain Pain relief VAS	244 (1 study) 6 weeks	Venlafaxine XR 75 mg: 51.0 mm Venlafaxine XR 150-225 mg: 59.9 mm Placebo : 43.6 mm Venlafaxine 75 vs placebo NS **Venlafaxine 150-225 vs placebo** **P<0.001** **SS in favour of venlafaxine 150-255**	⨁⨁⨀⨀ **LOW** Study quality: -2 (single study, unclear rando and alloc concealment, risk of selective reporting) Consistency: NA Directness: ok Imprecision: ok

Treatment-emergent adverse events	244 (1 study) 6 weeks	Venlafaxine XR 75 mg: 88% Venlafaxine XR 150-225 mg: 89% Placebo : 75% NS	⨁⨁⨀⨀ **LOW** Study quality: -2 (single study, unclear rando and alloc concealment, risk of selective reporting) Consistency: NA Directness: ok Imprecision: ok
Adverse event withdrawal	244 (1 study) 6 weeks	Venlafaxine XR 75 mg: 7% Venlafaxine XR 150-225 mg: 10% Placebo : 4% NS between 3 groups	⨁⨁⨀⨀ **LOW** Study quality: -2 (single study, unclear rando and alloc concealment, risk of selective reporting) Consistency: NA Directness: ok Imprecision: ok
Serious adverse events	244 (1 study) 6 weeks	Venlafaxine XR 75 mg: 9% Venlafaxine XR 150-225 mg: 12% Placebo : 10% NS	⨁⨁⨀⨀ **LOW** Study quality: -2 (single study, unclear rando and alloc concealment, risk of selective reporting) Consistency: NA Directness: ok Imprecision: ok

Cochrane Gallagher sought RCTs that compared venlafaxine to placebo or an active comparator, for neuropathic pain.

5 RCTs were found that compared venlafaxine to placebo. Four RCTs did not meet our inclusion criteria (sample size and/or duration). No meta-analysis was performed. Only one RCT (Rowbotham 2004), comparing two doses of venlafaxine with placebo in patients with painful diabetic neuropathy, did meet our inclusion criteria.

It had unclear randomization and allocation concealment, and not all quantitative data was clearly reported.

These methodological problems could lead to bias and limit our confidence in the results.

There was **no statistically significant difference** in **pain intensity reduction** or **pain relief** between venlafaxine XR 75 mg and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Treatment with venlafaxine XR 150-225 mg resulted in **more pain intensity reduction** and **pain relief** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **treatment-emergent adverse events** between venlafaxine and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **study withdrawal due to adverse events** between venlafaxine and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **serious adverse events** between venlafaxine and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

8.15 Direct comparisons of antidepressants for neuropathic pain

Duloxetine vs amitriptyline in neuropathic pain			
Bibliography: Cochrane Lunn(142), containing Kaur 2011(163)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain Overall pain relief >30%	65 (1 study) 6 weeks	Duloxetine: 64% Amitriptyline: 62% NS difference	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (single small study, selective reporting, unclear allocation concealment) Consistency: NA Directness: ok Imprecision: -1 (not evaluable)
Pain Overall pain relief >50%	65 (1 study) 6 weeks	Duloxetine: 59% Amitriptyline: 55% NS difference	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (single small study, selective reporting, unclear allocation concealment) Consistency: NA Directness: ok Imprecision: -1 (not evaluable)

Treatment-emergent adverse events	65 (1 study) 6 weeks	Duloxetine: 24% Amitriptyline: 51% **P<0.01** **SS more moderate to severe treatment-emergent adverse events with amitriptyline**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (single small study, selective reporting, unclear allocation concealment) Consistency: NA Directness: ok Imprecision: -1 (not evaluable)

Cochrane Lunn(142) sought randomised or quasi-randomised trials of duloxetine for the treatment of painful peripheral neuropathy or chronic pain in adults.

It found one RCT (Kaur 2011) that compared duloxetine to amitriptyline. This small cross-over study had unclear allocation concealment and high risk of selective reporting.

These methodological problems could lead to bias and limit our confidence in the results.

There was **no statistically significant difference** in **proportion of patients with >30% pain relief** between duloxetine and amitriptyline.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **proportion of patients with >50% pain relief** between duloxetine and amitriptyline.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

Treatment with amitriptyline resulted in **more moderate to severe treatment-emergent adverse events** compared to duloxetine.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

<u>Other direct comparisons of amitriptyline, nortriptyline, duloxetine and venlafaxine.</u>

Cochrane Lunn(142) sought RCTs evaluating duloxetine for painful peripheral neuropathy or chronic pain and found one RCT comparing duloxetine to amitriptyline: Kaur 2011(163), which has been reported previously.

Cochrane Moore 2015(131) sought RCTs comparing amitriptyline to placebo or an active comparator for neuropathic pain. It found:

- one RCT comparing amitriptyline to nortriptyline. It did not meet our inclusion criteria (sample size).
- one RCT comparing amitriptyline to duloxetine. It did not meet our inclusion criteria (sample size).

SR Moore 2015 did not find RCTs comparing amitriptyline to venlafaxine.

Cochrane Gallagher 2015(161) sought RCTs comparing venlafaxine with placebo or another active treatment for neuropathic pain and found no RCTs that compared venlafaxine to nortriptyline, amitriptyline or duloxetine.

Cochrane Derry 2015(141) sought RCTs comparing nortriptyline with placebo or another active treatment for chronic neuropathic pain and found 1 RCT comparing nortriptyline to amitriptyline. It did not meet our inclusion criteria (sample size & duration).

GRADE: insufficient evidence

8.16 Pregabaline vs placebo for neuropathic pain

Bibliography: Cochrane Derry 2019(164), containing: 1008-030(165), 1008-040(166), A0081071(167), A0081244(168), A0081279(169), A9011015(170), Arezzo 2008(171), Cardenas 2013(172), Dworkin 2003(173), Freynhagen 2005(174), Guan 2011(175), Holbech 2015(176), Huffman 2015(177), Kim 2011(178), Lesser 2004(179), Liu 2017(180), Moon 2010(181), Mu 2018(182), NCT00785577(183), Ogawa 2010(184), Raskin 2016(185), Rauck 2013(186), Richter 2005(187), Rosenstock 2004(188), Sabatowski 2004(189), Satoh 2011(190), Siddal 2006(191), Simpson 2010(192), Smith 2014(193), Stacey 2008(194), Tölle 2008(195), van Seventer 2006(196), van Seventer 2010(197), Vinik 2014(198), Ziegler 2015(199)

Pregabaline 150 mg vs placebo in neuropathic pain			
Bibliography: Cochrane Derry 2019(164)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**

At least 30% pain intensity reduction Postherpetic neuralgia	180 (1 study) 13 weeks	Pregabalin: 34/87 Placebo: 16/93 I^2= not applicable **RR 2.27 (1.35 to 3.81)** **SS in favour of pregabalin**	⊕⊕⊖⊖ **LOW** Study quality: -2 (single study, unclear randomization, allocation conc, blinding method, incomplete outcome data) Consistency: NA Directness: ok Imprecision: ok
At least 50% pain intensity reduction Postherpetic neuralgia	699 (4 studies) 5-13 weeks	Pregabalin: 83/339 Placebo: 45/360 I^2= 42% **RR 1.96 (1.41 to 2.74**) **SS in favour of pregabalin**	⊕⊕⊖⊖ **LOW** Study quality: -2 (1 study w short duration, 2 studies with unclear randomization and blinding method, 3 with unclear allocation conc and incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok
At least 50% pain intensity reduction Painful diabetic neuropathy	359 (2 studies) 6-12 weeks	Pregabalin: 48/178 Placebo: 42/181 I^2= 0% RR 1.14 (0.80 to 1.63) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (1 study with unclear randomization and blinding method, 2 with unclear allocation conc and incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok
Participants experiencing any adverse event	185 (1 study) weeks	Pregabalin: 65/87 Placebo: 62/98 I^2= not applicable RR 1.18 (0.97 to 1.43) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (single study, unclear randomization, allocation conc, blinding method, incomplete outcome data) Consistency: NA Directness: ok Imprecision: ok
Participants experiencing any serious adverse event	542 (3 studies) 8-13 weeks	Pregabalin: 11/267 Placebo: 11/275 I^2= 28% RR 1.03 (0.45 to 2.38) NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 (2 studies w unclear randomization, allocation conc, blinding method, 3 studies w risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: -1 (95%CI includes both appreciable harm and benefit)
Withdrawal because of adverse event	1058 (6 studies) 6-9 weeks	Pregabalin: 34/517 Placebo: 31/541 I^2= 0% RR 1.15 (0.72 to 1.83) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (1 study w short duration, 3 studies with unclear randomization and blinding method, 5 with unclear allocation conc and incomplete outcome data) Consistency: ok

			Directness: ok Imprecision: ok

Pregabaline 300 mg vs placebo in neuropathic pain			
Bibliography: Cochrane Derry 2019(164)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
At least 30% pain intensity reduction Postherpetic neuralgia	589 (3 studies) 4-13 weeks	Pregabalin: 149/297 Placebo: 72/292 I^2= 0% **RR 2.05 (1.63 to 2.57)** **SS in favour of pregabalin**	⊕⊕⊖⊖ **LOW** Study quality: -2 (1 study w short duration, 1 study w unclear randomization, allocation conc, blinding method, 2 studies w risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok
At least 30% pain intensity reduction Painful diabetic neuropathy	2320 (8 studies) 5-15 weeks	Pregabalin: 514/1105 Placebo: 510/1215 I^2= 54% **RR 1.11 (1.01 to 1.21)** **SS in favour of pregabalin**	⊕⊕⊖⊖ **LOW** Study quality: -2 (2 studies w short duration, 3 studies w unclear randomization, 4 w unclear allocation conc, 1 w unclear blinding method, 6 studies w risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok
At least 50% pain intensity reduction Postherpetic neuralgia	713 (4 studies) 4-13 weeks	Pregabalin: 114/351 Placebo: 47/362 I^2=0% **RR 2.52 (1.86 to 3.42)** **SS in favour of pregabalin**	⊕⊕⊖⊖ **LOW** Study quality: -2 (1 study w short duration, 2 studies w unclear randomization, 3 w unclear allocation conc, 2 w unclear blinding method, 3 studies w risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok

At least 50% pain intensity reduction Painful diabetic neuropathy	2931 (11 studies) 5-15 weeks	Pregabalin: 434/1415 Placebo: 358/1516 I^2=48% **RR 1.30 (1.15 to 1.46)** **SS in favour of pregabalin**	⊕⊕⊖⊖ **LOW** Study quality: -2 (2 studies w short duration, 4 studies w unclear randomization, 6 w unclear allocation conc, 4 w unclear blinding method, 9 studies w risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok
Participants experiencing any adverse event	3697 (15 studies) 4-14 weeks	Pregabalin: 1085/1811 Placebo: 954/1886 I^2= 44% **RR 1.21 (1.15 to 1.28)** **SS more participants experiencing an adverse event with pregabalin**	⊕⊕⊖⊖ **LOW** Study quality: -2 (1 study small sample size; 2 studies w short duration, 5 studies w unclear randomization, 8 w unclear allocation conc, 4 w unclear blinding method, 12 studies w risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok
Participants experiencing any serious adverse event	4112 (17 studies) 4-15 weeks	Pregabalin: 61/1979 Placebo: 54/2133 I^2= 0% RR 1.19 (0.83 to 1.70) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (1 study small sample size; 3 studies w short duration, 6 studies w unclear randomization, 10 w unclear allocation conc, 4 w unclear blinding method, 13 studies w risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok
Withdrawal because of adverse event	4317 (18 studies) 4-15 weeks	Pregabalin: 199/2133 Placebo: 112/2148 I^2= 0% **RR 1.86 (1.49 to 2.33)** **SS more withdrawals because of advere events with pregabalin**	⊕⊕⊖⊖ **LOW** Study quality: -2 (3 studies w short duration, 7 studies w unclear randomization, 11 w unclear allocation conc, 6 w unclear blinding method, 15 studies w risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok

Pregabaline 600 mg vs placebo in neuropathic pain			
Bibliography: Cochrane Derry 2019(164)			
Outcomes	**N° of participants (studies)** **Follow up**	**Results**	**Quality of the evidence (GRADE)**

At least 30% pain intensity reduction Postherpetic neuralgia	546 (3 studies) 4-13 weeks	Pregabalin: 167/270 Placebo: 65/267 I^2= 0% **RR 2.53 (2.01 to 3.18)** **SS in favour of pregabalin**	⊕⊕⊖⊖ **LOW** Study quality: -2 (1 study w short duration, 1 study w unclear randomization, unclear allocation conc, unclear blinding method, 2 studies w risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok
At least 30% pain intensity reduction Painful diabetic neuropathy	789 (3 studies) 5- 14 weeks	Pregabalin: 277/439 Placebo: 164/350 I^2=75% **RR 1.33 (1.16 to 1.51)** **SS in favour of pregabalin**	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 (1 study w short duration,2 studies w unclear randomization, unclear allocation conc, w risk of incomplete outcome data) Consistency: -1 (high heterogeneity) Directness: ok Imprecision: ok
At least 30% pain intensity reduction Mixed neuropathic pain	1367 (4 studies) 10-16 weeks	Pregabalin: 402/834 Placebo: 192/533 I^2= 68% **RR 1.24 (1.08 to 1.43)** **SS in favour of pregabalin**	⊕⊕⊖⊖ **LOW** Study quality: -2 (2 studies w unclear randomization, 2 w unclear allocation conc, 1 w unclear blinding method, 3 studies w risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok
At least 30% pain intensity reduction Central neuropathic pain	562 (3 studies) 12- 17 weeks	Pregabalin: 125/282 Placebo: 77/280 I^2= 60% **RR 1.62 (1.28 to 2.03)** **SS in favour of pregabalin**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (3 studies w risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok
At least 30% pain intensity reduction HIV neuropathy	664 (2 studies) 14-17 weeks	Pregabalin: 172/322 Placebo: 182/342 I^2= 0% RR 1.00 (0.87 to 1.16) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (1 study w unclear randomization, unclear allocation conc, 2 studies w risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok

At least 50% pain intensity reduction Postherpetic neuralgia	732 (4 studies) 4-13 weeks	Pregabalin: 151/367 Placebo: 56/365 I^2= 22% **RR 2.66 (2.04 to 3.48)** **SS in favour of pregabalin**	⊕⊕⊖⊖ **LOW** Study quality: -2 (1 study w short duration, 2 studies w unclear randomization, unclear allocation conc, unclear blinding method, 3 studies w risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok
At least 50% pain intensity reduction Painful diabetic neuropathy	1360 (7 studies) 5-14 weeks	Pregabalin: 263/630 Placebo: 185/730 I^2= 66% **RR 1.61 (1.37 to 1.88)** **SS in favour of pregabalin**	⊕⊕⊖⊖ **LOW** Study quality: -2 (1 study w short duration, 3 studies w unclear randomization, 5 w unclear allocation conc, 3 w unclear blinding method, 6 studies w risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok
At least 50% pain intensity reduction Mixed neuropathic pain	1367 (4 studies)	Pregabalin: 287/834 Placebo: 109/533 I^2= 42% **RR 1.51 (1.23 to 1.85)** **SS in favour of pregabalin**	⊕⊕⊖⊖ **LOW** Study quality: -2 (2 studies w unclear randomization, 2 w unclear allocation conc, 1 w unclear blinding method, 3 studies w risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok
At least 50% pain intensity reduction Central neuropathic pain	562 (3 studies) 12- 17 weeks	Pregabalin: 72/282 Placebo: 43/280 I^2= 42% **RR 1.67 (1.19 to 2.34)** **SS in favour of pregabalin**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (3 studies w risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok
At least 50% pain intensity reduction HIV neuropathy	674 (2 studies) 14-17 weeks	Pregabalin: 109/332 Placebo: 130/342 I^2= 0% RR 0.86 (0.70 to 1.06) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (1 study w unclear randomization, unclear allocation conc, 2 studies w risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok

Participants experiencing any adverse event	3963 (15 studies) 4-17 weeks	Pregabalin: 1475/2142 Placebo: 1030/1821 I^2= 55% **RR 1.30 (1.24 to 1.37)** **SS more participants experiencing an adverse event with pregabalin**	⊕⊕⊖⊖ **LOW** Study quality: -2 (1 study w short duration, 6 studies w unclear randomization, 7 w unclear allocation conc, 3 w unclear blinding method, 13 studies w risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok
Participants experiencing any serious adverse event	3995 (16 studies) 4- 17 weeks	Pregabalin: 70/2045 Placebo: 66/1950 I^2= 11% RR 1.07 (0.77 to 1.48) NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (2 studies w short duration, 6 studies w unclear randomization, 7 w unclear allocation conc, 4 w unclear blinding method, 13 studies w risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok
Withdrawal because of adverse event	5024 (21 studies) 4-17 weeks	Pregabalin: 300/2666 Placebo: 119/2358 I^2= 51% **RR 2.18 (1.78 to 2.68)** **SS more withdrawals because of an adverse event with pregabalin**	⊕⊕⊖⊖ **LOW** Study quality: -2 (2 studies w short duration, 9 studies w unclear randomization, 11 w unclear allocation conc, 6 w unclear blinding method, 18 studies w risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok

Pregabaline 150- 600 mg/day vs placebo in post-traumatic neuropathic pain			
Additional RCT: Markman 2018(200)			
Outcomes	**N° of participants (studies)** **Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain	542 (1 study) 15 weeks	post-traumatic peripheral neuropathic pain pregabalin: -2.12 (-2.42 to -1.82) placebo: -1.90 (-2.21 to -1.60) MD -0.22 (0.54 to 0.10) P= 0.18 NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (single study, risk of incomplete outcome data, unclear allocation concealment and randomization) Consistency: NA Directness: ok Imprecision: ok

In this systematic review and meta-analysis, double-blind RCTs of pregabalin compared to placebo or an active comparator, in adults with one or more chronic neuropathic conditions, were sought.

This SR pooled results according to dose of pregabalin (150 mg, 300 mg or 600 mg) and according to condition (painful diabetic neuropathy, postherpetic neuralgia, central neuropathic pain, HIV neuropathy, mixed neuropathic pain.)

Many of the RCTs had methodological problems such as unclear randomization, unclear allocation concealment, unclear blinding method and unclear risk of incomplete outcome data.

We found one additional RCT comparing pregabaline to placebo for post-traumatic peripheral neuropathic pain. There was unclear randomization and allocation concealment.

These methodological problems could lead to bias and limit our confidence in the results.

<u>Postherpetic neuralgia</u>

Pregabalin 150 mg resulted in **more patients with at least 30% pain intensity reduction** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Pregabalin 150 mg resulted in **more patients with at least 50% pain intensity reduction** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Pregabalin 300 mg resulted in **more patients with at least 30% pain intensity reduction** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Pregabalin 300 mg resulted in **more patients with at least 50% pain intensity reduction** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Pregabalin 600 mg resulted in **more patients with at least 30% pain intensity reduction** compared to placebo treatment.
GRADE: LOW quality of evidence

We have low confidence that the results of the studies reflect the true effect.

Pregabalin 600 mg resulted in **more patients with at least 50% pain intensity reduction** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Painful diabetic neuropathy

There was **no statistically significant difference** in **proportion of patients with at least 50% pain intensity reduction** between pregabalin 150 mg and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Pregabalin 300 mg resulted in **more patients with at least 30% pain intensity reduction** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Pregabalin 300 mg resulted in **more patients with at least 50% pain intensity reduction** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Pregabalin 600 mg resulted in **more patients with at least 30% pain intensity reduction** compared to placebo treatment.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

Pregabalin 600 mg resulted in **more patients with at least 50% pain intensity reduction** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Central neuropathic pain

Pregabalin 600 mg resulted in **more patients with at least 30% pain intensity reduction** compared to placebo treatment.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

Pregabalin 600 mg resulted in **more patients with at least 50% pain intensity reduction** compared to placebo treatment.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

HIV neuropathy

There was **no statistically significant difference** in **proportion of patients with at least 30% pain intensity reduction** between pregabalin 600 mg and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **proportion of patients with at least 50% pain intensity reduction** between pregabalin 600 mg and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Mixed neuropathy

Pregabalin 600 mg resulted in **more patients with at least 30% pain intensity reduction** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Pregabalin 600 mg resulted in **more patients with at least 50% pain intensity reduction** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Safety – all neuropathic pain
There was **no statistically significant difference** in p**articipants experiencing any adverse event** between pregabalin 150 mg and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in p**articipants experiencing any serious adverse event** between pregabalin 150 mg and placebo.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **withdrawals because of adverse events** between pregabalin 150 mg and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Pregabalin 300 mg resulted in **more participants experiencing any adverse event** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in p**articipants experiencing any serious adverse event** between pregabalin 300 mg and placebo.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

Pregabalin 300 mg resulted in **more withdrawals because of adverse events** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Pregabalin 600 mg resulted in **more participants experiencing any adverse event** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in p**articipants experiencing any serious adverse event** between pregabalin 600 mg and placebo.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

Pregabalin 600 mg resulted in **more withdrawals because of adverse events** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Post-traumatic peripheral neuropathic pain

There was **no statistically significant difference** in **pain** between pregabalin 150-600 mg and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

8.17 Gabapentin vs placebo for neuropathic pain

Gabapentin vs placebo in neuropathic pain			
Bibliography: Cochrane Wiffen 2017(201), containing: Backonja 1998(202), Backonja 2011(203), CTR 945-1008(204), CTR 945-224(205), Gong 2008(206), Irving 2009(207), Perez 2000(208), Rauck 2013a(186), Rice 2001(209), Sandercock 2012(210), Sang 2013(211), Serpell 2002(212), Wallace 2010(213), Zhang 2013(214)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
pain intensity reduction of 50% or greater For postherpetic neuralgia	2031 (7 studies) 3-13 weeks	Gabapentin: 415/1252 Placebo: 146/779 I^2= 62% **RR 1.69 (1.46 to 2.00)** **SS in favour of gabapentin**	⨁⨁⨀⨀ **LOW** Study quality: -2 (2 studies short duration, 2 studies unclear randomization and alloc concealment, unclear or high risk of incomplete outcome data in 3 studies) Consistency: ok Directness: ok Imprecision: ok
pain intensity reduction of 50% or greater For painful diabetic neuropathy	1277 (6 studies) 4-12 weeks	Gabapentin: 304/798 Placebo: 101/479 I^2=43% **RR 1.86 (1.53 to 2.27)** **SS in favour of gabapentin**	⨁⨁⨀⨀ **LOW** Study quality: -2 (2 studies not meeting inclusion criteria, 1 study unclear randomization and 2 unclear alloc concealment, 4 unclear risk of incomplete outcome data) Consistency: ok Directness: ok Imprecision: ok
pain intensity reduction of 50% or greater For mixed neuropathic pain	305 (1 study) 10 weeks	Gabapentin: 32/153 Placebo: 22/152 I^2= not applicable RR 1.45 (0.88 to 2.37) NS	⨁⨁⨀⨀ **LOW** Study quality: -2 (single study, unclear alloc concealment) Consistency: NA Directness: ok Imprecision: ok

Participants experiencing at least one adverse event	4279 (18 studies)	Gabapentin: 630/1000 Placebo: 490/1000 **RR 1.3 (1.2 to 1.4)** **SS more participants experiencing at least one adverse event with gabapentin**	As assessed by Cochrane Wiffen ⊕⊕⊕⊖ **MODERATE** -1 limited quality of reporting adverse events
Serious adverse events	3948 (19 studies)	Gabapentin: 32/1000 Placebo: 28/1000 RR 1.2 (0.8 to 1.7) NS	As assessed by Cochrane Wiffen ⊕⊕⊕⊖ **MODERATE** -1 due to the limited number of events

In this systematic review and meta-analysis, RCTs were sought that compared gabapentin to placebo or an active comparator, for neuropathic pain.

The Cochrane review pooled RCTs according to indication.

7 RCTs reported pain intensity reduction of 50% or greater for **postherpetic neuralgia**. The studies had a follow-up of 3 to 13 weeks. Two of the studies did not meet our inclusion criteria for duration. 2 studies had unclear randomization and 2 had unclear allocation concealment. There was an unclear or high risk of incomplete outcome data in 3 studies.

6 RCTs reported pain intensity reduction of 50% or greater for **painful diabetic neuropathy.** The studies had a follow-up of 4 to 12 weeks. Two of the studies did not meet our inclusion criteria (duration, sample size). One study had unclear randomization and 2 had unclear allocation concealment. There was an unclear or high risk of incomplete outcome data in 4 studies.

1 RCT reported pain intensity reduction of 50% or greater for **mixed neuropathic pain.** The study had a follow-up of 10 weeks. It had unclear allocation concealment.

These methodological problems could lead to bias and limit our confidence in the results.

The Cochrane review did not report which studies were included in their pooled safety analyses, so we could not assess the quality of the evidence. Therefore we reported the GRADE assessment of the Cochrane review.

In postherpetic neuralgia, gabapentin treatment resulted in **more participants with a pain intensity reduction of 50% or greater** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

In painful diabetic neuropathy, gabapentin treatment resulted in **more participants with a pain intensity reduction of 50% or greater** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

In patients with **mixed neuropathic pain**, there was **no statistically significant difference** in **pain** between gabapentin and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Gabapentin treatment resulted in **more participants with at least one adverse event** compared to placebo treatment.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.
There was **no statistically significant difference** in **serious adverse events** between gabapentin and placebo.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

8.18 Carbamazepine vs placebo for neuropathic pain

Carbamazepine vs placebo in neuropathic pain			
Bibliography: Cochrane Wiffen 2014(215), containing: Campbell 1966(216), Killian 1968(217), Lechin 1989(218), Leijon 1989(135), Nicol 1969(219), Rull 1969(220), Wilton 1974(221)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**

Any pain improvement	188 (4 studies) 2 weeks – 46 months	Carbamazepine: 56/92 Placebo: 9/96 I^2= 50% **RR 6.46 (3.43 to 12.17)** **SS in favour of carbamazepine**	⊕⊕⊖⊖ **LOW** Study quality: -2 (3 studies small sample size, 1 open label) Consistency: ok Directness: ok Imprecision: ok
At least 1 adverse event	346 (4 studies) 2-8 weeks	Carbamazepine: 113/173 Placebo: 47/173 I^2= 65% **RR 2.40 (1.85 to 3.12)** **SS greater proportion of participants with at least 1 adverse event**	⊕⊕⊖⊖ **LOW** Study quality: -2 (small sample size, short duration, duration) Consistency: ok Directness: ok Imprecision: ok

In this systematic review and meta-analysis, RCTs were sought that compared carbamazepine to placebo or an active comparator, for neuropathic pain.

7 RCTs comparing carbamazepine with placebo were found. The duration of follow-up varied from 2 weeks to 46 months.

None of the individual RCTs met our inclusion criteria (sample size, duration, no blinding).

These methodological problems could lead to bias and limit our confidence in the results.

Carbamazepine treatment resulted in **more frequent pain improvement** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Carbamazepine treatment resulted in a **greater proportion of participants with at least 1 adverse event** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

8.19 Direct comparisons of anticonvulsants for neuropathic pain

Direct comparisons of pregabalin, gabapentin and carbamazepine.

Cochrane Derry 2019(164) sought double blind RCTs comparing pregabalin and placebo or another active treatment. One RCT comparing pregabalin vs gabapentin was found. It did not meet our inclusion criteria (duration). No RCTs comparing pregabalin vs carbamazepine were found.

Cochrane Wiffen 2017(201) sought RCTs comparing gabapentin and placebo or another active treatment. One RCT was found comparing gabapentin to pregabalin. It did not meet our inclusion criteria (duration).

Cochrane Wiffen 2014(215) sought double blind RCTs comparing carbamazepine with placebo or active control. No RCTs that compared carbamazepine to pregabalin or gabapentin and met our inclusion criteria were found.

GRADE: insufficient evidence

8.20 Adjuvant analgesics in cancer pain

Huang 2019(222) sought RCTs comparing any systematic pharmaceutical intervention and/or combination in treating chronic cancer pain.

Two RCT's comparing amitriptyline vs placebo were found. They did not meet our inclusion criteria (duration).

One RCT comparing duloxetine vs placebo was found. It did not meet our inclusion criteria (duration).

No RCTs were found directly comparing amitriptyline, duloxetine, nortriptyline or venlafaxine.

Two RCT's comparing gabapentin vs placebo were found. They did not meet our inclusion criteria (duration).

Two RCT's comparing pregabalin vs placebo were found. They did not meet our inclusion criteria (duration).

One RCT was found comparing gabapentin vs pregabalin. It did not meet our inclusion criteria (duration).

GRADE: insufficient evidence

9 Summary and conclusions from the literature review. Topical analgesics

9.1 Topical diclofenac versus topical placebo for chronic musculoskeletal pain

Topical diclofenac versus topical placebo for chronic musculoskeletal pain			
Bibliography: Derry 2016 (223), including 102-93-1(224), Altman 2009 (225), Baer 2005 (226), Baraf 2011 (227), Bookman 2004 (228), Bruhlmann 2003 (229), Dreiser 1993 (230), Galeazzi 1993 (231), Grace 1999 (232), Niethard 2005 (233), Roth 1995 (234), Roth 2004 (235), Simon 2009 (42)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Clinical success (for example 50% reduction in pain)	2342 (4) 6-12 weeks	60% vs 50% RR 1.20 (1.12 to 1.29) NNT 9.8 (7.1 to 16) **SS in favour of diclofenac**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: ok Directness: -1 (only data for osteoarthritis) Imprecision: ok
Local adverse events	3658 (13) 14 days-12weeks	14% vs 7.8% RR 1.84 (1.54 to 2.21) NNH 16 (12 to 23) **SS: more adverse events with diclofenac**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency:-1 (high variation in incidence: I^2 76%) Directness: ok Imprecision: ok
Systemic adverse events	1266 (7) 14 days-12weeks	RR 0.89 (0.59 to 1.34) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 (selective reporting) Consistency: -1 (inconsistent reporting) Directness: ok Imprecision: ok
Serious adverse events		The majority of studies did not report this outcome, few events	⊕⊖⊖⊖ **VERY LOW**
Gastrointestinal adverse events	3240 (10) 14 days-12weeks	RR 1.10 (0.76 to 1.58) NS	⊕⊕⊖⊖ **LOW** Study quality:-2 (multiple studies with short duration and other unclear risks of bias) Consistency: ok Directness: ok Imprecision: ok
Withdrawals due to adverse events	3552 (12) 14 days-12weeks	RR 1.55 (1.14 to 2.11) NNH 51 (30 to 170) **SS: more withdrawals with diclofenac**	⊕⊕⊕⊖ **MODERATE** Study quality: : -1 (multiple studies with short duration) Consistency: ok Directness: ok Imprecision: ok

Withdrawals due to lack of efficacy	3455 (11) 14 days-12weeks	RR 0.59 (0.47 to 0.75) NNTp 26 (18 to 47) **SS: less withdrawals with diclofenac**	⊕⊕⊕⊖ **MODERATE** Study quality: : -1 (multiple studies with short duration) Consistency: ok Directness: ok Imprecision: ok

This Cochrane systematic review and meta-analysis by Derry 2016 compared topical diclofenac with topical placebo for **musculoskeletal pain** of at least moderate intensity. Four studies with a study duration between 6 weeks and 12 weeks were included for the outcome **clinical success** (for example 50% pain reduction).
All eligible studies were in osteoarthritis. There is no evidence for other chronic painful conditions. Three studies were about knee osteoarthritis (Baer 2005, Baraf 2011, Roth 2004) and one study about hand osteoarthritis (Altman 2009). Two studies used a gel formulation (Altman 2009, Baraf 2011) and two used a solution (Baer 2005, Roth 2004). Topical placebo was the carrier without diclofenac. Two studies used a dimethyl sulphoxide (DMSO)-based carrier (Baer 2005, Roth 2004). We refer to the Cochrane review for a description of the quantity of topical agent to be applied in each study.
There was a **statistical significant effect** of topical diclofenac compared to topical placebo for **clinical success** in patients with osteoarthritis.

GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

This Cochrane review included studies that did not meet our inclusion criteria for study duration (≥6 weeks) (some of these studies did also not meet our inclusion criteria for sample size). For all safety outcomes, we decided to include the pooled results of the Cochrane analysis, thus including the studies with a duration of ≤ 6 weeks. A total of 13 publications (15 studies; 1 publication combined 3 separate studies for analysis (Baraf 2011)) were found for the outcome **local adverse events** (at the application site)**.** One study was with participants with inflammatory peri- and extra-articular rheumatological diseases (Galeazzi 1993); all other studies with osteoarthritis. The study duration varied between 14 days and 12 weeks. The Cochrane authors found no consistent difference in reported event rates for different formulations of diclofenac and so combined them for analysis.
There were **significantly more local adverse events** with topical diclofenac compared to topical placebo.

GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

A total of 7 studies evaluated the outcome **systemic adverse events**. Many studies did not report this outcome. This Cochrane review also evaluated other topical NSAID. Events for topical NSAID in general were wide ranging, including headache, diarrhoea, drowsiness, and dyspepsia, and were usually described as mild.
There was no significant difference in the incidence of systemic adverse events between topical diclofenac and topical placebo.

GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

A total of 10 studies were eligible to evaluate the outcome **gastrointestinal adverse events**.
There was no significant difference in the incidence of gastrointestinal adverse events between topical diclofenac and topical placebo.

GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

A total of 12 studies were eligible to evaluate the outcome **withdrawals due to adverse events**.
There were **significantly more withdrawals due to adverse events** with topical diclofenac compared to topical placebo.

GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

A total of 11 studies were eligible to evaluate the outcome **withdrawals due to lack of efficacy**.
There were **significantly fewer withdrawals due to lack of efficacy** with topical diclofenac compared to topical placebo.

GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

9.2 Topical ketoprofen versus topical placebo for chronic musculoskeletal pain

Topical ketoprofen versus topical placebo for chronic musculoskeletal pain			
Bibliography: Derry 2016 (223); including Conaghan 2013 (77), Kneer 2013 (236), Rother 2007 (83), Rother 2013 (237)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Clinical success (for example 50% reduction in pain)	2573 (4) 12 weeks	63% vs 48% RR 1.1 (1.01 to 1.2) NNT 6.9 (5.4 to 9.3) **SS in favour of ketoprofen**	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: -1 (high heterogeneity: I^2 = 88%) Directness: ok Imprecision: ok

Local adverse events	2621 (4) 12 weeks	15% vs 13% RR 1.04 (0.85 to 1.27) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (some unclear risks for bias in some studies (e.g. allocation concealment) Consistency: ok Directness: ok Imprecision: ok
Gastrointestinal adverse events	1266 (4) 12 weeks	RR 0.96 (0.69 to 1.32) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (some unclear risks for bias in some studies (e.g. allocation concealment) Consistency: ok Directness: ok Imprecision: ok
Withdrawals due to adverse events	2621 (4) 12 weeks	RR 1.28 (0.92 to 1.78) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (some unclear risks for bias in some studies (e.g. allocation concealment) Consistency: ok Directness: ok Imprecision: ok
Withdrawals due to lack of efficacy	2885 (4) 12 weeks	RR 1.11 (0.80 to 1.55) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (some unclear risks for bias in some studies (e.g. allocation concealment) Consistency: ok Directness: ok Imprecision: ok

This Cochrane systematic review and meta-analysis by Derry 2016 compared topical ketoprofen with topical placebo for **musculoskeletal pain** of at least moderate intensity. Four studies with a study duration of 12 weeks were included for the outcome **clinical success** (for example 50% pain reduction). All eligible studies were in knee osteoarthritis and all used the same gel formulation. There is no evidence for other chronic painful conditions. Topical placebo was the carrier without ketoprofen. One study used a dimethyl sulphoxide (DMSO)-based carrier (Rother 2007). Two studies evaluated different doses of ketoprofen (Conaghan 2013, Kneer 2013). The Cochrane authors found no discernable difference between doses and combined all doses for their analysis. We refer to the Cochrane review for a description of the quantity of topical agent to be applied in each study.

Topical ketoprofen only just reached statistical significance over topical placebo. Clinical success was reported in a high proportion of patients (about 50%) with topical placebo. It is suggested that topical placebo has some analgesic activity of its own due to a 'biolubrication' mechanism, making it difficult to demonstrate a superior effect of topical NSAID. This is supported by direct comparison between topical placebo and oral placebo showing a clear difference in favour of topical placebo (Derry 2016).

There was a **statistical significant effect** of topical ketoprofen compared to topical placebo for **clinical success** in patients with osteoarthritis.

GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

The same four studies that were evaluated for efficacy were evaluated for all safety outcomes. There was no significant difference for **local adverse events** (at the application site) with topical ketoprofen compared to topical placebo.

GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

There was no significant difference in the **incidence of gastrointestinal adverse events** between topical ketoprofen and topical placebo.

GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

There was no significant difference for **withdrawals due to adverse events** between topical ketoprofen and topical placebo.

GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

There was no significant difference for **withdrawals due to lack of efficacy** between topical ketoprofen and topical placebo.

GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

9.3 Other topical NSAID besides diclofenac/ketoprofen versus placebo for chronic musculoskeletal pain

The Cochrane systematic review and meta-analysis by Derry 2016 (223) found for the outcome clinical success one study for ibuprofen (238), two studies for piroxicam ((239), (240)) and some additional studies for other topical NSAID not available in Belgium. None of these studies met our inclusion criteria for study duration.

Derry 2016 found for local adverse events two studies with ibuprofen ((238), (241)), two studies with piroxicam ((239), (240)), and some studies with other topical NSAID not available in Belgium. None of these studies met our inclusion criteria for study duration.

GRADE: Insufficient evidence

9.4 Topical NSAID versus any oral NSAID for chronic musculoskeletal pain

Topical NSAID versus any oral NSAID for chronic musculoskeletal pain			
Bibliography: Derry 2016 (223), including Dickson 1991 (242), Rother 2007(83), Sandelin 1997 (40), Simon 2009 (42), Tugwell 2004 (243), Zacher 2001 (244)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Clinical success (for example 50% reduction in pain)	1735 (5) 3-12 weeks	55% vs 54% RR 1.03 (0.95 to 1.12) NS	⨁⨁⨀⨀ **LOW** Study quality: -2 (different comparisons, 3 studies with short duration (<6 weeks)) Consistency: ok Directness: ok Imprecision: ok
Local adverse events	1735 (5) 4-12 weeks	22% vs 5.8% RR 3.74 (2.76 to 5.06) NNH 6.4 (5.3 to 8.0) **SS: more local adverse events with topical NSAID**	⨁⨀⨀⨀ **VERY LOW** Study quality: -2 (different comparisons, 2 studies with short duration (<6 weeks)) Consistency: -1 (heterogeneity I^2 90%) Directness: ok Imprecision: ok
Gastrointestinal adverse events	1961 (6) 3-12 weeks	17% vs 26% RR 0.66 (0.56 to 0.77) NNTp 10 (7.6 to 17) **SS: less adverse events with topical NSAID**	⨁⨀⨀⨀ **VERY LOW** Study quality: -2 (different comparisons, 3 studies with short duration (<6 weeks)) Consistency: -1 (heterogeneity I^2 62%) Directness: ok Imprecision: ok
Withdrawals due to adverse events	1961 (6) 3-12 weeks	RR 0.85 (0.68 to 1.06) NS	⨁⨁⨀⨀ **LOW** Study quality: -2 (different comparisons, 3 studies with short duration (<6 weeks)) Consistency: ok Directness: ok Imprecision: ok
Withdrawals due to lack of efficacy	1197 (3) 12 weeks	7% vs 3% RR 2.47 (1.45 to 4.22) NNTp 23 (14 to 52)	⨁⨁⨀⨀ **LOW** Study quality: -2 (different comparisons) Consistency: ok Directness: ok Imprecision: ok

	SS: more withdrawals due to lack of efficacy with topical NSAID

This Cochrane review of Derry 2016 compared topical NSAID with oral NSAID for **musculoskeletal pain**. A total of 5 studies were found with a study duration between 3 weeks and 12 weeks for the outcome **clinical success**. All studies were in osteoarthritis. All studies used the double dummy method to maintain blinding. Multiple topical NSAID (piroxicam, ketoprofen, diclofenac, eltenac) were compared with multiple oral NSAID (ibuprofen, celecoxib, diclofenac). Despite differences in comparisons and study durations, results were pooled to evaluate major differences in effect size.
There was **no difference in clinical success** between topical NSAID and oral NSAID.

GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

A total of 5 studies with a study duration between 4 weeks and 12 weeks were eligible for the outcome local adverse events. There were significantly **more local adverse events** with topical NSAID compared to oral NSAID.

GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

A total of 6 studies with a study duration between 3 weeks and 12 weeks were eligible for the outcome gastrointestinal adverse events. There were **fewer gastrointestinal adverse events** with topical NSAID compared to oral NSAID.

GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

A total of 6 studies with a study duration between 3 weeks and 12 weeks were eligible for the outcome withdrawals due to adverse events. There was no significant difference in **withdrawals due to adverse events** with oral NSAID compared to topical NSAID.

GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

9.5 Topical NSAID versus different topical NSAID for chronic musculoskeletal pain

The Cochrane systematic review and meta-analysis by Derry 2016 (223) found one study that compared topical NSAID with other topical NSAID (Burgos 2001). This study compared topical NSAID that are not available in Belgium and this study did not meet our inclusion criterion for study duration.

GRADE: Insufficient evidence

9.6 Topical NSAID versus different topical treatment for chronic musculoskeletal pain

The Cochrane systematic review and meta-analysis by Derry 2016 (223) found three studies that compared topical NSAID with different topical treatments ((245), (240), (246)). There were insufficient data for meta-analysis for any of these comparisons. None of these studies met our inclusion criterion for study duration.

GRADE: Insufficient evidence

9.7 DMSO (dimethyl sulfoxide) versus placebo for osteoarthritis

The systematic review of Brien 2008 (247) found four studies that compared DMSO with placebo ((248), (249), (228), (250)). None of the studies met our inclusion criterion for study duration.

The aim of the Cochrane review of Derry 2016 (223) (already discussed elsewhere in this report) for chronic musculoskeletal pain was not to compare DMSO with placebo. However 7 studies were included comparing topical NSAID with DMSO of which four undertook separate analyses of placebo with or without DMSO ((224), (251), (228), (42)). All four studies were conducted for osteoarthritis. One study (228), not meeting our inclusion criterion for study duration, was also included in the review of Brian 2008. Two studies ((224), (251)) were provided to the Cochrane authors only as a synopsis from the manufacturer. The Cochrane review does not report results of the comparison DMSO versus placebo. It is not clear if such an analysis was included in the original report of the manufacturer.

The study by Simon 2009 (42) with a study duration of 12 weeks compared topical diclofenac solution in a vehicle containing DMSO with topical placebo, DMSO vehicle, and oral diclofenac. The paper does not include statistical tests for efficacy and safety for the comparison DMSO versus placebo. However, in the results section the authors mention no significant efficacy advantage of the DMSO vehicle over placebo for the primary or secondary variables, except for patient overall health assessment.

GRADE: Insufficient evidence

9.8 Topical capsaicin (8%) versus topical placebo/control in neuropathic pain

Topical capsaicin versus placebo/control in postherpetic neuralgia

Topical capsaicin (8%) versus topical placebo/control in postherpetic neuralgia			
Bibliography: Derry 2017 (252) including Backonia 2008 (253), Irving 2011 (254), Webster 2010a (255), Webster 2010b (256)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
≥ 50% pain intensity reduction over weeks 2 to 8	870 (3) 12 weeks	29% vs 20% RR 1.4 (1.1 to 1.9) NNT 12 (7.2 to 41) **SS in favour of capsaicin 8%**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (some unclear risks in bias assessment (e.g. randomization not described), uncertain effects of LOCF imputation) Consistency: ok Directness: ok Imprecision: -1 (wide CI)
≥ 50% pain intensity reduction over weeks 2 to 12	571 (2) 12weeks	33% vs 24% RR 1.3 (1.0 to 1.7) NNT 11 (6.1 to 62) **SS in favour of capsaicin 8%**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (some unclear risks in bias assessment (e.g. randomization not described), uncertain effects of LOCF imputation) Consistency: ok Directness: ok Imprecision: -1 (wide CI)
≥ 30% pain intensity reduction over weeks 2 to 8	1272 (4) 12weeks	43% vs 34% RR 1.3 (1.1 to 1.5) NNT 11 (6.8 to 26) **SS in favour of capsaicin 8%**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (some unclear risks in bias assessment (e.g. randomization not described), uncertain effects of LOCF imputation) Consistency: ok Directness: ok Imprecision: -1 (wide CI)
≥ 30% pain intensity reduction over weeks 2 to 12	973 (3) 12weeks	46% vs 37% RR 1.3 (1.1 to 1.5) NNT 10 (6.3 to 28) **SS in favour of capsaicin 8%**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (some unclear risks in bias assessment (e.g. randomization not described), uncertain effects of LOCF imputation) Consistency: ok Directness: ok Imprecision: -1 (wide CI)

moderate benefit: Patient Global Impression of Change much or very much improved at week 8	571 (2) 12weeks	36% vs 25% RR 1.4 (1.1 to 1.8) NNT 8.8 (5.3 to 26) **SS in favour of capsaicin 8%**	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 (some unclear risks in bias assessment (e.g. randomization not described), uncertain effects of LOCF imputation) Consistency: ok Directness: ok Imprecision: -1 (wide CI)
moderate benefit: Patient Global Impression of Change much or very much improved at week 12	571 (2) 12weeks	39% vs 25% RR 1.6 (1.2 to 2.0) NNT 7.0 (4.6 to 15) **SS in favour of capsaicin 8%**	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 (some unclear risks in bias assessment (e.g. randomization not described), uncertain effects of LOCF imputation) Consistency: ok Directness: ok Imprecision: -1 (wide CI)

Topical capsaicin versus placebo/control in HIV neuropathy

Topical capsaicin (8%) versus topical placebo/control in HIV neuropathy			
Bibliography: Derry 2017 (252) including Clifford 2012 (257), Simpson 2008 (258)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
≥ 30% pain intensity reduction over weeks 2 to 12	801 (2) 12 weeks	39% vs 30% RR 1.4 (1.1 to 1.7) NNT 11 (6.2 to 47) **SS in favour of capsaicin 8%**	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 (unclear risk for bias (e.g. allocation concealment), uncertain effects of LOCF imputation) Consistency: ok Directness: ok Imprecision: -1 (wide CI)
Patient Global Impression of Change much or very much improved at week 12	307 (1) 12weeks	27% vs 10% RR 2.8 (1.4 to 5.6) NNT 5.8 (3.8 to 12) **SS in favour of capsaicin 8%**	⊕⊕⊖⊖ **LOW** Study quality: -2 (unclear risk for bias (e.g. allocation concealment), uncertain effects of LOCF imputation) Consistency: NA Directness: ok Imprecision: ok

Topical capsaicin versus placebo/control in peripheral diabetic neuropathy

Topical capsaicin (8%) versus topical placebo/control in peripheral diabetic neuropathy			
Bibliography: Derry 2017 (252) including STEP 2014 (259)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**

≥ 50% pain intensity reduction over weeks 2 to 8	369 (1) 12 weeks	21% vs 18% RR 1.2 (0.77 to 1.8) NNT not calculated NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (unclear risk for bias (e.g. allocation concealment), uncertain effects of LOCF imputation) Consistency: NA Directness: ok Imprecision: ok
≥ 50% pain intensity reduction over weeks 2 to 12	369 (1) 12weeks	22% vs 19% RR 1.2 (0.77 to 1.7) NNT not calculated NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (unclear risk for bias (e.g. allocation concealment), uncertain effects of LOCF imputation) Consistency: NA Directness: ok Imprecision: ok
≥ 30% pain intensity reduction over weeks 2 to 8	369 (1) 12weeks	40% vs 33% RR 1.2 (0.92 to 1.6) NNT not calculated NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (unclear risk for bias (e.g. allocation concealment), uncertain effects of LOCF imputation) Consistency: NA Directness: ok Imprecision: ok
≥ 30% pain intensity reduction over weeks 2 to 12	369 (1) 12weeks	41% vs 32% RR 1.3 (0.98 to 1.7) NNT not calculated NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (unclear risk for bias (e.g. allocation concealment), uncertain effects of LOCF imputation) Consistency: NA Directness: ok Imprecision: ok
moderate benefit: Patient Global Impression of Change much or very much improved at week 8	369 (1) 12weeks	38% vs 28% RR 1.3 (1.0 to 1.8) NNT 10 (5.2 to 520) **SS in favour of capsaicin 8%**	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 (unclear risk for bias (e.g. allocation concealment), uncertain effects of LOCF imputation) Consistency: NA Directness: ok Imprecision: -1 (wide CI)
moderate benefit: Patient Global Impression of Change much or very much improved at week 12	369 (1) 12weeks	36% vs 28% RR 1.2 (0.92 to 1.7) NNT not calculated NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (unclear risk for bias (e.g. allocation concealment), uncertain effects of LOCF imputation) Consistency: NA Directness: ok Imprecision: ok

Safety and withdrawals due to lack of efficacy (all conditions combined)

Topical capsaicin (8%) versus topical placebo/control in neuropathic pain

Bibliography: Derry 2017 (252) including Backonia 2008 (253), Bischoff 2014 (260), Clifford 2012 (257), Irving 2011 (254), Simpson 2008 (258), STEP 2014 (259), Webster 2010a (255), Webster 2010b (256)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Withdrawals due to lack of efficacy	2487 (8) 12 weeks	1.5% vs 3.1% RR 0.80 (0.36 to 1.8) NNTp not calculated NS	⊕⊕⊖⊖ **LOW** Study quality: -1 (unclear risk for bias (e.g. allocation concealment) Consistency: ok Directness: ok Imprecision: -1 (few events)
Serious adverse events	1993 (7) 12weeks	3.5% vs 3.2% RR 1.14 (0.70 to 1.86) NNH not calculated NS	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: ok Directness: ok Imprecision: -1 (few events)
<u>Patch tolerability</u> <90% application time	2074 (6) 12weeks	1.7% vs 0.3% RR 3.3 (1.2 to 9.2) NNH 77 (45 to 260) **SS: less tolerability with capsaicin 8%**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: ok Directness: ok Imprecision: -1 (wide CI)
<u>Patch tolerability</u> Dermal irritation score >2 (range:0-7) at 2 hours	1065 (3) 12weeks	11% vs 0.7% RR 12 (4.0 to 34) NNH 9.6 (7.7 to 13) **SS: more dermal irritation with capsaicin 8%**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: ok Directness: ok Imprecision: -1 (wide CI)
<u>Patch tolerability</u> Dermal irritation score >0 (range:0-7) at 2 hours	606 (2) 12weeks	40% vs 18% RR 2.3 (1.6 to 3.2) NNH 4.5 (3.3 to 6.7) **SS: more dermal irritation with capsaicin 8%**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: -1 (heterogeneity: I=90%) Directness: ok Imprecision: ok
<u>Patch tolerability</u> Pain medication 0 to 5 days	2442 (7) 12weeks	43% vs 17% RR 2.5 (2.2 to 2.9) NNH 3.8 (3.4 to 4.4) **SS: more pain medication with capsaicin 8%**	⊕⊕⊕⊕ **HIGH** Study quality: ok Consistency: ok Directness: ok Imprecision: ok

This Cochrane review by Derry 2017 (252) compared **capsaicin 8%** with topical placebo for **neuropathic pain**. Patients with postherpetic neuralgia, HIV neuropathy, peripheral neuropathy were evaluated separately for efficacy. Safety and withdrawal due to lack of efficiency was evaluated in all conditions combined. A total of 8 studies were included, all with a study duration of 12 weeks. In all studies, pain

was of at least moderate severity. Most studies permitted stable treatment with concomitant oral or transdermal drugs to be continued for neuropathic pain without change in dose or frequency.

Application of capsaicin to the skin, particularly at this high concentration, initially causes erythema (redness) and a burning or stinging sensation in many people. With the exception of 2 studies (Bischoff 2014, STEP 2014), all studies used a low dose (0.04%) of capsaicin in the control patch to produce some degree of skin irritation without effective analgesia, in an attempt to prevent participants from guessing their treatment allocation.
Because of the localized pain at the application site, no pain measurements were generally made in the first post-treatment week.

Efficacy in patients with postherpetic neuralgia

Capsaicin 8% **reduced pain more than 50%** at week 8 and 12 compared to topical placebo in patients with **postherpetic neuralgia**.

GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

Capsaicin 8% **reduced pain more than 30%** at week 8 and 12 compared to topical placebo in patients with **postherpetic neuralgia**.

GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

There were **more** patients with **Patient Global Impression of Change (PGIC) much or very much improved** at week 8 and week 12 in patients with capsaicin 8% compared with topical placebo.

GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

Efficacy in patients with HIV neuropathy

Capsaicin 8% **reduced pain more than 30%** at week 12 compared to topical placebo in patients with **HIV neuropathy**.

GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

There were **more** patients with **Patient Global Impression of Change (PGIC) much or very much improved** at week 12 in patients with capsaicin 8% compared with topical placebo.

GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Efficacy in patients with peripheral diabetic neuropathy
There was **no statistical significant difference** for **at least 30 or 50% pain reduction** in patients with **peripheral diabetic neuropathy**.

GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There were **more** patients with **Patient Global Impression of Change (PGIC) much or very much improved** at week 8 in patients with capsaicin 8% compared with topical placebo.

GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

There was no significant difference between capsaicin 8% and topical placebo for **Patient Global Impression of Change (PGIC) much or very much improved** at week 12.

GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Safety and withdrawals due to lack of efficacy (all conditions combined)
There was **no significant difference** between capsaicin 8% and topical placebo for **withdrawals due to lack of efficacy**.

GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no significant difference** between capsaicin 8% and topical placebo for **serious adverse events**.

GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

It was not possible to determine the number of participants with any type of local skin reaction. The Cochrane authors evaluated certain selected individual symptoms: erythema, pain, papules, pruritus, oedema. Because the original studies reported the adverse events differently, 2 analyses were performed: 2 groups. These adverse events were more frequent with capsaicin 8%. We refer to our detailed table in the full report for these results.

There were **significantly more** patients on capsaicin 8% who did **not complete at least 90% of the intended application time** compared to topical placebo.

GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

There were **significantly more** patients on capsaicin 8% who had a **dermal irritation score >2 at 2 hours** compared to topical placebo.

GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

There were **significantly more** patients on capsaicin 8% who had a **dermal irritation score >0 at 2 hours** compared to topical placebo.

GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

There were **significantly more** patients on capsaicin 8% who used **medication for treatment-related discomfort on days 0 to 5** compared to topical placebo.

GRADE: HIGH quality of evidence
We have high confidence that the results of the studies reflect the true effect.

9.9 Topical lidocaine versus placebo/active control for neuropathic pain

Topical lidocaine versus placebo/active control for neuropathic pain			
Bibliography: Palladini 2019 (261)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
change from baseline in 24 hour average pain intensity at Week 12 (PO)	363 (1) 12 weeks	lidocaine: LS mean (SE) -1.70 (0.16) 95%CI (-2.11, -1.37) placebo: LS mean (SE) -1.47 (0.16) 95%CI (-1.78, -1.03)	⨁⨁⨁⊖ **MODERATE** Study quality: ok (incomplete reporting) Consistency: NA Directness: ok Imprecision: -1 (only 1 study)

	Difference LS mean (SE) -0.23 (0.23) 95%CI : (-0.69, 0.22) p=0.1533, NS

A Cochrane review of Derry 2014 (8) searched for studies comparing any formulation of topical lidocaine with placebo or another active treatment in chronic neuropathic pain. A total of 12 studies were found but none of the studies met our inclusion criteria for sample size and/or study duration. We found one additional study (Palladini 2019) after the publication of Derry 2014.

This RCT of Palladini 2019 (261) compared topical lidocaine with topical placebo in patients with moderate to severe chronic **post-surgical neuropathic pain**.
There was **no statistical significant difference** for the primary outcome "**change from baseline in 24 hour average pain intensity at Week 12**". The authors argue that topical lidocaine led to a clinically relevant reduction of pain and that the lack of significant difference with topical placebo might in part be related to the mechanical protection provided by the placebo plaster.

GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

Additional analyses for secondary outcomes (responder analysis, patient global impression of change (PGIC), quality of life) are reported but no statistical test results are provided. The authors report adverse events but no statistical test results are provided.

More details can be found in the full document.

9.10 Non-opioid topical analgesics vs placebo/topical non-opioid analgesics in chronic cancer pain

The meta-analysis of Huang 2019(222) searched for studies comparing any systemic pharmaceutical intervention and/or combination thereof (including oral, transdermal, intravenous, and subcutaneous routes) for chronic cancer pain. None of the included studies of this network meta-analysis evaluated topical non-opioid analgesics.

GRADE: Insufficient evidence

10 Summary and conclusions from the literature review. Supplements

10.1 Curcuminoids vs placebo for osteoarthritis

Curcuminoids vs placebo for knee osteoarthritis			
Bibliography: SR Bannuru 2018(262), containing: Haroyan 2018(263), Madhu 2013(264), Moharamzad 2011(265), Nakagawa 2014(266), Panahi 2014(267). Additional RCT: Srivastava 2016(268)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain – WOMAC / VAS	331 (5 studies) 6-12 weeks	**SMD −0.81(−1.25 to −0.37), I^2= 71%** **SS in favour of curcuminoid**	⨁⨁⨀⨀ **LOW** Study quality:-1 (sample size) Consistency: -1 (moderate heterogeneity) Directness: ok Imprecision:ok
	160 (1 study) 17 weeks	**(VAS)** **Curcuma: 4.03 +- 0.08** **placebo: 5.11 +- 0.14** **P= 0.0001** **SS in favour of curcuma** (WOMAC) Curcuma: 9.48 +- 0.17 placebo: 10.16 +- 0.16 P= 0.06 NS	
Function	232 (3 studies) 6-12 weeks	**SMD −0.48(−0.74 to −0.22), I^2= 0%** **SS in favour of curcuminoid**	⨁⨁⨁⨀ **MODERATE** Study quality:-1 (sample size) Consistency: ok Directness: ok Imprecision:ok
Withdrawals due to adverse events	288 (4 studies) 6-12 weeks	RR 0.90 (0.21 to 3.79) I^2= 14% NS	⨁⨁⨀⨀ **LOW** Study quality: -1 (sample size) Consistency: ok Directness: ok Imprecision: -1 (95%CI includes both appreciable harm and benefit)

SR Bannuru 2018(262) searched for RCTs comparing orally administered curcuminoid or Boswellia formulations (alone or in combination) with placebo or NSAIDs, in subjects with knee osteoarthritis.

Five RCTs were found comparing curcuminoids with placebo. The duration of the RCTs varied from 6 to 12 weeks.

Four of these five RCTs did not meet our inclusion criteria for sample size.

We found one additional RCT with 17 weeks of follow-up, comparing curcuma to placebo in knee osteoarthritis. It was excluded from SR Bannuru because of concomitant treatment with an NSAID (diclofenac 50 mg/day) in both arms. As this was not an exclusion criterium in our literature review, we also evaluated this study.

Treatment with curcuminoids resulted in **more pain reduction** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflects the true effect.

Treatment with curcuminoids resulted **better function** compared to placebo treatment.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the study reflects the true effect.

There was **no statistically significant difference** in **withdrawals due to adverse events** between curcuminoids and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the study reflects the true effect.

10.2 Curcuminoids vs NSAID for osteoarthritis

Curcuminoids vs NSAIDs for knee osteoarthritis			
Bibliography: SR Bannuru 2018(262), containing: Kuptniratsaikul 2009(269), Kuptniratsaikul 2014(270), Kizhakkedath 2013(271)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain	422 (2 studies) 4-6 weeks	SMD −0.05 (−0.41 to 0.31) I^2 = 60% NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-2 (duration, open label) Consistency: ok Directness: -1 (atypical posology of comparator) Imprecision:ok
Withdrawals due to adverse events	474 (2 studies) 4-6 weeks	**RR 0.22 (0.05 to 0.99), I^2 = 0%** **SS fewer withdrawals with curcuminoids**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (duration, open label) Consistency: ok Directness: -1 (atypical posology of comparator) Imprecision: ok

SR Bannuru 2018(262) searched for RCTs comparing orally administered curcuminoid or Boswellia formulations (alone or in combination) with placebo or NSAIDs, in subjects with knee osteoarthritis.

Three RCTs were found comparing curcuminoids with NSAID. The duration of the RCTs varied from 4 to 12 weeks. Two RCTs compared curcuminoids to ibuprofen. One RCT compared curcuminoids to celecoxib.

One of these three RCTs did not meet our inclusion criteria for sample size. One RCT did not meet our inclusion criteria for duration. One RCT was not blinded. An atypical posology of ibuprofen (200 mg 6x/day) was used as the comparator in one study. These problems could lead to bias and limit our confidence in the results.

There was **no statistically significant difference** in **pain reduction** between curcuminoids and NSAID.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the study reflects the true effect.

Curcuminoid treatment resulted in **fewer withdrawals due to adverse events** compared to NSAID treatment.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the study reflects the true effect.

10.3 Curcuminoids vs placebo for painful diabetic neuropathy

Curcuminoids vs placebo for painful diabetic neuropathy

Bibliography: Asadi 2019(272)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Foot pain	80 (1 study) 8 weeks	Curcumin: Baseline: 30, week 8: 20 Placebo: Baseline: 34, week 8: 33 P for interaction: 0.07 NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-2 (sample size, unbalanced attrition between groups; possible selective reporting of outcomes) Consistency: NA Directness: ok Imprecision: -1 (unclear, no 95%CI reported)

One RCT was found comparing curcuminoids with placebo for painful diabetic neuropathy.

The duration of this RCT was 8 weeks.

This RCT had a small sample size, unbalanced drop-out between groups, and possible selective reporting of outcomes. This could lead to bias and limits our confidence in the results.

There was **no statistically significant difference** in **foot pain** between curcuminoids and placebo.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the study reflects the true effect.

10.4 Glucosamine vs placebo for osteoarthritis

Glucosamine vs placebo in osteoarthritis			
Bibliography: Zhu 2018(273), containing: Noack 1994(274), Houpt 1999(275), Reginster 2001(276), Pavelka 2002(277), Braham 2003(278), McAlindon 2004(279), Cibere 2004(280), Usha 2004(281), Clegg 2006(76), Herrero-Beaumont 2007(22), Rozendaal 2008(282), Giordano 2009(283), Fransen 2014(284), Kwoh 2014(285) Additional RCT: Sawitzke 2010(286)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**

Pain	2845 (14 studies) 4 - 144 weeks 662 (1 study) 24 months	SMD -0.105 (-0.254 to 0.045) p= 0.170 I^2: 72.5% NS 20% improvement WOMAC: OR 1.16 (0.65 to 2.04) NS OMERACT/OARSI: OR 1.16 (0.74 to 1.83) NS WOMAC (0-100) Difference -0.97 (-5.66 to 3.72) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 (unclear randomization and allocation concealment; very high attrition in one large study) Consistency: -1 (moderate heterogeneity) Directness: ok Imprecision: ok
Function	Number of participants not reported (11 studies) 4 – 144 weeks	SMD -0.126 (-0.264 to 0.012) p= 0.073 I^2: 64.1% NS WOMAC Difference 0.56 (-4.69 to 5.82) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (unclear randomization/allocation concealment) Consistency: ok Directness: ok Imprecision: ok
Adverse events (overall)	Number of participants not reported (8 studies) 12- 144 weeks	RR 0.90 (0.66 to 1.23) I^2= 24.3% NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (most studies had unclear allocation concealment) Consistency: ok Directness: ok Imprecision: ok

In this systematic review and meta-analysis, RCTs were sought that compared glucosamine, chondroitin, or the two in combination with placebo in patients with hip and/or knee osteoarthritis.

Fourteen RCTs were found that compared glucosamine with placebo. The duration of the trials varied between 4 and 144 weeks, with most trials being 12 or 24 weeks.

4 RCTs did not meet our inclusion criteria (sample size or duration). Of the remaining RCTs, 3 had unclear randomization, and 6 had unclear allocation concealment.

One additional RCT was found that compared glucosamine to placebo. It had 2 years follow-up. A high risk of bias was present due to a number of methodological issues (unclear randomization, very high attrition (53% drop-out), and unclear reporting of safety data.)

There was **no statistically significant difference** in **pain** between glucosamine and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **function** between glucosamine and placebo.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **adverse events** between glucosamine and placebo.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

10.5 Glucosamine vs NSAID for osteoarthritis

Glucosamine vs NSAID in osteoarthritis			
Bibliography: Towheed 2005(11), containing: Clegg 2006(76), Muller-FassBender 1994(287), Qiu 1998(288), Rovati 1997(289), Vaz 1982(290) Additional RCT: Chopra 2013(291)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain	997 (4 studies) 4 - 24 weeks 440 (1 study) 24 weeks	SMD -0.27 (-0.65 to 0.11) I^2=84% NS VAS: Difference 95%CI -1.20 to -0.60 Within a a priori selected range of ±1.5cm Equivalence between glucosamine and celecoxib WOMAC: MD 95%CI -1.52 to 0.20	⨁⨁⨀⨀ **LOW** Study quality: -1 (1 trial short duration, 1 trial unclear randomization, allocation concealment) Consistency: -1 (significant heterogeneity) Directness: ok Imprecision: ok

		Within a *a priori* selected range of ±2.5 Equivalence between glucosamine and celecoxib	
Number of patients reporting adverse events	580 (4 studies) 4- 20 weeks	**Glucosamine 25/285** **NSAID 90/295** **I^2=0%** **RR 0.29 (0.19 to 0.44)** **SS fewer patients reporting adverse events with glucosamine**	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (1 trial short duration, 1 trial unclear randomization, allocation concealment) Consistency: ok Directness: ok Imprecision: ok
Number of withdrawals due to adverse events	1215 (5 studies) 4- 24 weeks	**Glucosamine 10/602** **NSAID 41/613** **I^2=79%** **RR 0.16 (0.02 to 1.46)** **SS fewer withdrawals due to adverse events with glucosamine**	⊕⊕⊖⊖ **LOW** Study quality: -1 (1 trial short duration, 1 trial unclear randomization, allocation concealment) Consistency: -1 (significant heterogeneity) Directness: ok Imprecision: ok

In this systematic review and meta-analysis, RCTs were sought that compared glucosamine-only preparations with placebo or other comparators in patients with osteoarthritis.

Five RCTs were found that compared glucosamine with an NSAID. The duration of the trials varied between 4 and 24 weeks. 3 RCTs compared glucosamine with ibuprofen, one with celecoxib, and one with piroxicam.

2 RCTs did not meet our inclusion criteria (sample size or duration). Of the remaining RCTs, 1 had unclear randomization and allocation concealment.

One additional equivalence trial was found that compared glucosamine to celecoxib. This RCT had 24 weeks of follow-up. There was unclear reporting of allocation concealment and high and unbalanced attrition.

There was **no statistically significant difference** in **pain** between glucosamine and NSAID.

GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Glucosamine treatment resulted in **fewer patients reporting adverse events** compared to NSAID treatment.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

Glucosamine treatment resulted in **fewer withdrawals due to adverse events** compared to NSAID treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

10.6 Glucosamine vs placebo for low back pain

Glucosamine vs placebo in low back pain			
Bibliography: SR Sodha 2013(292) containing: RCT Wilkens 2010(293)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain	250 (1 study) 1 year	Low back pain at rest (NRS) Glucosamine: mean SD 2.5 (2.1 to 2.9) Placebo: 2.8 (2.4 to 3.1) Difference : -0.3 (-0.8 to 0.3) NS Low back pain when active (NRS) Glucosamine: mean SD 3.0 (2.5 to 3.4) Placebo: 2.9 (2.5 to 3.3) Difference): 0.1 (-0.5 to 0.6) NS	⨁⨁⨁⊖ **MODERATE** Study quality: -1 (single study) Consistency: NA Directness: ok Imprecision: ok

QoL	250 (1 study) 1 year	Health-related QoL (EQ-5D index) Glucosamine: mean SD 0.74 (0.70 to 0.78) Placebo: 0.70 (0.65 to 0.74) Difference: 0.0 (0.0 to 0.1) NS Health-related QoL (EQ-VAS) Glucosamine: mean SD 7.4 (7.0 to 7.7) Placebo: 6.6 (6.3 to 7.0) Difference: 0.7 (0.2 to 1.2) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (single study) Consistency: NA Directness: ok Imprecision: ok
Adverse events (all)	250 (1 study) 1 year	Glucosamine: 32% Placebo: 36.8% OR 0.83 (0.49 to 1.40) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (single study) Consistency: NA Directness: ok Imprecision: ok
Adverse events resulting in study agent termination	250 (1 study) 1 year	Glucosamine: 3.2% Placebo: 4.8% OR 0.66 (0.48 to 1.36) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (single study) Consistency: NA Directness: ok Imprecision: ok

In this systematic review and meta-analysis, RCTs were sought that evaluated glucosamine in adults with chronic back pain.

Three RCTs were found. Two RCTs did not meet our inclusion criteria (sample size <40 participants per study-arm). Only one RCT (Wilkens 2010) met our inclusion criteria.

This RCT compared glucosamine with placebo in 250 patients with chronic low back pain. The treatment lasted 6 months and the duration of follow-up one year. The results at 6 months and 1 year were consistent and did not show a statistically significant difference for pain or QoL.

This study had a low risk of bias.

There was **no statistically significant difference** in **pain** between glucosamine and placebo.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **quality of life** between glucosamine and placebo.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **adverse events** between glucosamine and placebo.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **adverse events resulting in study agent termination** between glucosamine and placebo.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

10.7 Chondroitin vs placebo for osteoarthritis

Chondroitin vs placebo in osteoarthritis			
Bibliography: Zhu 2018(273), containing: Bucsi 1998(294), Bourgeois 1998(295), Uebelhart 1998(296), Mazieres 2001(297), Uebelhart 2004(298), Michel 2005(299), Clegg 2006(76), Mazieres 2006(300), Kahan 2009(301), Wildi 2011(302), Zegels 2013(303), Fransen 2014(284) Additional RCTs: Sawitzke 2010(286), Reginster 2017(304)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**

Pain	3082 (12 studies) 12-96 weeks	**SMD -0.216 (-0.360 to -0.071)** **p= 0.003** **I^2: 70.8%** **SS in favour of chondroitin**	⊕⊕⊖⊖ **LOW** Study quality: -1 (unclear randomization and allocation concealment; very high attrition in one large study) Consistency: -1 (moderate heterogeneity, inconsistent results) Directness: ok Imprecision: ok
	662 (1 study) 24 months	20% improvement WOMAC: OR 0.69 (0.40 to 1.21) NS OMERACT/OARSI: OR 0.89 (0.53 to 1.50) NS WOMAC (0-100) Difference 2.30 (-3.08 to 7.68) NS	
	604 (1 study) 6 months	Pain (VAS) chondroitin: 28.6 placebo: 36.8 **chondroitin vs placebo p= 0.001** **SS in favour of chondroitin** VAS- MCII Proportion of patient reaching minimally important improvement (20 mm of VAS reduction) chondroitin: 68% placebo: 61% Celecoxib vs placebo p= 0.098 NS	
Function	Number of participants not reported (10 studies) 12 – 96 weeks	**SMD -0.220 (-0.358 to -0.081)** **p= 0.002** **I^2: 68.3%** **SS in favour of chondroitin**	⊕⊕⊖⊖ **LOW** Study quality: -1 (unclear randomization/allocation concealment) Consistency: -1 (possible heterogeneity Directness: ok Imprecision: ok
	662 (1 study)	WOMAC Difference 2.16 (-3.8 to 8.11) NS	

	24 months		
Adverse events (overall)	2714 (8 studies) 12- 96 weeks	RR 1.28 (0.96 to 1.70) I^2= 9.4 % NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (most studies had unclear allocation concealment) Consistency: ok Directness: ok Imprecision: ok

In this systematic review and meta-analysis, RCTs were sought that compared glucosamine, chondroitin, or the two in combination with placebo in patients with hip and/or knee osteoarthritis.

Twelve RCTs were found that compared chondroitin with placebo. The duration of the trials varied between 12 and 96 weeks.

3 RCTs did not meet our inclusion criteria (sample size). Of the remaining RCTs, 2 had unclear randomization, and 8 had unclear allocation concealment.

Two additional RCTs were found that compared chondroitin to placebo.
One RCT had 2 years of follow-up. A high risk of bias was present due to a number of methodological issues (possible breaking of randomization, very high attrition (53% drop-out), and unclear reporting of safety data.)

One RCT had 6 months of follow-up. There was unclear randomization and allocation concealment.

Chondroitin treatment resulted in **more pain reduction** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

Chondroitin treatment resulted in **better function** compared to placebo treatment.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **adverse events** between chondroitin and placebo.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

10.8 Chondroitin vs NSAID for osteoarthritis

Chondroitin vs celecoxib in osteoarthritis

Bibliography: Singh 2015(10) Additional RCTs: Pelletier 2016(305), Reginster 2017(304)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain	138 (1 study) 24 months	VAS Chondroitin: -24.38 Celecoxib: -26.12 p for difference= 0.697 NS WOMAC Chondroitin: -8.81 Celecoxib: -11.09 p for difference= 0.225 NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (unclear randomization and allocation concealment; high attrition, possible selective reporting) Consistency: ok Directness: ok Imprecision: unclear, no 95%CI calculated)
	604 (1 study) 6 months	VAS chondroitin: 28.6 celecoxib : 30.5 Chondroitin vs celecoxib p=0.446 NS VAS-MCII Proportion of patient reaching minimally important improvement (20 mm of VAS reduction) chondroitin: 68% celecoxib : 69% Chondroitin vs celecoxib p=0.914 ; NS	
Function	138 (1 study) 24 months	Chondroitin: -26.92 Celecoxib: -33.52 p for difference= 0.286 NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (single study with high attrition, possible selective reporting) Consistency: NA Directness: ok Imprecision: unclear, no 95%CI calculated)
QoL	138 (1 study) 24 months	QoL SF-36 Improvement in both groups without significant differences between groups	⊕⊕⊖⊖ **LOW** Study quality: -2 (single study with high attrition, possible selective reporting) Consistency: NA

		Data not shown	Directness: ok Imprecision: unclear, no 95%CI calculated)
At least one AE	138 (1 study) 24 months	Chondroitin: 78% Celecoxib: 77% p for difference= >0.999 NS	⨁⨁⨀⨀ **LOW** Study quality:-2 (single study with high attrition, possible selective reporting) Consistency: NA Directness: ok Imprecision: ok
Serious adverse events	138 (1 study) 24 months	Chondroitin: 10% Celecoxib: 6% p for difference= 0.435 NS	⨁⨁⨀⨀ **LOW** Study quality: -2 (single study with high attrition, possible selective reporting) Consistency: NA Directness: ok Imprecision: ok
AE related to study treatment	138 (1 study) 24 months	Chondroitin: 27% Celecoxib: 24% p for difference= 0.745 NS	⨁⨁⨀⨀ **LOW** Study quality: -2 (single study with high attrition, possible selective reporting) Consistency: NA Directness: ok Imprecision: ok
AE leading to study withdrawal	138 (1 study) 24 months	Chondroitin: 13% Celecoxib: 11% p for difference= 0.828 NS	⨁⨁⨀⨀ **LOW** Study quality: -2 (single study with high attrition, possible selective reporting) Consistency: NA Directness: ok Imprecision: ok

A systematic review sought RCTs that compared chondroitin with placebo or an active control (medication or supplements) in adults with osteoarthritis.

Three RCTs were found that compared chondroitin to an active control, but none met our inclusion criteria.

Two additional RCTs were found by our literature search. Both compared chondroitin to celecoxib.

One RCT had a high risk of incomplete outcome data due to high attrition (36,5%), and possible selective reporting of outcomes. The second trial had unclear reporting of randomization and allocation concealment. These methodological problems could lead to bias and limits our confidence in the results.

There was **no statistically significant difference** in **pain** between chondroitin and celecoxib.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **function** between chondroitin and celecoxib.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **quality of life** between chondroitin and celecoxib.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **adverse events** between chondroitin and celecoxib.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **serious adverse events** between chondroitin and celecoxib.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **study treatment-related adverse events** between chondroitin and celecoxib.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **study withdrawals due to adverse events** between chondroitin and celecoxib.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

10.9 Glucosamine + chondroitin vs placebo for osteoarthritis

Glucosamine+ chondroitin vs placebo in osteoarthritis			
Bibliography: Zhu 2018(273), containing: Clegg 2006(76), Fransen 2014(284), Lugo 2016(306), Roman-Blas 2017(307) Additional RCT: Sawitzke 2010(286)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**

Pain	1200 (4 studies) 24-96 weeks 662 (1 study) 24 months	SMD 0.792 (-0.296 to 1.880) p= 0.153 I^2: 98.50% NS 20% improvement WOMAC: OR 0.83 (0.51 to 1.34) NS OMERACT/OARSI: OR 0.85 (0.55 to 1.31) NS WOMAC (0-100) Difference 0.21 (-4.29 to 4.70) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 (unclear randomization and allocation concealment; very high attrition in one large study) Consistency: -1 (significant heterogeneity) Directness: ok Imprecision: ok
Function	1200 (4 studies) 24-96 weeks 662 (1 study) 24 months	SMD 0.556 (-0.368 to 1.480) p= 0.238 I^2: 98% NS WOMAC Difference 3.20 (-2.21 to 8.61) NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (unclear randomization/allocation concealment) Consistency: -1 (significant heterogeneity) Directness: ok Imprecision: ok
Adverse events (overall)	1090 (3 studies) 24-96 weeks	RR 1.40 (0.78 to 2.51) I^2= 0% NS	⊕⊕⊕⊖ **MODERATE** Study quality: -1 (most studies had unclear allocation concealment) Consistency: ok Directness: ok Imprecision: ok

In this systematic review and meta-analysis, RCTs were sought that compared glucosamine, chondroitin, or the two in combination with placebo in patients with hip and/or knee osteoarthritis.

Four RCTs were found that compared glucosamine+ chondroitin with placebo. The duration of the trials varied between 24 and 96 weeks.

One RCT had unclear randomization, and all had unclear allocation concealment.

One additional RCT was found that compared glucosamine to placebo. It had 2 years follow-up. A high risk of bias was present due to a number of methodological issues (unclear randomization, very high attrition (53% drop-out), and unclear reporting of safety data.)

There was **no statistically significant difference** in **pain** between glucosamine+ chondroitin and placebo.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **function** between glucosamine+ chondroitin and placebo.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **adverse events** between glucosamine+ chondroitin and placebo.
GRADE: MODERATE quality of evidence
We have moderate confidence that the results of the studies reflect the true effect.

10.10 Glucosamine + chondroitin vs NSAID for osteoarthritis

Chondroitin sulfate + glucosamine vs celecoxib in osteoarthritis			
Bibliography: Singh 2015(10) Additional RCTs: Hochberg 2016(308)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Pain	606 (1 study) 6 months	WOMAC Chondroitin+ glucosamine: -185.7 Celecoxib: -186.8 Treatment difference : -1.1 (-22.0 to 19.8) p=0.92 Chondroitin+ glucosamine is non-inferior to celecoxib VAS Chondroitin+ glucosamine: -35.1 Celecoxib: -35.3 Treatment difference : -0.22 (-4.8 to 4.3)	⨁⨁⊖⊖ **LOW** Study quality: -2 (single study with unclear allocation concealment; high attrition) Consistency: NA Directness: ok Imprecision: ok

		P= 0.92 NS	
Function	606 (1 study) 6 months	WOMAC Chondroitin+ glucosamine: -504.4 Celecoxib: -525.6 Treatment difference : -21.2 (-87.3 to 45.0) p=0.53 NS	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 (single study with unclear allocation concealment; high attrition) Consistency: NA Directness: ok Imprecision: -1 (95%CI includes both appreciable harm and benefit)
QoL	606 (1 study) 6 months	EuroQoL-5D VAS Chondroitin+ glucosamine: 69.1 Celecoxib: 70.2 Treatment difference P=0.54 NS	⊕⊕⊖⊖ **LOW** Study quality: -2 (single study with unclear allocation concealment; high attrition) Consistency: NA Directness: ok Imprecision: unclear, no 95%CI calculated)
Proportion of subjects having at least one treatment-emergent adverse event	606 (1 study) 6 months	Chondroitin+ glucosamine: 51.0% Celecoxib: 50.5% No statistical test	⊕⊕⊖⊖ **LOW** Study quality:-2 (single study with unclear allocation concealment; high attrition) Consistency: NA Directness: ok Imprecision: NA
Serious adverse events	606 (1 study) 6 months	Chondroitin+ glucosamine: 2.3% Celecoxib: 3.3% No statistical test	⊕⊕⊖⊖ **LOW** Study quality:-2 (single study with unclear allocation concealment; high attrition) Consistency: NA Directness: ok Imprecision: NA

A systematic review sought RCTs that compared chondroitin with placebo or an active control (medication or supplements) in adults with osteoarthritis.

It found 4 studies; 2 of which did not meet our inclusion criteria (sample size). The remaining 2 RCTs did not analyze the comparison of GLU + CHON vs NSAID, but rather compared each arm to placebo. These were previously reported in the chapter "Glucosamine + chondroitin vs placebo".

One additional RCT was found by our literature search. It compared chondroitin + glucosamine to celecoxib and had a follow-up of 6 months.

There was unclear reporting of allocation concealment and high attrition (23%). These methodological problems could lead to bias and limits our confidence in the results.

There was **no statistically significant difference** in **pain** between chondroitin + glucosamine and celecoxib.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **function** between chondroitin + glucosamine and celecoxib.
GRADE: VERY LOW quality of evidence
We have very low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **quality of life** between chondroitin + glucosamine and celecoxib.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **adverse events** between chondroitin + glucosamine and celecoxib.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

There was **no statistically significant difference** in **serious adverse events** between chondroitin + glucosamine and celecoxib.
GRADE: LOW quality of evidence
We have low confidence that the results of the studies reflect the true effect.

10.11 Hyaluronic acid for chronic pain

We found no systematic reviews or RCTs evaluating oral hyaluronic acid in chronic pain that met our inclusion criteria.

Oe 2016(309) “Oral hyaluronan relieves knee pain: a review” is a narrative review focusing on oral hyaluronic acid for knee pain. The RCTs reported in this review did not meet our inclusion criteria (sample size <40 per study arm).

GRADE: *insufficient evidence*

10.12 Traumeel for chronic pain

We found one systematic review(310) that searched for systematic reviews or meta-analyses of complementary and alternative medicine (with or without conventional cancer treatments) on adult cancer pain.
This systematic review found an SR including two RCTs evaluating Traumeel for cancer pain. They did not meet our inclusion criteria (sample size <40 per study arm).

We did not find RCTs or SRs (meeting our inclusion criteria) evaluating Traumeel in other settings.

GRADE: *insufficient evidence*

11 Summary and conclusions from the literature review. Safety.

11.1 Paracetamol and respiratory adverse events

Paracetamol use and incident asthma in childhood

A systematic review by SR Cheelo 2015(311) searched for prospective and retrospective cohort studies that examined the association of incident asthma in the child to exposure to paracetamol during pregnancy or early childhood. Ten cohort studies were found. Four found a statistically significant association between paracetamol use and an increased risk of incident asthma years later; six did not.

The studies that adjusted for respiratory infections did not find a significant association; while those who did not adjust for respiratory infections did find an SS association.

Five additional cohort studies were found by our search. Conflicting results were found.

GRADE: LOW to VERY LOW quality of evidence

Paracetamol use in childhood asthma

An RCT by Sheehan 2016(312) did not find a SS difference of number of asthma exacerbations between paracetamol use and ibuprofen use for fever in children with mild persistent asthma.

GRADE: LOW quality of evidence

Paracetamol use and incident asthma in adults

Two cohort studies(313), (314) evaluating the association of paracetamol use with the risk of incident asthma in adult women were found.

Conflicting results were found. The results were not adjusted for respiratory infections.

GRADE: LOW to VERY LOW quality of evidence

Paracetamol use in adult asthma

One small RCT by Ioannides 2014(315) in adults with asthma did not find a difference of bronchial hyperresponsiveness between paracetamol or placebo after 12 weeks of use.

GRADE: LOW quality of evidence

11.2 Paracetamol and hepatic adverse events

Therapeutic use of paracetamol and acute liver failure in adults

A systematic review by Dart 2007(316) sought articles involving repeated dosing of a therapeutic dose (4 g/day or less) of paracetamol of at least 24 hours.

The authors evaluated information on 30865 patients who were enrolled in RCTs and observational studies.

The median duration of treatment with paracetamol in these studies was 6 days.

- No reports of liver failure, transplantation, or death were made.
- An increase in the serum aminotransferase level that exceeded the upper limit of normal was reported in 129 patients (0.4%)

A comparison group was not reported or evaluated.

11.3 NSAIDs and gastrointestinal adverse events

NSAID use and the risk of upper gastrointestinal complications

SR Castellsague 2012(317) sought observational studies (case-control or cohort studies) comparing the risk of upper gastrointestinal complications (peptic ulcer perforations, obstructions and bleeding) of individual NSAIDs with non-use of NSAIDs.

The following pooled results were found:

- **more upper gastrointestinal complications with ibuprofen; RR 1.94 (1.62 to 2.32)**
- **more upper gastrointestinal complications with naproxen; RR 3.67 (2.84 to 4.75)**
- **more upper gastrointestinal complications with diclofenac; RR 3.33 (2.51 to 4.41)**

SR Arias 2018(318) sought observational studies (case-control, case-crossover or cohort studies) comparing the risk of any gastrointestinal event of COX-2-selective NSAID with non-use of NSAID.

More gastrointestinal adverse outcomes with celecoxib were found; RR 1.53 (1.19 to 1.97), although no statistically significant difference was found in the only cohort study that was included for this comparison.

11.4 NSAIDs and renal adverse events

NSAID use and acute kidney injury (AKI)

SR Zhang(319) searched for cross-sectional, cohort and case-control studies evaluating the association between NSAID use and acute kidney injury. 10 case-control studies were found. We do not report details of these studies as they did not meet our inclusion criteria.

- A higher pooled odds ratio of acute kidney injury was found for current NSAID exposure compared to no exposure: OR 1.73 (1.44 to 2.07).
- A risk of OR 2.51 (1.52 to 2.68) was observed in older people.

A systematic review and meta-analysis (Ungprasert 2015(320)) sought observational studies comparing the risk of acute kidney injury in NSAID users versus non-users.

One retrospective cohort study and four case-control studies were found. This publication calculated risk of acute kidney injury according to NSAID used.

- A higher risk of AKI was found for ibuprofen and naproxen, though this association was not significant in the cohort study.
- No difference was found for diclofenac; this result was also found in the cohort study.

NSAID use and progression of chronic kidney disease

A systematic review and meta-analysis (Nderitu 2013(321)) searched observational studies evaluating the association between NSAID use and chronic kidney disease progression.

- There was no difference in risk of accelerated chronic kidney disease progression for NSAID use in a regular dose.
- NSAID use in a high dose was significantly associated with accelerated CKD progression: OR 1.26 (1.06 to 1.50)

NSAID use and analgesic nephropathy

A systematic review (Yaxley 2016)(322) searched for observational studies evaluating the association between long-term heavy NSAID use and renal insufficiency.

5 cohort studies were found.

None of them identified a relationship between long-term heavy NSAID use and the development of chronic renal impairment.

11.5 NSAIDs and cardiovascular adverse events

NSAID use and cardiovascular events

A systematic review by Gunter 2016(323) sought RCTs and prospective cohort studies that evaluated cardiovascular risks of 8 NSAIDs (**ibuprofen**, **diclofenac**, **naproxen**, meloxicam, **etoricoxib**, **celecoxib**, lumiracoxib, rofecoxib) against other NSAID or against placebo.

8 RCTs and 1 cohort study evaluating the NSAIDs of interest in this literature study were found.

- There was no difference for the outcomes myocardial infarction, stroke, CV death or a composite of the three CV outcomes with NSAID (celecoxib, diclofenac, naproxen) compared to placebo.
- There were SS **fewer strokes** with **celecoxib** compared to nonselective NSAID (ibuprofen, naproxen or diclofenac).

11.6 Topical NSAIDs versus oral NSAIDs

We did not find any systematic reviews of observational studies that searched for and reported safety outcomes of topical NSAIDs versus oral NSAIDs.

12 Additional safety information from other sources

12.1 Paracetamol

12.1.1 Contra-indications

- Severe renal failure (1)

12.1.2 Adverse events

- Adverse events of paracetamol are rare and usually mild (2)
- Little or no irritation of the gastro-intestinal tract. (1)
- In case of overdose: hepatotoxicicy with jaundice and sometimes fatal necrosis, usually only after 24 to 48 hours after the ingestion of large doses.
- 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. (1)
- 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. (1)
    - 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. (324)
    - 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. (325)
- Rare: Haematological reactions and serious skin reactions have been reported. (2).
- Hypersensitivity has also rarely beenreported. (2)

12.1.3 Pregnancy and lactation

- Paracetamol appears to be safe during pregnancy and while breastfeeding. (1)

12.1.4 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.(1)
- 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. (1)
- 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. (1)

- 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. (1)
- Patients with toothache appear to be an important risk group for accidental paracetamol intoxication. (1)
- The absorption of paracetamol from suppositories varies; oral administration is preferable, also in infants. (1)
- The sodium content in effervescent preparations (tablets, powders, granules) can cause problems for patients on a strict low-salt diet. (1)
- The controlled release preparations with paracetamol were withdrawn from the market in 2018 due to the risks of overdose. (1)

12.2 NSAID

12.2.1 Contra-indications

- Active gastroduodenal ulcer.. (1)
- Antecedents of asthma or urticaria due to the intake of acetylsalicylic acid or an NSAID. (1)
- Liver insufficiency. (1)
- Severe heart failure. (1)
- For certain specialties, renal insufficiency is mentioned as a contra-indication in the SPC (summary of product characteristics).
- COX-2 selective NSAIDs as well as non-COX-2 selective NSAIDs aceclofenac, diclofenac and long-term, high-dose ibuprofen: coronary artery disease, antecedents of cerebrovascular disease, peripheral vascular disease and moderate to severe heart failure. (1)
- Etoricoxib: also uncontrolled hypertension. (1)

12.2.2 Adverse events

- Gastrointestinal (GI) discomfort is the most frequent (GI discomfort, nausea, diarrhea; usually mild and reversible) (2). However, in some patients lesions of the GI mucosae: ulceration, bleeding, perforation. (1)
    - All NSAIDs can result in serious GI adverse events, sometimes without prior symptoms. (1)
    - GI injuries can occur with administration of NSAIDs regardless of the route of administration, including parenterally and rectally. (1)
    - 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. (1)
- Increased risk of myocardial infarction and cerebrovascular accidents. (1)
    - 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. (1)
    - The risk is likely to increase with the dose and the duration of treatment. (1)
- Fluid retention with worsening heart failure: all NSAIDs increase the risk of acute heart failure. (1)

Caution in the elderly, history of heart failure, high dose and long half-life (2).

- Blood pressure increase (2).
  A meta-analysis shows an average blood pressure increase of 5 mmHg. The effect is greatest in patients taking antihypertensive therapy (2).
- Acute and chronic renal failure. (1)
  - 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.
  - Approximately 1 in 200 patients older than 65 years develop an acute kidney problem within 45 days after the start of NSAID treatment.
  - Acute renal failure has also been observed in children with dehydration (with fever or diarrhea) or at high doses.
  - Rare: interstitial nephritis, nephrotic syndrome
  - Long-term use or abuse of analgesics, including NSAIDs, is associated with nephropathy (2).
- Bleeding, hematologic abnormalities. (2)
- Hypersensitivity (eg bronchospasm, angioneurotic edema), sometimes with cross-sensitivity with acetylsalicylic acid and between the NSAIDs.
- Hyperkalaemia, especially in patients with renal insufficiency and patients taking potassium supplements, potassium-sparing diuretics, ACE inhibitors or sartans or using heparins. (1)
- Suspicion of reversible reduction in female fertility with long-term use. (1) (2)
- Headache, vertigo and confusion, especially with arylacetic acid and indole derivatives. Hearing loss and tinnitus are also associated with use of NSAID (2).
- Hepatotoxicity: reversible elevation of transaminases is common; rarely potentially fatal acute liver failure. Diclofenac is most often associated with hepatotoxicity. (1)
- Deterioration and provoking of all sorts of skin disorders ranging to Lyell syndrome and Stevens-Johnson syndrome with all NSAIDs (especially with piroxicam). (1)
- Increased incidence of serious skin complications (abscess, necrosis) in patients with varicella or zona treated with an NSAID. (1)
- Possible increase of the risk of complications with pneumonia. (1)
- Photodermatosis has been described with systemic use (probably mainly piroxicam and topical use (probably mainly ketoprofen gel). (326)
- NSAIDs (including ibuprofen) have also been associated with hyponatremia. The incidence is probably low. (327)
- Optical neuropathy has been described with NSAIDs. (328)
- There is no evidence of added value of nabumetone in terms of adverse events, compared to other NSAIDs such as ibuprofen or the COX-2 selective NSAIDs. (329)

12.2.3 Pregnancy and lactation

- NSAIDs are not recommended during pregnancy. (1)
- First trimester: risk of spontaneous abortion and suspicion of teratogenicity. (1)
- Third trimester: with repeated use, prolongation of pregnancy and labour, bleeding in mother, fetus and newborn, early closure of the ductus arteriosus, and pulmonary hypertension. Even with short-term use, renal failure (with possible oligohydramnion) and heart failure may occur in the fetus and the newborn. (1)

12.2.4 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. (1)
- When associating acetylsalicylic acid, also low dose, the gastrointestinal benefit of the COX-2 selective NSAIDs disappears completely. (1)
- 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). (1)
- 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. (1)
- Increased risk of nephrotoxicity of cyclosporin. (1)
- 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. (1)
- Increased risk of lactic acidosis triggered by metformin. (1)
- Reduced effect of diuretics and most antihypertensive drugs. (1)
- More pronounced increase in kalemia when associated with potassium-sparing diuretics, potassium supplements, ACE inhibitors, sartans and heparins. (1)
- 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. (1)
- Increased risk of heart failure when associated with pioglitazone. (1)
- Increase in the plasma concentration of lithium due to reduced renal excretion.
- Diclofenac, ibuprofen, naproxen and piroxicam are substrates of CYP2C9. (1)
- Celecoxib is a substrate of CYP2C9 and an inhibitor of CYP2D6. (1)

12.2.5 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). (1)
- 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. The oxicams have a long half-life. (1)
- Association with a proton pump inhibitor (PPI), a double-dose H2 antihistamine or misoprostol allows to reduce the gastrointestinal toxicity of the NSAIDs; only for misoprostol and PPIs there is limited evidence of 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 . (1)
- For the COX-2 selective NSAIDs and for aceclofenac, diclofenac and high doses of ibuprofen, cardiovascular adverse events, one should be cautious in patients with cardiovascular

disease (see section "Contraindications"), with hypertension and with high cardiovascular risk. (1)
- NSAIDs should be used with caution in patients with inflammatory bowel disease as they may aggravate the condition. (1)
- 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. (1)
- The sodium content in effervescent preparations (tablets, powders, granules) can cause problems for patients on a strict low-salt diet. (1)
- 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 (2).

12.3 Antidepressants : TCA (amitriptyline en nortriptyline) en SNRI (venlafaxine, duloxetine)

12.3.1.1 Contra-indications TCA

- Association with MAO inhibitors. (1)
- Recent myocardial infarction. (1)
- Cardiac arrhythmias (especially AV block). (1)
- Anticholinergic adverse events for products with an anticholinergic effect (especially amitriptyline). (1)
- Liver insufficiency. (1)

12.3.1.2 Contra-indications SNRI

- Association with MAO inhibitors. (1)
- Duloxetine: also uncontrolled hypertension; severe renal insufficiency; liver insufficiency. (1)
- Venlafaxine: also uncontrolled hypertension. Increased risk of ventricular arrhythmia (2)

12.3.1.3 Adverse events antidepressants: general

- Frequent: sexual disorders (ejaculation and erectile dysfunction, problems with libido and orgasm). (1)
- Trembling and excessive sweating. (1)
  TCAs and venlafaxine can aggravate a physiological tremor. (330)
- 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. Such symptoms occur most frequently after use of high doses, after a long period of use and after discontinuation of products with a short half-life. These symptoms can occur despite the fact that antidepressants do not induce dependence. (1)
- Lowering the convulsion threshold, especially with TCAs, SSRIs and bupropion. (1)
- Initiating a manic phase in patients with bipolar disorder, with a higher risk for TCAs and venlafaxine than for SSRIs. (1)
- Hyponatraemia with risk of agitation and confusion, especially in the elderly (more frequently with the SSRIs and the serotonin and noradrenaline reuptake inhibitors. (1)

- 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. (1)

12.3.1.4 Adverse events TCA

- •Weight gain. (1)
- 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. (1)
- Anticholinergic effects (especially amitriptyline). (1)
- 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 (nortriptyline); they sometimes cause anxiety, agitation and insomnia, and are preferably not taken in the evening. (1)
- Neurological symptoms such as peripheral neuropathy, tremor, ataxia, rarely extrapyramidal symptoms. Confusion, hallucinations, especially in the elderly. (2)
- In the event of overdose (suicide attempt), the TCAs present a higher risk of fatal outcome than the other antidepressants. (1)
- Rarely hypersensitivity reactions, photosensitization, blood abnormalities. (2)
- Endocrine effects, sexual dysfunction (2)

12.3.1.5 Pregnancy and lactation antidepressants general

- Antidepressants should be avoided as much as possible during the entire duration of the pregnancy. (1)
- A teratogenic effect cannot be excluded for any antidepressant. (1)
- Problems with the newborn child when used shortly before delivery (1):
    - respiratory problems, drinking problems, convulsions, persistent crying, muscle rigidity with maternal use of SSRIs and some other antidepressants (eg venlafaxine, mirtazapine);
    - anticholinergic effects (excitation, suction disorders and, less frequently, arrhythmias, intestinal motility disorders and urinary retention) when the mother uses anti-depressants with anticholinergic properties.

12.3.1.6 Interactions antidepressants general

- Increased risk of convulsions when associated with other agents that may provoke convulsions. (1)
- Increased risk of serotonin syndrome when associated with other agents with serotoninergic activity: amitriptyline, venlafaxine, duloxetine (1)
- Exaggerated sedation when associating antidepressants with sedative effect (amitriptyline) with other drugs with sedative effect or with alcohol. (1)
- Increased risk of hyponatraemia when associating with agents that also have such an effect, such as thiazides and loop diuretics, NSAIDs, carbamazepine. (1)
- 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. (1)

12.3.1.7 Interactions TCA

- Reduced effect of antihypertensive drugs with central action by most TCAs and related antidepressants. (1)
- Enhanced effect of sympathomimetics, eg used as decongestants, by most TCAs and related antidepressants. (1)
- Increased risk of anticholinergic adverse events when associated with other agents with an anticholinergic effect. (1)
- Amitriptyline and nortriptyline are substrates of CYP2D6. (1)

12.3.1.8 Interactions SNRI

- Increased risk of bleeding when associated with antithrombotic drugs, NSAIDs or acetylsalicylic acid. (1)
- Increased risk of hyponatraemia when associated with diuretics. (1)
- Duloxetine is a substrate of CYP1A2 and CYP2D6, and inhibitor of CYP2D6 (1)
- Venlafaxine is a substrate and inhibitor of CYP2D6. (1)

12.3.1.9 Special precautions SNRI

- Check blood pressure during treatment (2)
- Venlafaxine: Caution in case of moderate to severe liver or kidney failure (2)
- Caution in case of history of convulsions, bleeding, mania (2)
- Follow-up of patients with increased intra-ocular pressure or risk of closed-angle glaucoma (2)

12.4 Anti-epileptics (carbamazepine, gabapentin, pregabalin)

12.4.1 Contra-indications anti-epileptics

12.4.1.1 Contra-indications carbamazepine

- Atrioventricular block. (1)
- Concomittant use with MAO-inhibitor. (1)

12.4.2 Adverse events anti-epileptics

12.4.2.1 Adverse events anti-epileptics general

- Anti-epileptics are drugs with a narrow therapeutic-toxic margin. (1)
- Haematological disorders, electrolyte disorders, liver function disorders, osteo-articular disorders and, especially in the elderly, cognitive disorders: frequent. (1)
- Behavioral changes and mood disorders, including suicidal thoughts.
- Cardiac arrhythmias or conduction disorders with multiple anti-epileptics. (1)
- Serious ocular problems (contraction of the peripheral field of vision, glaucoma, pigment deposit in the retina) with some anti-epileptics. (1)
- Stevens-Johnson syndrome and Lyell syndrome with multiple anti-epileptics. (1)
- 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. (1)

12.4.2.2 Adverse events carbamazepine

- Frequent: dizziness, sleepiness, ataxia, gastrointestinal complaints, mild skin reactions. (1) (2)
- Worsening, sometimes to myoclonic or non-convulsive status epilepticus, in some generalized epilepsy such as epilepsy with absences. (1)

- Frequent and sometimes serious allergic reactions; very serious skin reactions such as Stevens-Johnson syndrome. The risk appears to be higher in patients who are carriers of the HLA-B1502 allele. (1)
- Aplastic anemia, leukopenia and thrombocytopenia. (1)
- Hepatic impairment, dyslipidemia. (1)
- Hyponatremia, more frequent in the elderly. (1)

12.4.2.3 Adverse events gabapentin

- Frequent: weight gain, dizziness, drowsiness, ataxia, tiredness, headache, tremor and vision disorders. (1)
- Rare: pancreatitis, erythema multiforme, glycaemic fluctuations (2)

12.4.2.4 Adverse events pregabalin

- Frequent: weight gain, dizziness, drowsiness, ataxia, tiredness, headache, tremor, visual disturbances and cardiac arrhythmias. (1)
- Also sexual disorders (2)
- Less frequent: syncope and congestive heart failure (2)
- Rarely reversible renal failure, rhabdomyolysis (2)

12.4.3 Pregnancy and lactation anti-epileptics

12.4.3.1 Pregnancy and lactation anti-epileptics general

- There is a risk of teratogenicity with many anti-epileptics. (1)
- 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. (1)
- Women on anti-epileptic treatment should be given 4 mg of folic acid per day from the time of stopping the contraception and certainly around conception. (1)

12.4.4 Interactions anti-epileptics

12.4.4.1 Interactions anti-epileptics general

- Excessive sedation when associated with other drugs with sedative effect or with alcohol. (1)
- Many anti-epileptics are enzyme-inducing and this can lead to numerous interactions with other agents (including contraceptives), with vitamin D and with other anti-epileptics. (1)

12.4.4.2 Interactions carbamazepine

- Carbamazepine is a substrate of CYP3A4, and inducer of CYP1A2, CYP2B6, CYP2C9, CYP3A4 and P-gp, with for example a decrease in the effect of the vitamin K antagonists and combination contraceptives. Carbamazepine also induces its own metabolism at the start of treatment, resulting in significant variability in plasma concentrations. (1)
- Decreased plasma concentration of carbamazepine with chronic excessive alcohol consumption. (1)

12.4.4.3 Interactions gabapentin

- Gabapentin enhances the euphoric effects of opioids (1)

12.4.4.4 Interactions pregabalin

- Pregabalin enhances the euphoric effects of opioids. (1)

12.4.5 Special precautions anti-epileptics

12.4.5.1 Special precautions anti-epileptics 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. (1)

12.4.5.2 Special precautions gabapentin

- Caution is advised in the elderly. (1)
- Cases of abuse and dependence have been reported; caution is required in the case of a history of drug and medicine abuse. (1)

12.4.5.3 Special precautions pregabalin

- Caution is advised in the elderly. (1)
- Cases of abuse and dependence have been reported; caution is required in the case of a history of drug and medicine abuse. (1)

12.5 Other drugs: oral

12.5.1 Hyaluronic acid

No data in our sources about oral preparations.

12.5.2 Curcumin

No data in Commented Drug Repertory and Folia Pharmacotherapeutica

Turmeric oleoresin: thyroid dysfunction in pigs (2)

12.5.3 Glucosamine

Most glucosamine preparations (often in combination with chondroitin) are not registered as a drug but as a dietary supplement. (1)

12.5.3.1 Contra-indications

- Allergy for shelfish. (1)

12.5.3.2 Adverse events

- Gastrointestinal discomfort, headache, fatigue. (1)
- Allergic reactions such as rash, angioedema and urticaria: rare. (1)
- Concerns about disruption of glucose metabolism in diabetics could not be confirmed in randomized trials. Glycaemia monitoring recommended until more details are known. (2)

12.5.3.3 Interactions

Attention should be paid to the possibility of interactions, especially with vitamin K antagonists (with risk of bleeding). (1)

12.5.4 Chondroitin

No data in our sources.

12.5.5 Traumeel

No data in our sources about oral preparations.

12.6 Other topical drugs

12.6.1 Capsaicin

12.6.1.1 Adverse events

- Possible adverse events are redness and burning or stabbing pain at the application site. (1)
    - This feeling usually disappears after a few days. (2)
    - Topical capsaicin produced a burning pain at the application site in more than half of the patients. (331)
- A risk of neurological disorders in the long term (332)
- Coughing, sneezing or other signs of irritation when vapor or dried residue from topical preparations are inhaled. (2)

12.6.2 Lidocaine, prilocaine, tetracaine

12.6.2.1 Adverse events

- Allergic reactions with the esters (tetracaine) (and rarely with the amides (lidocaine, prilocaine)): mainly local reactions; anaphylactic reactions are rare. In vitro diagnosis is not possible. There is important cross-sensitivity between esters; there is little cross-sensitivity between esters and amides. (1)
- (Pseudo) allergic reactions to preservatives such as parabens and bisulfites. (1)
- Toxicity to the central nervous system (agitation, anxiety, shaking, convulsions) followed by cardiovascular collapse, bradycardia, cardiac conduction disorders, cardiac arrest: with overdose or with intravascular injection. Over-dosing can also occur with locally used products. (1)
- Risk of corneal injuries when contact with eyes. (1)
- Prilocaine: also methaemoglobinaemia, especially in the child and when applying large quantities. (1)

12.6.2.2 Pregnancy and lactation

- Local anesthetics pass through the placental barrier, with the possibility of adverse events in the fetus and the newborn. (1)
- Lidocaine is the most studied and appears to be safe; very little data exists for other local anesthetics. (1)

12.6.2.3 Special precautions

- Local anesthetics applied to the skin: avoid contact with eyes. (1)
- Some plasters contain aluminum (mentioned in the specialties). In MRI scanning, such patches must be removed in the zone to be examined because of the risk of burns (1)

12.6.3 DMSO (dimethyl sulfoxide)

No data in our sources

12.7 NSAIDs for topical use

12.7.1 Contra-indications

- Hypersensitivity (local or systemic) to the drug itself, other NSAIDs or acetylsalicylic acid. (1)
- Ketoprofen local: exposure to the sun (even in cloudy weather) and to UV radiation during treatment and up to 2 weeks after stopping treatment. (1)

12.7.2 Adverse events

- Skin irritation. (1)
- Allergic reactions. (1)
- Etofenamate, piroxicam and especially ketoprofen: frequent contact allergy and sometimes persistent photosensitivity. Photo allergy outside the application area is also possible. (1)
- With local application, the systemic adverse events of NSAIDs are rare. Nevertheless, caution is required in patients with renal insufficiency, as well as in long-term treatment of large areas. (1)
- Nephrotic syndrome and interstitial nephritis have appeared after the use of piroxicam gel (2)

12.7.3 Special precautions

- Some patches contain aluminum (listed with the specialties): during MRI scanning they must be removed in the area to be examined because of the risk of burns. (1)

13 Appendix. Evidence tables. Paracetamol

13.1 Paracetamol vs placebo for osteoarthritis

Meta-analysis: Acetaminophen for osteoarthritis (Review) (27) Inclusion criteria: Published randomized controlled trials (RCTs) evaluating the efficacy and safety of acetaminophen alone in OA were considered for inclusion. Search strategy: MEDLINE (up to July 2005), EMBASE (2002-July 2005), Cochrane Central Register of Controlled Trials (CENTRAL), ACP Journal Club, DARE, Cochrane Database of Systematic Reviews (all from 1994 to July 2005). Reference lists of identified RCTs and pertinent review articles were also hand searched. Assessment of quality of included trials: yes ITT analysis: Where possible, data from an intention-to-treat analysis were extracted. Other methodological remarks: Jadad and Schultz assessment of quality of included trials NNT for continuous outcomes was calculated using Wells calculator Various pain and function scales used in included trials Functional outcomes less frequently reported

Ref	Comparison	N/n	Outcomes	Result (95% CI)
ref* Cochrane Towheed 2006(27)	Paracetamol vs placebo	N= 5 n= 1835 (Case 2003, Golden 2004, Miceli-	Overall pain (multiple methods)	SMD -0.13 [-0.22, -0.04] SS in favour of paracetamol The authors state that this is of questionable clinical significance

Design: SR + MA Search date: July 2005		Richard 2004, Pincus a 2004, Pincus b 2004)		NNT 16 (treat 16 patients for the duration of the study to achieve the minimally important clinical difference in 1 (additional) patient) In the included trials and subanalyses, The NNT to achieve an improvement in pain ranged from 4 to 16 SS difference in favour of paracetamol in 5 of 7 trials SS difference in favour of paracetamol in most pain outcomes
		N= 2 n= 829 (Case 2003, Miceli-Richard 2004)	WOMAC function	SMD -0.04 [-0.18, 0.10] NS Also NS difference in other functional outcome scales
		N= 6 n= 2385 (Amadio 1983, Golden 2004, Miceli-Richard 2004, Pincus a 2004, Pincus b 2004, Zoppi 1995)	Total number of patients with adverse event	RR 1.02 [0.89, 1.17]
		N= 6 n=2146	Withdrawals due to toxicity	RR 1.24 [0.87, 1.77]

		(Case 2003, Golden 2004, Miceli-Richard 2004, Pincus a 2004, Pincus b 2004, Zoppi 1995)		
		N= 3 n=1237 (Altman 2007, Herrero-Beaumont 2007, Prior 2014)	Abnormal liver function tests	**RR 3.79 (1.94 to 7.39)** **SS** **More abnormal liver function test results with paracetamol**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology Jadad score as assessed by Towheed 2006
Amadio 1983(19) Cross over	25	Adults having radiographic evidence of typical OA of the knee. Median age 64 years. 88% female. Most likely enrolled those with primary (idiopathic) OA	6w	Acetaminophen (1000 mg po qid) versus placebo	overall score of 3/5 (lacking the description of withdrawals and dropouts) ALLOCATION CONC: Unclear
Case 2003(20)	82	Adults (aged 40-75 years) having clinical and radiographic OA of the knee. Mean age 62.2 years. 50%	12w	Acetaminophen (1000 mg po qid) versus diclofenac (75	overall quality score of 3/5, (lacking a description of withdrawals and dropouts)

Randomized, double-blind, parallel group trial		female. Primary OA of the knee enrolled		mg twice per day) versus placebo	ALLOCATION CONC: Unclear
Golden 2004(21) randomized, double-blind, placebo-controlled multidose, parallel group trial	465	Adults aged over 25 years with at least moderate pain in the knee from OA. Radiographic confirmation of OA diagnosis	7d	Naproxen sodium 220 mg po tid versus acetaminophen 1000 mg po qid versus placebo	overall quality score of 4/5 (lacking a description of the method of randomization) ALLOCATION CONC: Unclear
Miceli-Richard 2004(23) Randomized, double-blind, parallel group, placebo controlled trial	779	Adults with symptomatic OA of the knee.	6w	Acetaminophen 4 gm/day versus placebo	overall quality score of 3/5, with randomization, double-blinding and withdrawals and dropouts reported ALLOCATION CONC: unclear
Pincus a 2004(24) randomized, double-blind, placebo controlled, crossover trial	524	Adults (age >= 45 years) with symptomatic, radiographically confirmed OA of the knee or hip	6w	Celecoxib 200 mg/day versus acetaminophen 1000 mg po qid, versus placebo.	overall quality score of 3/5 (lacking a description of the method of randomization and a statement on withdrawals and dropouts) ALLOCATION CONC: Low risk
Pincus b 2004(24) randomized, double-blind, placebo controlled, crossover trial	556	Adults (age >= 45 years) with symptomatic, radiographically confirmed OA of the knee or hip	6w	Celecoxib 200 mg/day versus acetaminophen 1000 mg po qid, versus placebo.	overall quality score of 3/5 (lacking a description of the method of randomization and a statement on withdrawals and dropouts) ALLOCATION CONC: Low risk

Zoppi 1995(26) Randomized, double-blind, parallel group trial	60	Adults with radiographic OA of the knee. Mean age 56 years. 62% female	7d	Acetaminophen 1000 mg po tid versus placebo.	overall quality score of 2/5, (lacking a description of the method of randomization and lacking a description of withdrawals) ALLOCATION CONC: unclear

Remarks
As this is an older Cochrane review, no GRADE assessment was performed by the authors

Meta-analysis: Paracetamol versus placebo for knee and hip osteoarthritis (Review)(17)

Inclusion criteria: randomised controlled trials comparing paracetamol with placebo in adults with osteoarthritis of the hip or knee.
Search strategy: Cochrane Central Register of Controlled Trials, MEDLINE, Embase, AMED, CINAHL, Web of Science, LILACS, and International Pharmaceutical Abstracts to 3 October 2017, and ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (ICTRP) portal on 20 October 2017.
Assessment of quality of included trials: yes, GRADE
ITT analysis: not reported
Other methodological remarks:
GRADE assessment of quality of included trials

Ref	Comparison	N/n	Outcomes	Result (95% CI)

ref* Cochrane Leopoldino 2019(17) Design: SR + MA Search date: Oct 2017	Paracetamol vs placebo	N= 7 n= 2355 (Altman 2007 1 and 2, Case 2003, Herrero-Beaumont 2007, Miceli-Richard 2004, Pincus 2004a, Pincus 2004b, Prior 2014)	Mean change in pain (0-100 scale) Short term (3-12 weeks) , where 0 = no pain	MD -3.23 (-5.43 to -1.02) SS in favour of paracetamol The mean change in pain score in the placebo group was -23 The mean change in pain score in the paracetamol group was 3.2 points lower (1.0 lower to 5.4 lower)
		N= 7 n= 2354 (Altman 2007 1 and 2, Case 2003, Herrero-Beaumont 2007, Miceli-Richard 2004, Pincus 2004a, Pincus 2004b, Prior 2014)	Physical function (WOMAC function 0- 100) 3-12 weeks, 0 = better function	MD -2.92 (-4.89 to -0.95) SS in favour of paracetamol The mean change in physical function score in the placebo group was -12 The mean physical function score in the paracetamol group was 2.9 points lower (4.9 lower to 1.0 lower)
		N= 8 n= 3252 (Altman 2007 1 and 2, Amadio 1983, Golden 2004, Miceli-Richard 2004, Pincus 2004a, Pincus 2004b, Prior 2014, Zoppi 1995)	Total number of patients with adverse event 24 weeks	RR 1.01 (0.92 to 1.11) NS
		N=6 N= 3209 (Altman 2007, Herrero-Beaumont 2007, Miceli-Richard 2004, Pincus 2004a, Pincus 2004b, Prior 2014)	Total number of patients with serious adverse event 24 weeks	RR 1.36 (0.73 to 2.53) NS

		N= 7 n=3023 (Altman 2007, Herrero-Beaumont 2007, Miceli-Richard 2004, Pincus 2004a, Pincus 2004b, Prior 2014, Zoppi 1995)	Withdrawals due to adverse events 24 weeks	RR 1.19 (0.91 to 1.55) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology Risk of bias as assessed by Leopoldino 2019
Altman 2007(18) Multicentre, randomised, double-blind, parallel-group, placebo-controlled study	483	Symptomatic idiopathic osteoarthritis of the hip or knee for a minimum of 6 months with a history of hip or knee pain requiring the use of NSAIDs, paracetamol, or other analgesic on a regular basis (≥ 3 days/week) for ≥ 3 months before the screening visit. History of positive therapeutic benefit with paracetamol use for osteoarthritis pain.	12w	• paracetamol ER 3900 mg/day in 3 divided doses • paracetamol ER 1950 mg/day in 3 divided doses • oral placebo tablets (identical appearance)	RANDO: unclear ALLOCATION CONC: unclear BLINDING: low INCOMPLETE OUTCOME DATA: high SELECTIVE REPORTING: low OTHER: unclear
Amadio 1983(19) Cross over	25	Adults having radiographic evidence of typical OA of the knee. Median age 64 years. 88% female. Most likely enrolled those with primary (idiopathic) OA	6w	Acetaminophen (1000 mg po qid) versus placebo	RANDO: unclear ALLOCATION CONC: unclear BLINDING: low INCOMPLETE OUTCOME DATA: high SELECTIVE REPORTING: unclear OTHER: low
Case 2003(20)	57	Adults (aged 40-75 years) having clinical and radiographic OA of the	12w	Acetaminophen (1000 mg po qid) versus diclofenac (75	RANDO: unclear ALLOCATION CONC: unclear

Randomized, double-blind, parallel group trial		knee. Mean age 62.2 years. 50% female. Primary OA of the knee enrolled		mg twice per day) versus placebo	BLINDING: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER: low
Golden 2004(21) randomized, double-blind, placebo-controlled multidose, parallel group trial	303	Knee osteoarthritis diagnosis by image and clinical assessment Age (mean): paracetamol group: 61.1 years; placebo group: 60.3 years	7d	acetaminophen 1000 mg po qid versus placebo	RANDO: unclear ALLOCATION CONC: unclear BLINDING: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER: unclear
Herrero-Beaumont 2007(22) Randomised, double-blind, placebo-controlled trial	212	Knee osteoarthritis diagnosis by image and clinical assessment criteria according to the American College of Rheumatology Setting: Age (mean): paracetamol group: 63.8 years; placebo group: 64.9 years	6m?	• paracetamol 3000 mg/day, 1 tablet, 3 times daily • oral placebo tablets (identical appearance)	RANDO: low ALLOCATION CONC: low BLINDING: low INCOMPLETE OUTCOME DATA: unclear SELECTIVE REPORTING: low OTHER: unclear
Miceli-Richard 2004(23) Randomized, double-blind, parallel group, placebo controlled trial	779	Adults with symptomatic OA of the knee. Age (mean): 70 years	6w	paracetamol 4 gm/day versus placebo	RANDO: unclear ALLOCATION CONC: unclear BLINDING: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER: low
Pincus a 2004(24) randomized, double-blind, placebo controlled, crossover trial	524	Adults (age >= 45 years) with symptomatic, radiographically confirmed OA of the knee or hip	6w	Celecoxib 200 mg/day versus acetaminophen 1000 mg po qid, versus placebo.	RANDO: unclear ALLOCATION CONC: unclear BLINDING: low INCOMPLETE OUTCOME DATA: unclear SELECTIVE REPORTING: low OTHER: unclear
Pincus b 2004(24) randomized, double-blind, placebo	556	Adults (age >= 45 years) with symptomatic, radiographically confirmed OA of the knee or hip	6w	Celecoxib 200 mg/day versus acetaminophen 1000 mg po qid, versus placebo.	RANDO: unclear ALLOCATION CONC: unclear BLINDING: low

controlled, crossover trial					INCOMPLETE OUTCOME DATA: unclear SELECTIVE REPORTING: low OTHER: unclear
Prior 2014(25) Randomised, placebo-controlled, double-blind clinical trial	542	hip or knee osteoarthritis assessed by physical examination and radiographic evaluation Age (mean): paracetamol group: 61.7 years; placebo group: 61.7 years	12w	• paracetamol 3900 mg/day, 2 tablets, 3 times daily • oral placebo tablets (identical appearance)	RANDO: low ALLOCATION CONC: low BLINDING: low INCOMPLETE OUTCOME DATA: unclear SELECTIVE REPORTING: low OTHER: unclear
Zoppi 1995(26) Randomized, double-blind, parallel group trial	60	Adults with radiographic OA of the knee. Mean age 56 years. 62% female	7d	Acetaminophen 1000 mg po tid versus placebo.	RANDO: unclear ALLOCATION CONC: unclear BLINDING: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER: unclear

Remarks
This SR is more recent than Cochrane Towheed 2006. Cochrane Towheed had wider inclusion criteria (all osteoarthritis), but found only trials in patients with osteoarthritis of the knee or hip.

13.2 Paracetamol vs NSAID for osteoarthritis

Meta-analysis: Acetaminophen for osteoarthritis (Review) (27)

Inclusion criteria: Published randomized controlled trials (RCTs) evaluating the efficacy and safety of acetaminophen alone in OA were considered for inclusion.
Search strategy: MEDLINE (up to July 2005), EMBASE (2002-July 2005), Cochrane Central Register of Controlled Trials (CENTRAL), ACP Journal Club, DARE, Cochrane Database of Systematic Reviews (all from 1994 to July 2005). Reference lists of identified RCTs and pertinent review articles were also hand searched.
Assessment of quality of included trials: yes
ITT analysis: Where possible, data from an intention-to-treat analysis were extracted.
Other methodological remarks:
Jadad and Schultz assessment of quality of included trials
NNT for continuous outcomes was calculated using Wells calculator
Various pain and function scales used in included trials
Functional outcomes less frequently reported

Ref	Comparison	N/n	Outcomes	Result (95%CI)
ref* Cochrane Towheed 2006 Design: SR + MA Search date: July 2005	Paracetamol vs NSAID (ibuprofen 2400 mg, diclofenac, arthrotec, celecoxib, naproxen)	N= 8 n= 2358 (Bradley 1991 b, Case 2003,Golden 2004, Pincus 2001, Pincus a 2004, Pincus b 2004, Schnitzer 2005a Williams 1993)	Overall pain (multiple methods)	**SMD -0.25 [-0.33, -0.17]** **SS in favour of NSAID** SS differences on most pain scales
		N= 2 n= 832 (Case 2003, Schnitzer 2005a)	WOMAC function	**SMD -0.25 [-0.40, -0.11]** **SS in favour of NSAID** NS difference in HAQ disability and Lequesne Function (but small trial for Lequesne)

		N= 7 n= 3168 (Bradley 1991b, Geba 2002c, Golden 2004, Pincus 2001, Pincus a 2004, Pincus b 2004, Schnitzer 2005a)	Total number of patients with any adverse event	RR 1.01 [0.92, 1.11] NS
		N= 8 n= 2793 (Bradley 1991b, Case 2003, Geba 2002c, Pincus 2001, Pincus a 2004, Pincus b 2004, Schnitzer 2005a, Williams 1993)	Withdrawal due to toxicity	RR 0.79 [0.59, 1.05] NS
	Paracetamol vs NSAID	N=13 N=4205 (Boureau 2004,Bradley 1991a and b, Geba 2002 a and b and c, Golden 2004, Pincus 2001, Pincus a 2004, Pincus b 2004, Schnitzer 2005a and b and c, Williams 1993)	GI advserse events	traditional NSAID **RR 1.47 [1.08, 2.00]** **SS more GI adverse events with traditional NSAID** **NNH 12** Coxibs 0.98 [0.80, 1.20] NS
		N= 5 N=640 (Boureau 2004, Bradley 1991a and b, Case 2003, Williams 1993)	GI withdrawals	Traditional NSAID **RR 2.00 [1.05, 3.81]** **SS more withdrawals with NSAID**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (Jadad score as reported by Towheed 2006)
Bradley 1991a(28) Randomized, double-blind, parallel group trial	184	Adults having radiographic OA of the knee. Mean age 56.5 years. 75% female. Both primary and secondary (post-traumatic) OA enrolled	4w	Acetaminophen (1000 mg po qid) versus ibuprofen 1200 mg/day versus ibuprofen 2400 mg/day	Overall score of 4/5 ALLOCATION CONC: Unclear
Bradley 1991b(28) Randomized, double-blind, parallel group trial	184	Adults having radiographic OA of the knee. Mean age 56.5 years. 75% female. Both primary and secondary (post-traumatic) OA enrolled	4w	Acetaminophen (1000 mg po qid) versus ibuprofen 1200 mg/day versus ibuprofen 2400 mg/day	Overall score of 4/5 ALLOCATION CONC: Unclear
Boureau 2004(29) Randomized, double-blind, parallel group trial	222	Adults with symptomatic OA of the knee or hip.	14d	Acetaminophen 3000 mg/day versus ibuprofen 1200 mg/day	Overall quality score of 4/5, lacking the description of randomization ALLOCATION CONC: Unclear
Case 2003(20) Randomized, double-blind, parallel group trial	82	Adults (aged 40-75 years) having clinical and radiographic OA of the knee. Mean age 62.2 years. 50% female. Primary OA of the knee enrolled	12w	Acetaminophen (1000 mg po qid) versus diclofenac (75 mg twice per day) versus placebo	Overall quality score of 3/5, (lacking a description of withdrawals and dropouts) ALLOCATION CONC: Unclear
Geba 2002a(30) Randomized, double-blind, parallel group trial	382	Adults (> = 40 years) with primary OA of the knee that was previously treated with NSAIDs or acetaminophen. Mean age 62.6 years. 68% female. ACR criteria for OA of the knee was used	6w	Acetaminophen (1000 mg po qid) versus celecoxib 200 mg/day versus rofecoxib 12.5 mg/day versus rofecoxib 25 mg/day	Overall quality score of 4/5 ALLOCATION CONC: Unclear
Geba 2002b(30) Randomized, double-blind, parallel group trial	382	Adults (> = 40 years) with primary OA of the knee that was previously treated with NSAIDs or acetaminophen. Mean	6w	Acetaminophen (1000 mg po qid) versus celecoxib 200 mg/day versus rofecoxib	ALLOCATION CONC: Unclear

		age 62.6 years. 68% female. ACR criteria for OA of the knee was used		12.5 mg/day versus rofecoxib 25 mg/day	
Geba 2002 c(30) Randomized, double-blind, parallel group trial	382	Adults (> = 40 years) with primary OA of the knee that was previously treated with NSAIDs or acetaminophen. Mean age 62.6 years. 68% female. ACR criteria for OA of the knee was used	6w	Acetaminophen (1000 mg po qid) versus celecoxib 200 mg/day versus rofecoxib 12.5 mg/day versus rofecoxib 25 mg/day	ALLOCATION CONC: Unclear
Golden 2004(21) randomized, double-blind, placebo-controlled multidose, parallel group trial	465	Adults aged over 25 years with at least moderate pain in the knee from OA. Radiographic confirmation of OA diagnosis	7d	Naproxen sodium 220 mg po tid versus acetaminophen 1000 mg po qid versus placebo	Overall quality score of 4/5 (lacking a description of the method of randomization) ALLOCATION CONC: Unclear
Pincus 2001(31) Randomized, double-blind, cross-over clinical trial	227	Adults (age > 40 years) with radiographic OA of the knee or hip. Mean age 61.5 years. 71% female	6w	Acetaminphen (1000 mg po qid) versus diclofenac/misoprostol (75/200 po bid)	Overall quality score of 4/5 ALLOCATION CONC: Low risk
Pincus a 2004(24) randomized, double-blind, placebo controlled, crossover trial	524	Adults (age >= 45 years) with symptomatic, radiographically confirmed OA of the knee or hip	6w	Celecoxib 200 mg/day versus acetaminophen 1000 mg po qid, versus placebo.	Overall quality score of 3/5 (lacking a description of the method of randomization and a statement on withdrawals and dropouts) ALLOCATION CONC: Low risk
Pincus b 2004(24) randomized, double-blind, placebo controlled, crossover trial	556	Adults (age >= 45 years) with symptomatic, radiographically confirmed OA of the knee or hip	6w	Celecoxib 200 mg/day versus acetaminophen 1000 mg po qid, versus placebo.	Overall quality score of 3/5 (lacking a description of the method of randomization and a statement on withdrawals and dropouts) ALLOCATION CONC: Low risk

Schnitzer 2005a(32) Randomized, parallel group, multicentre, double-blind trial	1578	Adults (aged > = 40 years) meeting ACR criteria for symptomatic OA of the knee	6w	Acetaminophen 4000 mg/day versus celecoxib 200 mg/day versus rofecoxib 12.5 mg/day versus rofecoxib 25 mg/day for 6 weeks duration	Overall quality score of 5/5 ALLOCATION CONC: Low risk
Shen 2004(33) Randomized, parallel group trial	20	20 patients with symptomatic OA of the knee. Lacking other details (abstract only)	3m	Acetaminophen (up to 4 gms/day) versus rofecoxib 25 mg/day.	Abstract, could not be adequately scored ALLOCATION CONC: Unclear
Williams 1993(34) Randomized, double-blind, cross-over clinical trial	178	Adults with radiographic OA of the knee. Mean age 59.6 years. 75% female	2y	Acetaminophen 650 mg po qid versus naproxen 375 mg po bid	Overall score of 5/5 ALLOCATION CONC: Unclear

Remarks
As this is an older Cochrane review, no GRADE assessment was performed by the authors

Author's conclusions
"The evidence to date suggests that NSAIDs are superior to acetaminophen for improving knee and hip pain in people with OA. The size of the treatment effect was modest, and the median trial duration was only six weeks, therefore, additional considerations need to be factored in when making the decision between using acetaminophen or NSAIDs. In OA subjects with moderate-to-severe levels of pain, NSAIDs appear to be more effective than acetaminophen."(27)

13.3 Paracetamol vs ibuprofen for osteoarthritis

The Cochrane review by Towheed 2006(27) found 3 RCTs comparing paracetamol to ibuprofen in osteoarthritis. All three trials were shorter than 6 weeks and one was only published as an abstract.

Meta-analysis: Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis (333)

Inclusion criteria: Large-scale randomised controlled trials of patients with knee or hip osteoarthritis, comparing any of the following interventions: NSAIDs, paracetamol (acetaminophen), or placebo, for the treatment of osteoarthritis pain.
Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL) for eligible trials (appendix 2) from Jan 1, 1980, to Feb 24, 2015; Embase and MEDLINE from Jan 1, 2009, to Feb 24, 2015; internal database of musculoskeletal trials consisting of 721 trials; reference lists; ClinicalTrials.gov
Assessment of quality of included trials: yes
Other methodological remarks: This was a network meta-analysis. No direct comparisons were reported.

Ref + design	n	Population	Duration	Comparison	Results	Methodology As assessed by Da Costa 2016
Doherty 2011(334)	892 (446 taking monotherapy)	community-derived people aged 40 years and older with chronic knee pain. Osteoarthritis of the knee, Mean age 61 y	13 w	Ibuprofen (400 mg/tid) vs paracetamol (1000 mg/tid) (vs ibuprofen + paracetamol combination tablet)	WOMAC 13 weeks Pctm -15.9+/-16.3 Ibu: -17.6+/-19.6 Statistical test not reported WOMAC 13w LOCF	Concrealed allocation unclear Patient blinding low risk Invetgator blinding low risk Incomplete outcome data high risk

					Pctm -10.8 +/-18.6 Ibu: -13.3+/-20.7 Statistical test not reported PGA (patient global assessment) treatment excellent or good at 13 w Pctm 74/136 Ibu 93/161 Statistical test not reported Any AE Pctm 81.1% Ibu 78.1% Statistical test not reported	Industry funded ___ 299 completed trial This study aimed to compare a ibuprofen/paracetamol combination tablet once or twice daily to paracetamol and ibuprofen.

Remarks
This network meta-analysis(333) included 1 trial (334) comparing paracetamol to ibuprofen that met our inclusion criteria. This was a trial comparing a combination tablet of ibuprofen and paracetamol to both drugs in monotherapy. No statistical tests were reported for the comparison between ibuprofen and paracetamol in monotherapy.

13.4 Paracetamol vs placebo for low back pain

Meta-analysis: Cochrane review. Paracetamol for low back pain (Review) (3)

Inclusion criteria: Randomised trials comparing the efficacy of paracetamol with placebo for non-specific LBP

Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL, which includes the Back and Neck Review Group trials register), MEDLINE, EMBASE, CINAHL, AMED, Web of Science, LILACS, and IPA from their inception to 7 August 2015. We also searched the reference lists of eligible papers and trial registry websites (WHO ICTRP and ClinicalTrials.gov).
Assessment of quality of included trials: yes, GRADE
ITT analysis: unclear.

Remarks
This SR found only 1 trial in chronic low back pain, comparing paracetamol to placebo. This trial was later retracted , one of the authors 'not having consented to the submission and publication of the trial'.

13.5 Paracetamol vs ibuprofen for low back pain

Meta-analysis: Cochrane review. Noninvasive Treatments for Low Back Pain (35)

Inclusion criteria: systematic reviews of randomized trials of pharmacological treatments and nonpharmacological treatments for nonradicular or radicular low back pain that addressed effectiveness or harms versus placebo, no treatment, usual care, a sham therapy, an inactive therapy, or another active therapy. Also included: randomized trials that were not in systematic reviews.

Search strategy: A prior systematic review (searches through October 2008), electronic databases (Ovid MEDLINE® and the Cochrane Libraries, January 2008 to April 2015), reference lists, and clinical trials registries.

Assessment of quality of included trials: yes

ITT analysis: unclear.

Remarks
This SR found no trials comparing paracetamol to ibuprofen in chronic low back pain.

13.6 Paracetamol for neuropathic pain

Meta-analysis: Cochrane review. Paracetamol (acetaminophen) with or without codeine or dihydrocodeine for neuropathic pain in adults (Review)(36)

Inclusion criteria: randomised, double-blind studies of two weeks' duration or longer, comparing paracetamol, alone or in combination with codeine or dihydrocodeine, with placebo or another active treatment in chronic neuropathic pain.

Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase from inception to July 2016, together with reference lists of retrieved papers and reviews, and two online study registries

Assessment of quality of included trials: yes

Remarks
This SR found no trials that met the inclusion criteria

13.7 Paracetamol for cancer pain

Meta-analysis: Cochrane review. Oral paracetamol (acetaminophen) for cancer pain (Review)(37)

Inclusion criteria: Randomised, double-blind, studies of five days' duration or longer, comparing paracetamol alone with placebo, or paracetamol in combination with an opioid compared with the same dose of the opioid alone, for cancer pain of any intensity. Singleblind and open studies were also eligible for inclusion. The minimum study size was 25 participants per treatment arm at the initial randomisation.

Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase from inception to March 2017, together with reference lists of retrieved papers and reviews, and two online study registries.

Assessment of quality of included trials: yes

Remarks
This SR found only three trials that lasted only 1 week. These are not eligible for inclusion in our review.

14 Appendix. Evidence tables. NSAID

14.1 Nonselective NSAID vs placebo in osteoarthritis

14.2 Diclofenac vs placebo in osteoarthritis

Meta-analysis: Jevsevar 2018(38) "Mixed treatment comparisons for nonsurgical treatment of knee osteoarthritis: a network meta-analysis"
Inclusion criteria: RCTs evaluating treatments of interest in patients with knee osteoarthritis. Treatments of interest: intra-articular hyaluronic acid, IA corticosteroids, IA PRP, IA placebo, acetominophen, diclofenac, ibuprofen, naproxen, celecoxib and oral placebo.
Search strategy: PubMed, EMBASE, and Cochrane Central Register of Controlled Trials were searched up to October 2015
Assessment of quality of included trials: yes
Other methodological remarks: This is a network meta-analysis. We only reported the direct comparisons. These were found in de supplementary materials.

Ref	Comparison	N/n	Outcomes	Result
Jevsevar 2018(38) Design: SR + MA Search date: October 2015	Diclofenac Vs Placebo	N= 4 n= 758 (Gibofsky 2014, Sandelin 1997, Sangdee 2002, Simon 2009)	Pain	**ES -0.41 (-0.63 to -0.19)** **SS in favour of diclofenac** I^2= 27.9%
		N= 4 n= 911	Function	**ES -0.92 (-1.3 to -0.54)** **SS in favour of diclofenac**

		(Dickson 2001, McKenna 2001, Sangdee 2002, Simon 2009)		I^2= 29.3%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (risk of bias, as assessed by Jevsevar 2018)
Gibofsky 2014(39)	201	Knee osteoarthritis	12 weeks	Diclofenac Vs Placebo	Quality: High RANDO: Low risk ALLOCATION CONC: Low risk BLINDING: Low risk INCOMPLETE OUTCOME DATA: High risk (>20% attrition) SELECTIVE REPORTING: Low risk OTHER BIAS: Unclear risk (one or more: industry funding; mismatch in data for subject loss and total N; significant differences in rescue acetaminophen consumption)
Sandelin 1997(40)	157	Knee osteoarthritis	4 weeks	Diclofenac Vs	RCT did not meet our inclusion criteria (duration)

				Placebo	
Sangdee 2002(41)	94	Knee osteoarthritis	4 weeks	Diclofenac Vs Placebo	RCT did not meet our inclusion criteria (duration)
Simon 2009(42)	306	Knee osteoarthritis	12 weeks	Diclofenac Vs Placebo	Quality: High RANDO: Low risk ALLOCATION CONC: Low risk BLINDING: Low risk INCOMPLETE OUTCOME DATA: High risk (>20% attrition) SELECTIVE REPORTING: Low risk OTHER BIAS: Unclear risk (one or more: industry funding; mismatch in data for subject loss and total N; significant differences in rescue acetaminophen consumption)
Dickson 2001(43)	112	Knee osteoarthritis	12 weeks	Diclofenac Vs Placebo	Quality: Moderate RANDO: Unclear risk (method not described) ALLOCATION CONC: Low risk BLINDING:

					Low risk INCOMPLETE OUTCOME DATA: High risk (>20% attrition) SELECTIVE REPORTING: Low risk OTHER BIAS: Unclear risk (one or more: industry funding; mismatch in data for subject loss and total N; significant differences in rescue acetaminophen consumption)
McKenna 2001(44)	399	Knee osteoarthritis	6 weeks	Diclofenac Vs Placebo	Quality: Moderate RANDO: Unclear risk (method not described) ALLOCATION CONC: Unclear risk (method not described) BLINDING: Low risk INCOMPLETE OUTCOME DATA: High risk (>20% attrition) SELECTIVE REPORTING: Low risk OTHER BIAS: Unclear risk (one or more: industry funding; mismatch in data for subject loss and total N; significant differences in rescue acetaminophen consumption)

Meta-analysis: da Costa 2016(45) "Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis"
Inclusion criteria: large-scale (>100 patients per group) randomised controlled trials of patients with knee or hip osteoarthritis, comparing any of the following interventions: NSAIDs, paracetamol (acetaminophen), or placebo, for the treatment of osteoarthritis pain.
Search strategy: the Cochrane Central Register of Controlled Trials (CENTRAL) and the reference lists of relevant articles were searched for trials published between Jan 1, 1980, and Feb 24, 2015.
Assessment of quality of included trials: yes
Other methodological remarks: This is a network meta-analysis. The results of the direct comparisons were not pooled. We report the individual studies that met our inclusion criteria.

Ref + design	n	Population	Duration	Comparison	Main results	Methodology (risk of bias, as assessed by Jevsevar 2018 or Da Costa 2017)
Bocanegra 1998(46)	572	Knee and hip osteoarthritis	6 weeks	Diclofenac 75 mg/bid Vs placebo	**Diclofenac SS more effective than placebo at improving OA symptoms** (abstract only, not clear what endpoint exactly)	ALLOCATION CONCEALMENT: Unclear BLINDING PATIENT/ INVESTIGATOR: Low/unclear INCOMPLETE OUTCOME DATA: Low
Yocum 2000(47)	779	Knee and hip osteoarthritis	12 weeks	Diclofenac 50 mg/bid Vs placebo	WOMAC Pain (change from baseline) Diclofenac -4.5 Placebo -2.2)	ALLOCATION CONCEALMENT: Unclear

					p≤0.001 compared to placebo **SS in favour of diclofenac** WOMAC Physical function(change from baseline) Diclofenac -14.9 Placebo -7.2 **p≤0.001 compared to placebo** **SS in favour of diclofenac**	BLINDING PATIENT/ INVESTIGATOR: unclear/unclear INCOMPLETE OUTCOME DATA: High

14.3 Ibuprofen vs placebo in osteoarthritis

Meta-analysis: Jevsevar 2018(38) “Mixed treatment comparisons for nonsurgical treatment of knee osteoarthritis: a network meta-analysis”
Inclusion criteria: RCTs evaluating treatments of interest in patients with knee osteoarthritis. Treatments of interest: intra-articular hyaluronic acid, IA corticosteroids, IA PRP, IA placebo, acetominophen, diclofenac, ibuprofen, naproxen, celecoxib and oral placebo.
Search strategy: PubMed, EMBASE, and Cochrane Central Register of Controlled Trials were searched up to October 2015
Assessment of quality of included trials: yes
Other methodological remarks: This is a network meta-analysis. We only reported the direct comparisons (table 1). Adverse events were not assessed by this SR.

Ref	Comparison	N/n	Outcomes	Result

Jevsevar 2018(38) Design: SR + MA Search date: October 2015	Ibuprofen Vs placebo	N= 2 n= 424 (Davies 1999, Puopolo 2007)	Pain	**ES -0.43 (-0.66 to -0.21)** **SS in favour of ibuprofen** I^2= 0%
		N= 2 n= 424 (Davies 1999, Puopolo 2007)	Function	**ES -0.78 (-1.38 to -0.18)** **SS in favour of ibuprofen** I^2= 0%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (risk of bias, as assessed by Jevsevar 2018)
Davies 1999(48)	104	Knee osteoarthritis	4 weeks	Ibuprofen Vs placebo	RCT did not meet our inclusion criteria (duration)
Puopolo 2007(49)	320	Knee osteoarthritis	12 weeks	Ibuprofen Vs placebo	Quality: High RANDO: Low risk ALLOCATION CONC: Low risk BLINDING: Low risk INCOMPLETE OUTCOME DATA: High risk (>20% attrition) SELECTIVE REPORTING: Low risk OTHER BIAS: Unclear risk (one or more: industry funding; mismatch in data for subject loss and total N; significant

					differences in rescue acetaminophen consumption)

Meta-analysis: da Costa 2016(45) "Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis"
Inclusion criteria: large-scale (>100 patients per group) randomised controlled trials of patients with knee or hip osteoarthritis, comparing any of the following interventions: NSAIDs, paracetamol (acetaminophen), or placebo, for the treatment of osteoarthritis pain.
Search strategy: the Cochrane Central Register of Controlled Trials (CENTRAL) and the reference lists of relevant articles were searched for trials published between Jan 1, 1980, and Feb 24, 2015.
Assessment of quality of included trials: yes
Other methodological remarks: This is a network meta-analysis. The results of the direct comparisons were not pooled. We report the individual studies that met our inclusion criteria.

Ref + design	n	Population	Duration	Comparison	Main results	Methodology (risk of bias, as assessed by Jevsevar 2018)
Day 2000(50)	809	Knee and hip osteoarthritis	7 weeks	Ibuprofen 800 mg 3x/day Vs placebo	Pain WOMAC Ibuprofen -33.55 (-36.26 to -30.84) Placebo -18.92 (23.72 to -14.12) **p≤0.009 compared to placebo** **SS in favour of ibuprofen**	ALLOCATION CONCEALMENT: Unclear BLINDING PATIENT/ INVESTIGATOR: low/low INCOMPLETE OUTCOME DATA: High
Hawkey 2000(51)	775	Knee and hip osteoarthritis	24 weeks	Ibuprofen 800 mg 3x/day Vs	**SS more ulcers at 12 weeks with ibuprofen compared to placebo**	ALLOCATION CONCEALMENT: Unclear

				placebo	29.2 vs 5.3	BLINDING PATIENT/ INVESTIGATOR: low/low INCOMPLETE OUTCOME DATA: High
Saag 2000(52)	736	Knee and hip osteoarthritis	6 weeks	Ibuprofen 800 mg 3x/day Vs placebo	**SS greater efficacy with ibuprofen compared to placebo** (abstract only, not clear what endpoint exactly)	ALLOCATION CONCEALMENT: Unclear BLINDING PATIENT/ INVESTIGATOR: low/low INCOMPLETE OUTCOME DATA: High
Wiesenhutter 2005(53)	528	Knee osteoarthritis	12 weeks	Ibuprofen 800 mg 3x/day Vs placebo	WOMAC and VAS Pain **Ibuprofen SS more effective than placebo**	ALLOCATION CONCEALMENT: low BLINDING PATIENT/ INVESTIGATOR: low/low INCOMPLETE OUTCOME DATA: High

Study details	n/Population	Comparison	Outcomes	Methodological
	n= 388		Efficacy	RANDO:

RCT Gordo 2017 (54) Design: RCT DB, PG Non-inferiority trial Duration of follow-up: 6 weeks	(celecoxib 153, ibuprofen 156, placebo 79) Mean age: 62 – 65y Other interventions for pain allowed during study: patients discontinued use of any NSAID and/or analgesic therapy. No rescue analgesia permitted during study treatment. Stable doses of aspirin (≤ 325 mg/day) for cardiovascular prophylaxis was permitted. <u>Inclusion</u> Osteoarthritis of the knee in a flare state	Celecoxib 200 mg 1x/day Vs Ibuprofen 800 mg 3x/day Vs placebo	Pain VAS (PO) (0-100) (per protocol population)	**Celecoxib vs ibuprofen** Difference in LS means: 2.76 (-3.38 to 8.90) Celecoxib is non-inferior to ibuprofen (when lower bound defined as greater than -10) *Also NS in mITT population* **Celecoxib vs placebo** Difference in LS means: -5.26 (-13.06 to 2.54) NS ***SS in mITT population:*** ***-9.41 (-16.34 to -2.52)*** ***P=0.0076*** **Ibuprofen vs placebo** Difference in LS means: -2.50 (-10.25 to 5.25) *Also NS in mITT population*	Adequate ALLOCATION CONC: Unclear (not described) BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: unclear: participants lost to follow included in category “defaulted” Drop-out and Exclusions: 19.6% • Described: unclear: category “other” and “defaulted” include most of the discontinuations, not clear what these categories mean • Balanced across groups: unclear: celecoxib 17.0%, ibuprofen 17.3%, placebo 29.1% ITT: Per protocol and mITT Modified ITT: all patients who were randomized and received at least one dose of study drug.

	≥ 40 y <u>Exclusion</u> Inflammatory arthritis, gout, previous surgical or invasive procedure on the joint, Malignancy, history of malignancy Active gastrointestinal disease, history of gastrointestinal perforations, obstructions or bleeding, cardiac, renal and/or hepatic disease, coagulation disorders				SELECTIVE REPORTING: no Other important methodological remarks: Celecoxib was declared to be as effective as ibuprofen if the lower bound of the two-sided 95% CI of the treatment difference (ibuprofen–celecoxib) lay above -10mm in the PPA population. (reason for this cut-off not provided) Sponsor: Pfizer
			Safety		

			Upper gastrointestinal events *Defined as a moderate or severe instance of one or more of abdominal pain, dyspepsia, and/or nausea*	Celecoxib: 1.3% Ibuprofen: 5.1% Placebo: 2.5% NS between-group differences	
			Patients with AEs	Celecoxib: 20.3% Ibuprofen: 30.8% Placebo: 26.6%	
			Patients with serious AEs	Celecoxib: 0 Ibuprofen: 1 Placebo: 0	
			Patients discontinued due to AEs	Celecoxib: 3.3% Ibuprofen: 6.4% Placebo: 6.3%	

14.4 Naproxen vs placebo in osteoarthritis

Meta-analysis: Jevsevar 2018(38) “Mixed treatment comparisons for nonsurgical treatment of knee osteoarthritis: a network meta-analysis”
Inclusion criteria: RCTs evaluating treatments of interest in patients with knee osteoarthritis. Treatments of interest: intra-articular hyaluronic acid, IA corticosteroids, IA PRP, IA placebo, acetominophen, diclofenac, ibuprofen, naproxen, celecoxib and oral placebo.
Search strategy: PubMed, EMBASE, and Cochrane Central Register of Controlled Trials were searched up to October 2015
Assessment of quality of included trials: yes
Other methodological remarks: This is a network meta-analysis. We only reported the direct comparisons. These were found in de supplementary materials.

Ref	Comparison	N/n	Outcomes	Result
Jevsevar 2018(38) Design: SR + MA Search date: October 2015	Naproxen Vs placebo	N= 6 n= 2122 (Essex 2014, Hochberg 2011a, Hochberg 20011b, Schnitzer 2010, Schnitzer 2011, Svensson 2006)	Pain	**ES -0.38 (-0.47 to -0.30)** **SS in favour of naproxen** I^2= 3.9%
		N= 6 n= 2122 (Essex 2014, Hochberg 2011a, Hochberg 20011b, Schnitzer 2010, Schnitzer	Function	**ES -1.27 (-1.51 to -1.03)** **SS in favour of naproxen** I^2= 0%

		2011, Svensson 2006)		

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (risk of bias, as assessed by Jevsevar 2018)
Essex 2014(55)	190	Knee osteoarthritis	6 weeks	Naproxen Vs placebo	Quality: High RANDO: Low risk ALLOCATION CONC: Low risk BLINDING: Low risk INCOMPLETE OUTCOME DATA: High risk (>20% attrition) SELECTIVE REPORTING: Low risk OTHER BIAS: Unclear risk (one or more: industry funding; mismatch in data for subject loss and total N; significant differences in rescue acetaminophen consumption)
Hochberg 2011 a(56)	370	Knee osteoarthritis	12 weeks	Naproxen Vs placebo	Quality: High RANDO: Low risk ALLOCATION CONC:

					Low risk BLINDING: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS: Unclear risk (one or more: industry funding; mismatch in data for subject loss and total N; significant differences in rescue acetaminophen consumption)
Hochberg 2011 b(56)	363	Knee osteoarthritis	12 weeks	Naproxen Vs placebo	Quality: High RANDO: Low risk ALLOCATION CONC: Low risk BLINDING: Low risk INCOMPLETE OUTCOME DATA: High risk (>20% attrition) SELECTIVE REPORTING: Low risk OTHER BIAS: Unclear risk (one or more: industry funding; mismatch in data for subject loss and total N; significant differences in rescue acetaminophen consumption)
Schnitzer 2010(57)	333	Knee osteoarthritis	13 weeks	Naproxen Vs	Quality: High

				placebo	RANDO: Low risk ALLOCATION CONC: Low risk BLINDING: Low risk INCOMPLETE OUTCOME DATA: High risk (>20% attrition) SELECTIVE REPORTING: Low risk OTHER BIAS: Unclear risk (one or more: industry funding; mismatch in data for subject loss and total N; significant differences in rescue acetaminophen consumption)
Schnitzer 2011(58)	511	Knee osteoarthritis	53 weeks	Naproxen Vs placebo	Quality: High RANDO: Unclear risk (method not described) ALLOCATION CONC: Unclear risk (method not described) BLINDING: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS: Unclear risk (one or more: industry funding; mismatch in data for

					subject loss and total N; significant differences in rescue acetaminophen consumption)
Svensson 2006(59)	355	Knee osteoarthritis	6 weeks	Naproxen Vs placebo	Quality: High RANDO: Unclear risk (method not described) ALLOCATION CONC: Unclear risk (method not described) BLINDING: Low risk INCOMPLETE OUTCOME DATA: Low risk SELECTIVE REPORTING: Low risk OTHER BIAS: Unclear risk (one or more: industry funding; mismatch in data for subject loss and total N; significant differences in rescue acetaminophen consumption)

Meta-analysis: da Costa 2016(45) "Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis"
Inclusion criteria: large-scale (>100 patients per group) randomised controlled trials of patients with knee or hip osteoarthritis, comparing any of the following interventions: NSAIDs, paracetamol (acetaminophen), or placebo, for the treatment of osteoarthritis pain.
Search strategy: the Cochrane Central Register of Controlled Trials (CENTRAL) and the reference lists of relevant articles were searched for trials published between Jan 1, 1980, and Feb 24, 2015.
Assessment of quality of included trials: yes
Other methodological remarks: This is a network meta-analysis. The results of the direct comparisons were not pooled. We report the individual studies that met our inclusion criteria.

Ref + design	n	Population	Duration	Comparison	Main results	Methodology (risk of bias, as assessed by Jevsevar 2018)
Baerwald 2010(60)	810	Hip osteoarthritis	15 weeks	Naproxen 500 mg 2x/day Vs placebo	WOMAC Pain Naproxen -24.31 Placebo -21.27 **LS MD -6.34 (-11.04 to -1.65)** **SS in favour of naproxen** WOMAC Function Naproxen -25.97 Placebo -16.67 **LS MD -8.22 (-12.78 to -3.66)** **SS in favour of naproxen**	ALLOCATION CONCEALMENT: Unclear BLINDING PATIENT/ INVESTIGATOR: low/ Unclear INCOMPLETE OUTCOME DATA: Low
Bensen 1999(61)	1004	Knee osteoarthritis	12 weeks	Naproxen 500 mg 2x/day Vs placebo	**SS in favour of naproxen for improving composite OA scores**	ALLOCATION CONCEALMENT: Unclear BLINDING PATIENT/ INVESTIGATOR: low/low

						INCOMPLETE OUTCOME DATA: Low
Essex 2012a(62)	322	Knee osteoarthritis	6 weeks	Naproxen 500 mg 2x/day Vs placebo	Pain VAS Naproxen -38.0 Placebo -33.5 TD -5.5 mm (-14.0 to 2.9) NS	ALLOCATION CONCEALMENT: Unclear BLINDING PATIENT/ INVESTIGATOR: low/low INCOMPLETE OUTCOME DATA: High
Lohmander 2005(63)	970	Knee and hip osteoarthritis	7 weeks	Naproxen 500 mg 2x/day Vs placebo	Lanza score Incidence (%) of significant gastroduodenal damage (Lanza scores 3 and 4) Naproxen 43.7 Placebo 7.0 No statistical analysis for this comparison Pain WOMAC Naproxen -14.7 Placebo -5.8 No statistical analysis for this comparison Function WOMAC Naproxen -14.9 Placebo -6.1 No statistical analysis for this comparison	ALLOCATION CONCEALMENT: Unclear BLINDING PATIENT/ INVESTIGATOR: low/ Unclear INCOMPLETE OUTCOME DATA: High

Makarowski 2002(64)	467	Hip osteoarthritis	12 weeks	Naproxen 500 mg 2x/day Vs placebo	Pain VAS Naproxen -22.0 Placebo -15.2 NS	ALLOCATION CONCEALMENT: Unclear BLINDING PATIENT/ INVESTIGATOR: low/ Unclear INCOMPLETE OUTCOME DATA: High
Reginster 2007(65)	997	Knee and hip osteoarthritis	12 weeks	Naproxen 500 mg 2x/day Vs placebo	Pain WOMAC (VAS) Naproxen -28.57 Placebo -15.31 **SS in favour of naproxen** Physical function WOMAC (VAS) Naproxen -23.70 Placebo -10.27 **SS in favour of naproxen**	ALLOCATION CONCEALMENT: Unclear BLINDING PATIENT/ INVESTIGATOR: low/low INCOMPLETE OUTCOME DATA: High
Schnitzer 2005(66)	672	Knee osteoarthritis	6 weeks	Naproxen 500 mg 2x/day Vs placebo	No statistical analysis for this comparison	ALLOCATION CONCEALMENT: Unclear BLINDING PATIENT/ INVESTIGATOR: low/unclear INCOMPLETE OUTCOME DATA:

						High

14.5 Nabumetone vs placebo for osteoarthritis

Study details	n/Population	Comparison	Outcomes		Methodological
Blechman 1987(67) Design: RCT DB, PG	n= 106 Mean age: not reported Previous pain intervention: at least 3 months treatment	Nabumetone 1000 mg Vs placebo	Efficacy		RANDO: unclear ALLOCATION CONC: unclear BLINDING : Participants: yes Assessors: unclear FOLLOW-UP:
			Patient's assessment of degree of pain due to OA	Nabumetone: -0.87 Placebo: -0.19 **Treatment difference** **P<0.01** **SS in favour of nabumetone**	
			Safety		

Duration of follow-up: 6 weeks	with analgesics or NSAIDs Other interventions for pain allowed during study: no <u>Inclusion</u> Patients with osteoarthritis <u>Exclusion</u> Osteoarthritis limited to the spine Prior concomitant use of more than one anti-inflammatory drug History of ulcer, significant gastrointestinal disease, urinary tract disease, prior use of oral or intra-articular steroid within three months of entry in the study, any serious illness that coul affect		At least one adverse experience	Nabumetone: 9/53 Placebo: 6/53 P= 1.00 NS	Drop-out and Exclusions: 10 % • Described: yes • Balanced across groups: yes ITT: unclear SELECTIVE REPORTING: unclear Other important methodological remarks: washout phase with placebo: only patients who had a flare within two to 14 days were included in the study Sponsor: Unclear (not reported)

	the potential safety of the patient				

Study details	n/Population	Comparison	Outcomes		Methodological
Weaver 1995(68) Design: RCT DB, PG	n= 110 nabumetone 109 oxaprozin 109 placebo Mean age: 62.6y Previous pain intervention:	Nabumetone 1000 mg Vs Oxaprozin 1200 mg Vs placebo	Efficacy		RANDO: unclear ALLOCATION CONC: unclear BLINDING : Participants: yes Assessors: unclear FOLLOW-UP: Lost-to follow-up: <1% Drop-out and Exclusions: 18.5 %
			Knee pain on weight bearing week 6 (PO)	Nabumetone vs placebo NS (no further quantitative data provided)	
			Knee pain on motion week 6 (PO)	Nabumetone vs placebo NS (no further quantitative data provided)	
			Safety		

Duration of follow-up: 6 weeks	analgesics or other NSAID Other interventions for pain allowed during study: no <u>Inclusion</u> Osteoarthritis of the knee at least 6 months Experiencing a flare within 2 weeks of discontinuing usual OA medication (NSAID or analgesic) <u>Exclusion</u> History of hypersensitivity to NSAID, other arthritis, history of nasal polyps or angioedema, inflammatory bowel disease, history of GI complications, intra-articular joint steroid injection within 30		Adverse effects	"Difference among treatment groups was not statistically significant"	• Described: yes • Balanced across groups: unclear (15% nabumetone, 24% placebo) ITT: Unclear (authors report ITT but no definition is given) SELECTIVE REPORTING: yes (no quantitative data for nabumetone v placebo) Other important methodological remarks: Four different efficacy outcomes at four different timepoints were all deemed "primary outcomes". Washout period of 14 days; only patients experiencing flare during this period were enrolled Sponsor: Unclear (not reported)

	days, malignancy, abnormal laboratory values on screening that might reflect renal or hepatic disesase,…				

Study details	n/Population	Comparison	Outcomes		Methodological
Makarowski 1996(69) Design: RCT DB PG Duration of follow-up:	n= 347 116 oxaprozin 115 nabumetone 116 placebo Mean age: 61.1 y Previous pain intervention: unclear	Oxaprozin 1200 mg/day Vs Nabumetone 1500 mg/day Vs placebo	Efficacy		RANDO: unclear ALLOCATION CONC: unclear BLINDING : Participants: yes Assessors: unclear FOLLOW-UP: Drop-out and Exclusions: 7% • Described: yes • Balanced across groups: yes ITT:
			Knee pain on weight bearing (week 6)	Nabumetone vs placebo NS No further quantitative data provided	
			Knee pain on motion (week 6)	**Nabumetone vs placebo** **SS** **No further quantitative data provided**	
			Pain intensity (VAS) (week 6)	**Nabumetone vs placebo** **SS** **No further quantitative data provided**	
			Safety		

6 weeks	Other interventions for pain allowed during study: n <u>Inclusion</u> Knee osteoarthritis (>6 months) Flare during washout period <u>Exclusion</u> History of hypersensitivity to NSAID, other arthritis, history of nasal polyps or angioedema, inflammatory bowel disease, history of GI complications, intra-articular joint steroid injection within 30 days, malignancy, abnormal laboratory values on screening that might reflect renal or hepatic disesase,…		Adverse events	Nabumetone: 69.6% Placebo: 49.1% **Nabumetone vs placebo** **SS**	No (authors define ITT as "at least 80% compliant with the study medication, completed at least 39 days of treatment or withdrew from the study after 5 days of treatment due to treatment failure or adverse events, and completed efficacy evaluations at the final visit or at week 6" SELECTIVE REPORTING: yes (no quantitative data on most results) Other important methodological remarks: Washout period of 14 days; only patients experiencing flare during this period were enrolled Sponsor: GD Searle & Co., Skokie, Illinois

Study details	n/Population	Comparison	Outcomes		Methodological
Kivitz	n= 1042	Rofecoxib 12.5	Efficacy		RANDO:
2004(70)	rofecoxib 424	mg/d	Walking pain (WOMAC	Nabumetone	Adequate
	nabumetone 410		VAS)	Placebo	ALLOCATION CONC:
	placebo 208	Vs			unclear
Design:				**Nabumetone vs placebo**	BLINDING :
	Mean age: 63.1y			**Mean difference -11.4 mm(-15.5 to -**	Participants: yes
RCT		Nabumetone		**7.3)**	Assessors: yes
DB PG		1000 mg/d		**SS in favour of nabumetone**	
	Other interventions for	Vs			FOLLOW-UP:
	pain allowed during				Lost-to follow-up: 0.6 %
	study: paracetamol up	placebo	Safety		Drop-out and Exclusions: 21%
			Adverse events	"similar"	

Duration of follow-up: 6 weeks	to 2600 mg/day as a rescue medication, except during the first 6 days of therapy and 24 hours before evaluations <u>Inclusion</u> Knee osteoarthritis >6 months Age ≥40 years <u>Exclusion</u> concurrent medical/arthritic disease that could alter study outcome or a significant systemic disease that contraindicated NSAID therapy. Patients were also excluded who used corticosteroids, misoprostol, sucralfate, histamine blockers, antacids,		Serious adverse events	Nabumetone 2.0% Placebo 0.5%	• Described: yes • Balanced across groups: yes ITT: "modified ITT" including all patients who had a baseline value at the flare visit, took at least one dose of study drug, and had a postbaseline efficacy assessment SELECTIVE REPORTING: yes, not all quantative outcome data reported Sponsor: Merck & co

	proton pump inhibitors, analgesics, warfarin, ticlopidine, high-dose aspirin, appetite suppressants, and other medications for chronic diseases for a predefined period before the study or if their use was required during the trial. Low-dose aspirin (≤81 mg/d) was allowed if previously prescribed for cardiovascular prophylaxis.				

14.6 COX-2-selective NSAID vs placebo in osteoarthritis

14.7 Celecoxib vs placebo in osteoarthritis

Meta-analysis: Cochrane Puljak 2017(71): "Celecoxib for osteoarthritis"

Inclusion criteria: RCTs comparing celecoxib 200 mg daily versus no intervention, placebo or other nonselective NSAID in knee and/or hip osteoarthritis
Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and clinical trials registers were searched up to April 2017
Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result
Cochrane Puljak 2017(71) Design: SR + MA Search date: April 2017	Celecoxib Vs placebo	N= 4 n= 1622 (Clegg 2006, Hochberg 2011 study 307, Hochberg 2011 study 309, Rother 2007)	Pain	I^2=0% **Std. MD -0.22 (-0.32 to -0.12)** **SS less pain with celecoxib**
		N= 4 n= 1622 (Clegg 2006, Hochberg 2011 study 307, Hochberg 2011 study 309, Rother 2007)	Physical function	I^2= 0% **Std. MD -0.17 (-0.27 to -0.07)** **SS in favour of celecoxib**
		N= 28 n= 12965 (Asmus 2014 study 1, Asmus 2014 study 2, Bensen 1999, Bingham 2007 study 1, Bingham 2007 study 2, Birbara 2006 study 1, Birbara 2006 study 2, Clegg 2006, Conaghan 2013, DeLemos 2011, Essex 2012b, Essex 2014, Fleischmann 2005, Gibofsky 2003, Hochberg 2011 study 307, Hochberg 2011 study 309,	Number withdrawn due to adverse events	Celecoxib: 428/ 7685 Placebo: 303/ 5280 I^2=22% Peto OR 0.99 (0.85 to 1.15) NS

		Kivitz 2001, Lehmann 2005, McKenna 2001a, McKenna 2001b, Rother 2007, Schnitzer 2011, Sheldon 2005, Smugar 2006 study 1, Smugar 2006 study 2, Tannenbaum 2004, Williams 2000, Williams 2001)		
		N= 28 n= 13393 (Asmus 2014 study 1, Asmus 2014 study 2, Bingham 2007 study 1, Bingham 2007 study 2, Birbara 2006 study 1, Birbara 2006 study 2, Boswell 2008 study a, Boswell 2008 study b, Clegg 2006, Conaghan 2013, DeLemos 2011, Essex 2012b, Fleischmann 2005, Gibofsky 2003, Hochberg 2011 study 307, Hochberg 2011 study 309, Lehmann 2005, McKenna 2001a, McKenna 2001b, Pincus 2004 PACES-a, Pincus 2004 PACES-b, Rother 2007, Schnitzer 2011, Sheldon 2005, Smugar 2006 study 1, Smugar 2006 study 2, Tannenbaum 2004, Williams 2001)	Number experiencing any serious adverse events	Celecoxib: 71/7745 Placebo: 56/5648 I^2=12% Peto OR 0.95 (0.66 to 1.36) NS
		N= 8 n= 3263 (Bensen 1999, Boswell 2008 study a, Boswell 2008 study b, Clegg 2006, Essex 2014, Gibofsky 2003, Smugar 2006 study 1, Smugar 2006 study 2)	Number experiencing gastro-intestinal events (perforation, ulcer, bleeds)	Celecoxib: 3/2010 Placebo: 1/1523 I^2= 24% Peto OR 1.91 (0.24 to 14.90) NS

		N= 5 n= 2947 (Clegg 2006, Rother 2007, Schnitzer 2011, Smugar 2006 study 1, Smugar 2006 study 2)	Number experiencing cardiovascular events (myocardial infarction, stroke)	Celecoxib: 6/1785 Placebo: 1/1162 I^2= 0% Peto OR 3.40 (0.73 to 15.88) NS

Ref + design	n	Population	Duration	Comparison	Methodology (risk of bias) As assessed by Puljak 2017
Asmus 2014 study 1(72)	380 randomized 270 completed	Knee osteoarthritis	6 weeks	Celecoxib 200 mg vs Placebo	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (method not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (Attrition 19.5% in celecoxib and 34.2% in placebo group):LOCF SELECTIVE REPORTING: Low OTHER BIAS: Low
Asmus 2014 study 2(72)	388 randomized 294 completed	Knee osteoarthritis	6 weeks	Celecoxib 200 mg vs Placebo	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (method not described) BLINDING Participants & personnel: Low

					BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (Attrition 19% in celecoxib and 29% in placebo group); LOCF SELECTIVE REPORTING: Low OTHER BIAS: Low
Bensen 1999(61)	Randomized: 1003 Completed: 569	Knee osteoarthritis	12 weeks	Celecoxib 100 mg Celecoxib 200 mg Celecoxib 400 mg naproxen 1000 mg Placebo	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (method not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (high attrition 43%; LOCF) SELECTIVE REPORTING: Low OTHER BIAS: Unclear (possible selection bias in favor of participants tolerant of naproxen)
Bingham 2007 study 1(73)	Randomized 599 Completed 468	Knee osteoarthritis	Part one: 12 week Part two:	Celecoxib 200 mg Etoricoxib 30 mg Placebo	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (method not described) BLINDING Participants & personnel: Low

			14 weeks		BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (attrition 20% in celecoxib, 36% in placebo group) SELECTIVE REPORTING: Low OTHER BIAS: Unclear (number of rescue medication used not reported)
Bingham 2007 study 2(73)	Randomized 608 Completed 474	Knee osteoarthritis	Part one: 12 week Part two: 14 weeks	Celecoxib 200 mg Etoricoxib 30 mg Placebo	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (method not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (attrition 18% in celecoxib, 48% in placebo group) SELECTIVE REPORTING: Low OTHER BIAS: Unclear (number of rescue medication used not reported)
Birbara 2006 study 1(74)	Randomized 395 Completed 345	Knee osteoarthritis	6 weeks	Celecoxib 200 mg Rofecoxib 12.5 mg Placebo	RANDO: Low ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel:

					Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (attrition 27% in placebo group, 8.9% in celecoxib group; LOCF) SELECTIVE REPORTING: Low OTHER BIAS: Unclear (amount of co-interventions used in each group not reported)
Birbara 2006 study 2(74)	Randomized 413 Completed 344	Knee osteoarthritis	6 weeks	Celecoxib 200 mg Rofecoxib 12.5 mg Placebo	RANDO: Low ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (attrition 30.4% in placebo group, 15.4% in celecoxib group; LOCF) SELECTIVE REPORTING: Low OTHER BIAS: Unclear (amount of co-interventions used in each group not reported)

Boswell 2008 study a(75)	Randomized 649 Completed 556	Knee osteoarthritis	12 weeks	Celecoxib 200 mg GW406381 10 mg GW406381 20 mg GW406381 35 mg GW406381 50 mg Placebo	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (method not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: Unclear (attrition and reasons for attrition not reported per group; LOCF) SELECTIVE REPORTING: High (data not provided for secondary outcomes) OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported)
Boswell 2008 study b(75)	Randomized 1331 Completed 1038	Knee osteoarthritis	12 weeks	Celecoxib 200 mg GW406381 1 mg GW406381 5 mg GW406381 10 mg GW406381 25 mg GW406381 50 mg Placebo	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (method not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: Unclear (attrition 22%, attrition and reasons for attrition not reported per group; LOCF)

					SELECTIVE REPORTING: High (data not provided for secondary outcomes) OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported)
Clegg 2006(76)	Randomized 1583 Completed 1258	Knee osteoarthritis	24 weeks	Celecoxib 200 mg Glucosamine 1500 mg/day Chondroitin sulfate 1200 mg/day Glucosamine 1500 mg plus chondroitin sulfate 1200 mg daily Placebo	RANDO: Low ALLOCATION CONC: Low BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: Unclear (attrition 20.8% in placebo group, 16.4% in celecoxib group) SELECTIVE REPORTING: High (certain secondary points and AE not fully reported) OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported)
Conaghan 2013(77)	Randomized 1399 Completed 1256	Knee osteoarthritis	12 weeks	Celecoxib 200 mg IDEA-033/ketoprofen 50 mg IDEA-033/ketoprofen 100 mg 2.2 g TDT 064/vehicle	RANDO: Low ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel:

				4.4 g TDT 064/vehicle Placebo	Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: Low SELECTIVE REPORTING: Low OTHER BIAS: Low
DeLemos 2011(78)	Randomized 1011 Completed 555	Knee and/or hip osteoarthritis	12 weeks	Celecoxib 200 mg Tramadol ER 100 mg Tramadol ER 200 mg Tramadol ER 300 mg Placebo	RANDO: Unclear (not described) ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (high attrition 49%) SELECTIVE REPORTING: Low OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported)
Essex 2012b(62)	Randomized 322 Completed 253	Knee osteoarthritis	6 weeks	Celecoxib 200 mg Naproxen 1000 mg/day Placebo	RANDO: Low ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low

					BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (high attrition; 20% celecoxib; 16% naproxen; 34% placebo) SELECTIVE REPORTING: High (not all secondary outcomes reported) OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported)
Essex 2014(55)	Randomized 318 Completed 236	Knee osteoarthritis	6 weeks	Celecoxib 200 mg Naproxen 1000 mg/day Placebo	RANDO: Low ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: Unclear (attrition 24% celecoxib, 28% naproxen; 26% placebo) SELECTIVE REPORTING: High (not all secondary outcomes reported) OTHER BIAS: Low
Fleischmann 2005(79)	Randomized 1608 Completed	Knee osteoarthritis	13 weeks	Celecoxib 200 mg Lumiracoxib 200 mg Lumiracoxib 400 mg	RANDO: Unclear (method not described) ALLOCATION CONC:

	1238			Placebo	Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: Unclear (attrition high 22% celecoxib; 29% placebo) SELECTIVE REPORTING: High (QoL not provided, all adverse events not reported) OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported)
Gibofsky 2003(80)	Randomized 477 Completed 383	Knee osteoarthritis	6 weeks	Celecoxib 200 mg Rofecoxib 25 mg Placebo	RANDO: Low ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (attrition 16% celecoxib; 35% placebo; LOCF) SELECTIVE REPORTING: Low OTHER BIAS:

					Unclear (amount of co-interventions consumed per group not reported)
Hochberg 2011 study 307(56)	Randomized 619 Completed 521	Knee osteoarthritis	12 weeks	Celecoxib 200 mg Naproxen 1000 mg plus esomeprazole 40 mg magnesium tablets daily Placebo	RANDO: Low ALLOCATION CONC: Low BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: Unclear (attrition 16% celecoxib, 15% placebo; LOCF) SELECTIVE REPORTING: Unclear (not all AE reported) OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported)
Hochberg 2011 study 309(56)	Randomized 615 Completed 488	Knee osteoarthritis	12 weeks	Celecoxib 200 mg Naproxen 1000 mg plus esomeprazole 40 mg magnesium tablets daily Placebo	RANDO: Low ALLOCATION CONC: Low BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: Unclear (attrition 24% celecoxib; 21 placebo; LOCF)

					SELECTIVE REPORTING: Low OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported)
Kivitz 2001(81)	Randomized 1061 Completed 538	Hip osteoarthritis	12 weeks	Celecoxib 200 mg Celecoxib 200 mg Celecoxib 400 mg Naproxen 1000 mg Placebo	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (attrition very high 64% placebo; 46% celecoxib) SELECTIVE REPORTING: Unclear (no statistical measure of dispersion reported for VAS pain; only AE affecting more than 3% of group reported) OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported)
Lehmann 2005(82)	Randomized 1684 Completed 1488	Knee osteoarthritis	13 weeks	Celecoxib 200 mg Lumiracoxib 100 mg Lumiracoxib 100 mg with an initial (loading) dose of 200 mg for the first two weeks of	RANDO: Low ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel:

				the study Placebo	Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: Low SELECTIVE REPORTING: Low OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported)
McKenna 2001a(44)	Randomized 182 Completed 142	Knee osteoarthritis	6 weeks	Celecoxib 200 mg Rofecoxib 25 mg Placebo	RANDO: Low ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: Unclear (Attrition 22% celecoxib; 27% placebo) SELECTIVE REPORTING: Unclear (no statistical measure of dispersion reported for VAS pain; only AE affecting more than 5% of group reported) OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported)
McKenna 2001b(44)	Randomized	Knee osteoarthritis	6 weeks	Celecoxib 200 mg	RANDO:

	600 Completed 450			Diclofenac 150 mg (50 mg three times a day) Placebo	Unclear (method not described) ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (attrition 36% placebo; 21% celecoxib; 19% diclofenac) SELECTIVE REPORTING: Low OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported)
Pincus 2004 PACES-a(24)	Randomized 524 Completed: not reported	Knee or hip osteoarthritis	14 weeks	Celecoxib 200 mg Acetaminophen 1000 mg (four times a day) Placebo	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: Unclear (completion rates only for end of cross-over study; not for first period; reasons for attrition not give: LOCF) SELECTIVE REPORTING:

					High (Data not shown for multiple outcomes) OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported)
Pincus 2004 PACES-b(24)	Randomized 524 Completed: not reported	Knee or hip osteoarthritis	14 weeks	Celecoxib 200 mg Acetaminophen 1000 mg (four times a day) Placebo	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: Unclear (completion rates only for end of cross-over study; not for first period; reasons for attrition not give: LOCF) SELECTIVE REPORTING: High (Data not shown for multiple outcomes) OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported)
Rother 2007(83)	Randomized 397 Completed 324	Knee osteoarthritis	6 weeks	Celecoxib 200 mg Epicutaneous ketoprofen 110mg in 4.8 g Transfersome Placebo (2 formulations)	RANDO: Low ALLOCATION CONC: Low BLINDING Participants & personnel:

					Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: Low SELECTIVE REPORTING: Low OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported)
Schnitzer 2011(84)	Randomized 1262 Completed 951	Hip osteoarthritis	13 weeks	Celecoxib 200 mg Lumiracoxib 100 mg Placebo	RANDO: Low ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (attrition 22% celecoxib; 31% placebo) SELECTIVE REPORTING: Low OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported
Sheldon 2005(85)	Randomized 1551 Completed 1182	Knee osteoarthritis	13 weeks	Celecoxib 200 mg Lumiracoxib 100 mg (4 times a day)	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (not described)

				Lumiracoxib 100 mg 4 times a day, with a loading dose of 200 mg 4 times daily for the first 2 weeks of the study Placebo	BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (attrition 20% celecoxib; 34% placebo; LOCF) SELECTIVE REPORTING: Unclear (AE reported if incidence >3% in any treatment group) OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported
Smugar 2006 study 1(86)	Randomized 1521 Completed 1248	Knee or hip osteoarthritis	6 weeks	Celecoxib 200 mg Rofecoxib 12.5 mg Rofecoxib 25 mg Placebo	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (attrition 18% celecoxib; 38% placebo; LOCF) SELECTIVE REPORTING: High (data missing for one outcome) OTHER BIAS:

					Unclear (amount of co-interventions consumed per group not reported
Smugar 2006 study 2(86)	Randomized 1082 Completed 897	Knee or hip osteoarthritis	6 weeks	Celecoxib 200 mg Rofecoxib 25 mg Placebo	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (attrition 15% celecoxib; 38% placebo; LOCF) SELECTIVE REPORTING: High (data missing for one outcome) OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported
Tannenbaum 2004(87)	Randomized 1702 Completed 1423	Knee osteoarthritis	13 weeks	Celecoxib 200 mg Lumiracoxib 200 mg Lumiracoxib 400 mg Placebo	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: Low

					SELECTIVE REPORTING: Unclear* (AE reported if incidence >3% in any treatment group) (*evaluation changed from high to unclear for consistency with other evaluations) OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported
Williams 2000(88)	Randomized 686 Completed 522	Knee osteoarthritis	6 weeks	Celecoxib 200 mg (100 mg twice daily) Celecoxib 200 mg (once daily) Placebo	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (attrition 37% placebo; 16% in two celecoxib groups; LOCF) SELECTIVE REPORTING: Unclear* (AE reported if incidence >3% in any treatment group) (*evaluation changed from high to unclear for consistency with other evaluations) OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported

Williams 2001(89)	Randomized 718 Completed 549	Knee osteoarthritis	6 weeks	Celecoxib 200 mg (100 mg twice daily) Celecoxib 200 mg (once daily) Placebo	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (attrition 33% placebo; 20% and 17% in celecoxib groups; LOCF) SELECTIVE REPORTING: Unclear (AE reported if incidence >3% in any treatment group) OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported

Remarks
The main analysis of this Cochrane review evaluated only RCTs with low risk of bias for randomization, allocation concealment and blinding. There were no differences with the analysis with all eligible studies for the comparison of **celecoxib and placebo**.

Author's conclusions
"We are highly reserved about results due to pharmaceutical industry involvement and limited data. We were unable to obtain data from three studies, which included 15,539 participants, and classified as awaiting assessment. Current evidence indicates that celecoxib is slightly better than placebo and some tNSAIDs in reducing pain and improving physical function. We are uncertain if harms differ among celecoxib and placebo or tNSAIDs due to risk of bias, low quality evidence for many outcomes, and that some study authors and Pfizer declined to provide data from completed studies with large

numbers of participants. To fill the evidence gap, we need to access existing data and new, independent clinical trials to investigate benefits and harms of celecoxib versus tNSAIDs for people with osteoarthritis, with longer follow-up and more direct head-to-head comparisons with other tNSAIDs."

Study details	n/Population	Comparison	Outcomes		Methodological
Essex 2016(90) Design: RCT DB, PG Duration of follow-up: 6 weeks	n= 367 Mean age: 64-66y Other interventions for pain allowed during study: any prior NSAID/analgesic drug was discontinued prior to the first dose of study medication. Rescue analgesia with acetaminophen (up to 2g/day) was permitted (except 24h prior to baseline arthritis assessments) <u>Inclusion</u> Patients of Asian descent (in the US) Age ≥45 y Knee osteoarthritis	Celecoxib 200 mg/day vs Naproxen 500 mg 2x/day Vs Placebo	Efficacy		RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (not described) BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: not specified Drop-out and Exclusions: 23% • Described: yes • Balanced across groups: unclear: 18.6% celecoxib; 27.1% naproxen, 24.4% placebo ITT: Modified ITT: randomized patients with at least one dose of study medication and post-baseline follow-up efficacy
			Pain (VAS in mm) at week 6 (PO)	Celecoxib: -37.1 Naproxen: -37.5 Placebo: -33.6 Naproxen vs celecoxib LSM -0.4 (-5.2 to 4.5) NS Celecoxib vs placebo LSM -3.5 (-9.3 to 2.3) NS	
			Safety		
			Treatment-related treatment-emergent adverse events	Celecoxib: 13% Naproxen: 24% Placebo: 8%	
			Discontinuation due to a treatment-related treatment-emergent adverse event	Celecoxib: 5% Naproxen: 9% Placebo: 1%	

			SAE/ death	No events	measure
	Exclusion Not described in article				SELECTIVE REPORTING: no Sponsor: Pfizer Inc.

Study details	n/Population	Comparison	Outcomes		Methodological
Lee 2017(91) Design: RCT DB, PG Duration of follow-up: 6 weeks	n= 362 (polmacoxib 146, celecoxib 145, placebo 71) Mean age: Other interventions for pain allowed during study: no; subjects were required to discontinue existing treatment with NSAID and/or other analgesics. Rescue analgesia was not	Celecoxib 200 mg Vs Polmacoxib 2 mg vs Placebo	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 0 % Drop-out and Exclusions: 10 % • Described: yes • Balanced across groups: unclear: placebo 7.0%; celecoxib 9.0% polmacoxib 13.7%
			Pain (WOMAC) week 6 (PO)	Celecoxib: -5.7 Polmacoxib: -5.1 Placebo: -2.6 **Celecoxib vs placebo** **TD -3.1 (-5.1 to -1.2)** **SS in favour of celecoxib**	
			Physical function (WOMAC) week 6	Celecoxib: -14.9 Polmacoxib: -14.3 Placebo: -7.9 **Celecoxib vs placebo** **TD -7.0 (-13.1 to -0.9)** **SS in favour of celecoxib**	
			Safety		

	allowed during the treatment period. <u>Inclusion</u> Age ≥20 y Knee or hip osteoarthritis <u>Exclusion</u> Use of anticoagulants within 2 weeks of screening; Use of corticosteroids, herbal medicines, traditional Korean medicines, nutraceuticals, glucosamine, chondroitin sulfate; Requirement for knee or hip arthroplasty within 2 months of screening; NYHA stage II-IV heart failure, ischemic heart disease, uncontrolled hypertension,		Treatment-emergent adverse events	Celecoxib: 18.8% Polmacoxib: 28.6% Placebo: 14.1%	ITT: Yes; all randomized subjects SELECTIVE REPORTING: no Sponsor: unclear
			Serious adverse events	4 occurred (no clear which group); none deemed related to treatment	
			Adverse events leading to discontinuation	Celecoxib: 2.8% Polmacoxib: 9.5% Placebo: 2.8%	

	peripheral arterial disease and/or cerebrovascular disease; Pregnancy, breast-feeding; Ulcer, GI bleeding, severe renal or hepatic disorders; Psychiatric disorders,…				

Study details	n/Population	Comparison	Outcomes	Methodological
	n= 388		Efficacy	RANDO:

RCT Gordo 2017 (54) Design: RCT DB, PG Non-inferiority trial Duration of follow-up: 6 weeks	(celecoxib 153, ibuprofen 156, placebo 79) Mean age: 62 – 65y Other interventions for pain allowed during study: patients discontinued use of any NSAID and/or analgesic therapy. No rescue analgesia permitted during study treatment. Stable doses of aspirin (≤ 325 mg/day) for cardiovascular prophylaxis was permitted. <u>Inclusion</u> Osteoarthritis of the knee in a flare state	Celecoxib 200 mg 1x/day Vs Ibuprofen 800 mg 3x/day Vs placebo	Pain VAS (PO) (0-100) (per protocol population)	**Celecoxib vs ibuprofen** Difference in LS means: 2.76 (-3.38 to 8.90) Celecoxib is non-inferior to ibuprofen (when lower bound defined as greater than -10) *Also NS in mITT population* **Celecoxib vs placebo** Difference in LS means: -5.26 (-13.06 to 2.54) NS ***SS in mITT population:*** ***-9.41 (-16.34 to -2.52)*** ***P=0.0076*** **Ibuprofen vs placebo** Difference in LS means: -2.50 (-10.25 to 5.25) *Also NS in mITT population*	Adequate ALLOCATION CONC: Unclear (not described) BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: unclear: participants lost to follow included in category “defaulted” Drop-out and Exclusions: 19.6% • Described: unclear: category “other” and “defaulted” include most of the discontinuations, not clear what these categories mean • Balanced across groups: unclear: celecoxib 17.0%, ibuprofen 17.3%, placebo 29.1% ITT: Per protocol and mITT Modified ITT: all patients who were randomized and received at least one dose of study drug.

	≥ 40 y <u>Exclusion</u> Inflammatory arthritis, gout, previous surgical or invasive procedure on the joint, Malignancy, history of malignancy Active gastrointestinal disease, history of gastrointestinal perforations, obstructions or bleeding, cardiac, renal and/or hepatic disease, coagulation disorders				SELECTIVE REPORTING: no Other important methodological remarks: Celecoxib was declared to be as effective as ibuprofen if the lower bound of the two-sided 95% CI of the treatment difference (ibuprofen–celecoxib) lay above -10mm in the PPA population. (reason for this cut-off not provided) Sponsor: Pfizer
			Safety		

			Upper gastrointestinal events *Defined as a moderate or severe instance of one or more of abdominal pain, dyspepsia, and/or nausea*	Celecoxib: 1.3% Ibuprofen: 5.1% Placebo: 2.5% NS between-group differences	
			Patients with AEs	Celecoxib: 20.3% Ibuprofen: 30.8% Placebo: 26.6%	
			Patients with serious AEs	Celecoxib: 0 Ibuprofen: 1 Placebo: 0	
			Patients discontinued due to AEs	Celecoxib: 3.3% Ibuprofen: 6.4% Placebo: 6.3%	

14.8 Etoricoxib vs placebo in osteoarthritis

Meta-analysis: da Costa 2016(45) "Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis"
Inclusion criteria: large-scale (>100 patients per group) randomised controlled trials of patients with knee or hip osteoarthritis, comparing any of the following interventions: NSAIDs, paracetamol (acetaminophen), or placebo, for the treatment of osteoarthritis pain.
Search strategy: the Cochrane Central Register of Controlled Trials (CENTRAL) and the reference lists of relevant articles were searched for trials published between Jan 1, 1980, and Feb 24, 2015.
Assessment of quality of included trials: yes
Other methodological remarks: This is a network meta-analysis. The results of the direct comparisons were not pooled. We report the individual studies that met our inclusion criteria.

Ref + design	n	Population	Duration	Comparison	Main results	Methodology (risk of bias, as assessed by Jevsevar 2018)
Gottesdiener 2002(92)	617	Knee osteoarthritis	14 weeks	Etoricoxib 30 mg 4x/day Etoricoxib 60 mg 4x/day Etoricoxib 90 mg 4x/day Vs placebo	Pain WOMAC (Difference from placebo in LS mean) Etoricoxib 30 mg: -13.86 (-20.55 to -15.68) Etoricoxib 60 mg -22.29 (-28.91 to -15.68) Etoricoxib 90 mg -19.16 (-25.76 to -12.55) **Etoricoxib SS more pain reduction compared to placebo** Physical function WOMAC (sec endpoint) **SS in favour of etoricoxib**	ALLOCATION CONCEALMENT: low BLINDING PATIENT/ INVESTIGATOR: low/low INCOMPLETE OUTCOME DATA: High
Leung 2002(93)	501	Knee and hip osteoarthritis	12 weeks	Etoricoxib 60 mg 4x/day	WOMAC pain WOMAC physical function	ALLOCATION CONCEALMENT: Unclear

				Vs placebo	**SS in favour of etoricoxib** (abstract only)	BLINDING PATIENT/ INVESTIGATOR: low/low INCOMPLETE OUTCOME DATA: High
Puopolo 2007(49)	548	Knee and hip osteoarthritis	12 weeks	Etoricoxib 30 mg 4x/day Vs placebo	Pain WOMAC (Difference from placebo in LS mean) **-11.66 (-16.31 to -7.01)** **SS in favour of etoricoxib** Physical function WOMAC (Difference from placebo in LS mean) **-10.15 (-14.74 to -5.57)** **SS in favour of etoricoxib**	ALLOCATION CONCEALMENT: low BLINDING PATIENT/ INVESTIGATOR: low/low INCOMPLETE OUTCOME DATA: High
Reginster 2007(65)	997	Knee and hip osteoarthritis	12 weeks	Etoricoxib 60 mg 4x/day Vs placebo	Pain WOMAC (VAS) Etoricoxib -27.94 Placebo -15.31 **SS in favour of etoricoxib** Physical function WOMAC (VAS) Etoricoxib -22.81 Placebo -10.27 **SS in favour of etoricoxib**	ALLOCATION CONCEALMENT: Unclear BLINDING PATIENT/ INVESTIGATOR: low/low INCOMPLETE OUTCOME DATA: High
Wiesenhutter 2005(53)	528	Knee osteoarthritis	12 weeks	Etoricoxib 30 mg 4x/day Vs	WOMAC and VAS Pain **Etoricoxib SS more effective than placebo**	ALLOCATION CONCEALMENT: low BLINDING PATIENT/ INVESTIGATOR: low/low

				placebo		INCOMPLETE OUTCOME DATA: High

14.9 COX-2-selective NSAID vs nonselective NSAID in osteoarthritis

Meta-analysis: Cochrane Puljak 2017(71): "Celecoxib for osteoarthritis"

Inclusion criteria: RCTs comparing celecoxib 200 mg daily versus no intervention, placebo or other nonselective NSAID in knee and/or hip osteoarthritis
Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and clinical trials registers were searched up to April 2017
Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result
Cochrane Puljak 2017(71) Design: SR + MA Search date: April 2017	Celecoxib Vs Nonselective NSAID	N= 2 n= 1180 (Dahlberg 2009, Sowers 2005)	Pain	I^2=65% MD -4.52 (-10.65 to 1.61) NS
		N= 1 n= 264 (Sowers 2005)	Physical function	I^2=/ **MD -4.00 (-11.40 to -0.60)** **SS in favour of celecoxib**
		N= 8 n= 3150 (Bensen 1999, Dahlberg 2009, Emery 2008, Essex 2012b, Essex	Number withdrawn due to adverse events	Celecoxib: 114/1577 Nonselective NSAID: 117/1573 I^2= 34% Peto OR 0.97 (0.74 to 1.27)

		2014, Kivitz 2001, McKenna 2001b, Sowers 2005)		NS
		N= 5 n= 2404 (Dahlberg 2009, Emery 2008, Essex 2012a, Essex 2012b, McKenna 2001b)	Number experiencing any serious adverse events	Celecoxib: 76/1204 Nonselective NSAID: 82/1200 I^2= 32% Peto OR 0.92 (0.66 to 1.28) NS
		N= 4 n= 1755 (Bensen 1999, Dahlberg 2009, Emery 2008, Essex 2014)	Number experiencing gastro-intestinal events (perforation, ulcer, bleeds)	Celecoxib: 3/877 Nonselective NSAID: 5/878 I^2= 38% Peto OR 0.61 (0.15 to 2.43) NS
		N= 1 n= 916 (Dahlberg 2009)	Number experiencing cardiovascular events (myocardial infarction, stroke)	Celecoxib: 5/458 Nonselective NSAID: 11/458 I^2= / Peto OR 0.47 (0.17 to 1.25) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Bensen 1999(61)	Randomized: 1003 Completed: 569	Knee osteoarthritis	12 weeks	Celecoxib 100 mg Celecoxib 200 mg Celecoxib 400 mg naproxen 1000 mg Placebo	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (method not described) BLINDING Participants & personnel:

					Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (high attrition 43%; LOCF) SELECTIVE REPORTING: Low OTHER BIAS: Unclear (possible selection bias in favor of participants tolerant of naproxen)
Dahlberg 2009(94)	Randomized: 925 Completed: 550	Knee or hip osteoarthritis	52 weeks	Celecoxib 200 mg Diclofenac 100 mg/day	RANDO: Low ALLOCATION CONC: Low BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (attrition 39% placebo; 40% celecoxib) SELECTIVE REPORTING: Unclear (AE reported if incidence >5% in any treatment group) OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported
Emery 2008(95)	Randomized: 249	Hip osteoarthritis	12 weeks	Celecoxib 200 mg Diclofenac 150 mg/day	RANDO: Low ALLOCATION CONC:

	Completed: 149				Low BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (attrition 43% celecoxib; 37% naproxen) SELECTIVE REPORTING: High (AE not fully reported; unclear in which group SAE occurred; study protocol amended to change timepoint of primary endpoint from week 12 to week 6) OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported
Essex 2012a(96)	Randomized 589 Completed 391	Knee osteoarthritis	6 months	Celecoxib 200 mg Naproxen 1000 mg/day	RANDO: Low ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (high attrition; 32% celecoxib; 35% naproxen) SELECTIVE REPORTING:

					Unclear (AE reported if incidence >2% in any treatment group; not all details about statistical analyses reported) OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported)
Essex 2012b(62)	Randomized 322 Completed 253	Knee osteoarthritis	6 weeks	Celecoxib 200 mg Naproxen 1000 mg/day Placebo	RANDO: Low ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (high attrition; 20% celecoxib; 16% naproxen; 34% placebo) SELECTIVE REPORTING: High (not all secondary outcomes reported) OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported)
Essex 2014(55)	Randomized 318 Completed 236	Knee osteoarthritis	6 weeks	Celecoxib 200 mg Naproxen 1000 mg/day Placebo	RANDO: Low ALLOCATION CONC: Unclear (not described)

					BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: Unclear (attrition 24% celecoxib, 28% naproxen; 26% placebo) SELECTIVE REPORTING: High (not all secondary outcomes reported) OTHER BIAS: Low
Kivitz 2001(81)	Randomized 1061 Completed 538	Hip osteoarthritis	12 weeks	Celecoxib 200 mg Celecoxib 200 mg Celecoxib 400 mg Naproxen 1000 mg Placebo	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (attrition very high 64% placebo; 46% celecoxib) SELECTIVE REPORTING: Unclear (no statistical measure of dispersion reported for VAS pain; only AE affecting more than 3% of group reported) OTHER BIAS:

					Unclear (amount of co-interventions consumed per group not reported)
McKenna 2001b(44)	Randomized 600 Completed 450	Knee osteoarthritis	6 weeks	Celecoxib 200 mg Diclofenac 150 mg (50 mg three times a day) Placebo	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (attrition 36% placebo; 21% celecoxib; 19% diclofenac) SELECTIVE REPORTING: Low OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported)
Sowers 2005(97)	Randomized 404 Completed 323	Knee or hip osteoarthritis	12 weeks	Celecoxib 200 mg Rofecoxib 25 mg Naproxen 1000 mg	RANDO: Low ALLOCATION CONC: Low BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: Unclear (Attrition 16% celecoxib; 21% naproxen)

					SELECTIVE REPORTING: High (AE not reported) OTHER BIAS: Unclear (amount of co-interventions consumed per group not reported)

Remarks
The main analysis of this Cochrane review evaluated only RCTs with low risk of bias for randomization, allocation concealment and blinding. In the comparison between **celecoxib and nonselective NSAID,** only one outcome showed a difference between the low risk of bias analysis and the analysis of all eligible trials: physical function: 6% absolute improvement in low risk of bias, no difference in all eligible studies.

Author's conclusions
"We are highly reserved about results due to pharmaceutical industry involvement and limited data. We were unable to obtain data from three studies, which included 15,539 participants, and classified as awaiting assessment. Current evidence indicates that celecoxib is slightly better than placebo and some tNSAIDs in reducing pain and improving physical function. We are uncertain if harms differ among celecoxib and placebo or tNSAIDs due to risk of bias, low quality evidence for many outcomes, and that some study authors and Pfizer declined to provide data from completed studies with large numbers of participants. To fill the evidence gap, we need to access existing data and new, independent clinical trials to investigate benefits and harms of celecoxib versus tNSAIDs for people with osteoarthritis, with longer follow-up and more direct head-to-head comparisons with other tNSAIDs."

14.10 Celecoxib vs ibuprofen in osteoarthritis

Study details	n/Population	Comparison	Outcomes	Methodological
	n= 388		Efficacy	RANDO:

RCT Gordo 2017 (54) Design: RCT DB, PG Non-inferiority trial Duration of follow-up: 6 weeks	(celecoxib 153, ibuprofen 156, placebo 79) Mean age: 62 – 65y Other interventions for pain allowed during study: patients discontinued use of any NSAID and/or analgesic therapy. No rescue analgesia permitted during study treatment. Stable doses of aspirin (≤ 325 mg/day) for cardiovascular prophylaxis was permitted. <u>Inclusion</u> Osteoarthritis of the knee in a flare state	Celecoxib 200 mg 1x/day Vs Ibuprofen 800 mg 3x/day Vs placebo	Pain VAS (PO) (0-100) (per protocol population)	**Celecoxib vs ibuprofen** Difference in LS means: 2.76 (-3.38 to 8.90) Celecoxib is non-inferior to ibuprofen (when lower bound defined as greater than -10) *Also NS in mITT population* **Celecoxib vs placebo** Difference in LS means: -5.26 (-13.06 to 2.54) NS ***SS in mITT population:*** ***-9.41 (-16.34 to -2.52)*** ***P=0.0076*** **Ibuprofen vs placebo** Difference in LS means: -2.50 (-10.25 to 5.25) *Also NS in mITT population*	Adequate ALLOCATION CONC: Unclear (not described) BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: unclear: participants lost to follow included in category “defaulted” Drop-out and Exclusions: 19.6% • Described: unclear: category “other” and “defaulted” include most of the discontinuations, not clear what these categories mean • Balanced across groups: unclear: celecoxib 17.0%, ibuprofen 17.3%, placebo 29.1% ITT: Per protocol and mITT Modified ITT: all patients who were randomized and received at least one dose of study drug.

	≥ 40 y <u>Exclusion</u> Inflammatory arthritis, gout, previous surgical or invasive procedure on the joint, Malignancy, history of malignancy Active gastrointestinal disease, history of gastrointestinal perforations, obstructions or bleeding, cardiac, renal and/or hepatic disease, coagulation disorders				SELECTIVE REPORTING: no Other important methodological remarks: Celecoxib was declared to be as effective as ibuprofen if the lower bound of the two-sided 95% CI of the treatment difference (ibuprofen–celecoxib) lay above -10mm in the PPA population. (reason for this cut-off not provided) Sponsor: Pfizer
			Safety		

			Upper gastrointestinal events *Defined as a moderate or severe instance of one or more of abdominal pain, dyspepsia, and/or nausea*	Celecoxib: 1.3% Ibuprofen: 5.1% Placebo: 2.5% NS between-group differences	
			Patients with AEs	Celecoxib: 20.3% Ibuprofen: 30.8% Placebo: 26.6%	
			Patients with serious AEs	Celecoxib: 0 Ibuprofen: 1 Placebo: 0	
			Patients discontinued due to AEs	Celecoxib: 3.3% Ibuprofen: 6.4% Placebo: 6.3%	

14.11 Celecoxib vs diclofenac in osteoarthritis

Meta-analysis: Cochrane Puljak 2017(71): "Celecoxib for osteoarthritis"

Inclusion criteria: RCTs comparing celecoxib 200 mg daily versus no intervention, placebo or other nonselective NSAID in knee and/or hip osteoarthritis
Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and clinical trials registers were searched up to April 2017
Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result
Cochrane Puljak 2017(71) Design: SR + MA Search date: April 2017	Celecoxib Vs Diclofenac 100 mg	N= 1 n= 916 (Dahlberg 2009)	Pain	I^2= / MD -2.0 (-5.32 to 1.32) NS
		N= 1 n= 916 (Dahlberg 2009)	Number withdrawn due to adverse events	Celecoxib: 27/458 Nonselective NSAID: 19/458 I^2= / Peto OR 1.44 (0.80 to 2.61) NS
		N= 1 n= 916 (Dahlberg 2009)	Number experiencing any serious adverse events	Celecoxib: 62/458 Nonselective NSAID: 68/458 I^2= / Peto OR 0.90 (0.62 to 1.30) NS
		N= 1 n= 916 (Dahlberg 2009)	Number experiencing gastro-intestinal events (perforation, ulcer, bleeds)	Celecoxib: 0/458 Nonselective NSAID: 2/458 I^2= / Peto OR 0.14 (0.01 to 2.16) NS

		N= 1 n= 916 (Dahlberg 2009)	Number experiencing cardiovascular events (myocardial infarction, stroke)	Celecoxib: 5/458 Nonselective NSAID: 11/458 I^2= / Peto OR 0.47 (0.17 to 1.25) NS
	Celecoxib Vs Diclofenac 150 mg	N= 1 n= 398 (McKenna 2001b	Pain VAS at 6 weeks	I^2= / MD 1.90 (-3.68 to 7.48) NS
		N= 1 n= 398 (McKenna 2001b	Pain WOMAC at 6 weeks	I^2= / MD 0.30 (-0.52 to 1.12) NS
		N= 1 n= 398 (McKenna 2001b	Physical function WOMAC at 6 weeks	I^2= / MD 1.90 (-0.72 to 4.52) NS
		N= 2 n= 650 (Emery 2008, McKenna 2001b)	Number withdrawn due to adverse events	Celecoxib: 27/325 Nonselective NSAID: 34/325 I^2= 10% Peto OR 0.78 (0.46 to 1.32) NS
		N= 2 n= 647 (Emery 2008, McKenna 2001b)	Number experiencing any serious adverse events	Celecoxib: 4/325 Nonselective NSAID: 5/322 I^2= 82% Peto OR 0.79 (0.21 to 2.93) NS
		N= 1 n= 252 (Emery 2008)	Number experiencing gastro-intestinal events	Celecoxib: 2/126 Nonselective NSAID: 0/126 I^2= /

				Peto OR 7.45 (0.46 to 119.74) NS

* Characteristics of included studies: see tables under “celecoxib vs nonselective NSAID for osteoarthritis”

14.12 Celecoxib vs naproxen in osteoarthritis

Meta-analysis: Cochrane Puljak 2017(71): “Celecoxib for osteoarthritis”

Inclusion criteria: RCTs comparing celecoxib 200 mg daily versus no intervention, placebo or other nonselective NSAID in knee and/or hip osteoarthritis
Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and clinical trials registers were searched up to April 2017
Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result
Cochrane Puljak 2017(71) Design: SR + MA	Celecoxib Vs Naproxen	N= 6 n= 1781 (Bensen 1999, Essex 2012a, Essex 2012b, Essex 2014, Kivitz 2001, Sowers 2005)	Pain	I^2=0% Std. MD -0.04 (-0.14 to 0.05) NS
		N= 6 n= 1817	Physical function	I^2= 69% Std. MD -0.01 (-0.18 to 0.16)

Search date: April 2017		(Bensen 1999, Essex 2012a, Essex 2012b, Essex 2014, Kivitz 2001, Sowers 2005)		NS
		N= 6 n= 2173 (Bensen 1999, Essex 2012a, Essex 2012b, Essex 2014, Kivitz 2001, Sowers 2005)	Number withdrawn due to adverse events	Celecoxib: 104/1090 Nonselective NSAID: 128/1083 I^2= 42% OR 0.81 (0.54 to 1.23) NS
		N= 2 n= 841 (Essex 2012a, Essex 2012b)	Number experiencing any serious adverse events	Celecoxib: 10/421 Nonselective NSAID: 9/420 I^2= 0% Peto OR 1.11 (0.45 to 2.75) NS
		N= 2 n= 587 (Bensen 1999, Essex 2014)	Number experiencing gastro-intestinal events (perforation, ulcer, bleeds)	Celecoxib: 1/293 Nonselective NSAID: 3/294 I^2= 0% Peto OR 0.37 (0.05 to 2.62) NS

* Characteristics of included studies: see tables under “celecoxib vs nonselective NSAID for osteoarthritis”

Study details	n/Population	Comparison	Outcomes	Methodological
	n= 367		Efficacy	RANDO:

Essex 2016(90) Design: RCT DB, PG Duration of follow-up: 6 weeks	Mean age: 64-66y Other interventions for pain allowed during study: any prior NSAID/analgesic drug was discontinued prior to the first dose of study medication. Rescue analgesia with acetaminophen (up to 2g/day) was permitted (except 24h prior to baseline arthritis assessments) <u>Inclusion</u> Patients of Asian descent (in the US) Age ≥45 y Knee osteoarthritis	Celecoxib 200 mg/day vs Naproxen 500 mg 2x/day Vs Placebo	Pain (VAS in mm) at week 6 (PO)	Celecoxib: -37.1 Naproxen: -37.5 Placebo: -33.6 Naproxen vs celecoxib LSM -0.4 (-5.2 to 4.5) NS Celecoxib vs placebo LSM -3.5 (-9.3 to 2.3) NS	Unclear (method not described) ALLOCATION CONC: Unclear (not described) BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: not specified Drop-out and Exclusions: 23% • Described: yes • Balanced across groups: unclear: 18.6% celecoxib; 27.1% naproxen, 24.4% placebo ITT: Modified ITT: randomized patients with at least one dose of study medication and post-baseline follow-up efficacy measure
			Safety		
			Treatment-related treatment-emergent adverse events	Celecoxib: 13% Naproxen: 24% Placebo: 8%	
			Discontinuation due to a treatment-related treatment-emergent adverse event	Celecoxib: 5% Naproxen: 9% Placebo: 1%	
			SAE/ death	No events	

	Exclusion Not described in article				SELECTIVE REPORTING: no Sponsor: Pfizer Inc.

14.13 Acetylsalicylic acid vs placebo for chronic low back pain

Meta-analysis: Cochrane Enthoven 2016(98): “Non-steroidal anti-inflammatory drugs from chronic low back pain” Inclusion criteria: RCTs of NSAIDs (including acetylsalicylic acid) for non-specific chronic low back pain, with exclusion of sciatica Search strategy: CENTRAL,MEDLINE, EMBASE, PubMed and two clinical trials registry databases were searched up until June 2015. Assessment of quality of included trials: yes

Remarks
No RCTs were found that compared acetylsalicylic acid with placebo.

14.14 COX-2-selective NSAID vs placebo for chronic low back pain

Meta-analysis: Cochrane Enthoven 2016(98): “Non-steroidal anti-inflammatory drugs from chronic low back pain”

Inclusion criteria: RCTs of NSAIDs (including acetylsalicylic acid) for non-specific chronic low back pain, with exclusion of sciatica
Search strategy: CENTRAL,MEDLINE, EMBASE, PubMed and two clinical trials registry databases were searched up until June 2015.
Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result
Cochrane Enthoven 2016(98) Design: SR + MA Search date: June 2015	Nonselective NSAID Vs placebo	N= 4 n= 847 (Allegrini 2009, Berry 1982, Katz 2011, Kivitz 2013)	Pain (change in pain intensity from baseline on 100 mm VAS)	**MD -5.96 (-10.96 to -0.96)** **SS in favour of nonselective NSAID** I^2= 55%
		N= 4 n= 847 (Allegrini 2009, Berry 1982, Katz 2011, Kivitz 2013)	Proportion of patients experiencing adverse events	Nonselective NSAID: 219/480 Placebo: 168/367 RR 0.94 (0.82 to 1.08) NS I^2= 0%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Allegrini 2009(101)	180	chronic low back pain	9 days	Piroxicam patch Piroxicam cream 1% Placebo patch	RCT did not meet our inclusion criteria (duration)
Berry 1982(102)	37	chronic low back pain	14 days	Naproxen 1100 mg/day Diflunisal 1000 mg/day	RCT did not meet our inclusion criteria (sample size)
Katz 2011(103)	217	chronic low back pain	12 weeks	Naproxen 1000 mg/day	RANDO:

				Tanezumab single IV infusion Placebo (oral + IV)	Unclear (not described) ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (attrition 32%) SELECTIVE REPORTING: Low OTHER BIAS: Low
Kivitz 2013(104)	1359	chronic low back pain	16 weeks	Naproxen 1000 mg/day Tanezumab IV infusion 5 mg Tanezumab IV infusion 10 mg Tanezumab IV infusion 20 mg Placebo (oral + IV)	RANDO: Unclear (not described) ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (high attrition; ITT and per protocol used, but unclear in what comparison) SELECTIVE REPORTING: Low OTHER BIAS: Low

Remarks
A sensitivity analysis with a moderate quality of evidence showed that the positive effect of NSAIDs compared to placebo was reduced and no longer statistically significant when only RCTs that were of low risk of bias were included.

Author's conclusions
"Six of the 13 included RCTs showed that NSAIDs are more effective than placebo regarding pain intensity. NSAIDs are slightly more effective than placebo regarding disability. However, the magnitude of the effects is small, and the level of evidence was low. When we only included RCTs at low risk of bias, differences in effect between NSAIDs and placebo were reduced. We identified no difference in efficacy between different NSAID types, including selective versus non-selective NSAIDs. Due to inclusion of RCTs only, the relatively small sample sizes and relatively short follow-up in most included trials, we cannot make firm statements about the occurrence of adverse events or whether NSAIDs are safe for long-term use."

14.15 Nonselective NSAID vs placebo for chronic low back pain

Meta-analysis: Cochrane Enthoven 2016(98): "Non-steroidal anti-inflammatory drugs from chronic low back pain"

Inclusion criteria: RCTs of NSAIDs (including acetylsalicylic acid) for non-specific chronic low back pain, with exclusion of sciatica
Search strategy: CENTRAL,MEDLINE, EMBASE, PubMed and two clinical trials registry databases were searched up until June 2015.
Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result
Cochrane Enthoven 2016(98)	Nonselective NSAID Vs	N= 4 n= 847 (Allegrini 2009, Berry 1982,	Pain (change in pain intensity from baseline on 100 mm VAS)	**MD -5.96 (-10.96 to -0.96)** **SS in favour of nonselective NSAID** I^2= 55%

Design: SR + MA Search date: June 2015	placebo	Katz 2011, Kivitz 2013)		
		N= 4 n= 847 (Allegrini 2009, Berry 1982, Katz 2011, Kivitz 2013)	Proportion of patients experiencing adverse events	Nonselective NSAID: 219/480 Placebo: 168/367 RR 0.94 (0.82 to 1.08) NS I^2= 0%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Allegrini 2009(101)	180	chronic low back pain	9 days	Piroxicam patch Piroxicam cream 1% Placebo patch	RCT did not meet our inclusion criteria (duration)
Berry 1982(102)	37	chronic low back pain	14 days	Naproxen 1100 mg/day Diflunisal 1000 mg/day	RCT did not meet our inclusion criteria (sample size)
Katz 2011(103)	217	chronic low back pain	12 weeks	Naproxen 1000 mg/day Tanezumab single IV infusion Placebo (oral + IV)	RANDO: Unclear (not described) ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (attrition 32%) SELECTIVE REPORTING: Low OTHER BIAS:

					Low
Kivitz 2013(104)	1359	chronic low back pain	16 weeks	Naproxen 1000 mg/day Tanezumab IV infusion 5 mg Tanezumab IV infusion 10 mg Tanezumab IV infusion 20 mg Placebo (oral + IV)	RANDO: Unclear (not described) ALLOCATION CONC: Unclear (not described) BLINDING Participants & personnel: Low BLINDING assessors: Low INCOMPLETE OUTCOME DATA: High (high attrition; ITT and per protocol used, but unclear in what comparison) SELECTIVE REPORTING: Low OTHER BIAS: Low

Remarks
A sensitivity analysis with a moderate quality of evidence showed that the positive effect of NSAIDs compared to placebo was reduced and no longer statistically significant when only RCTs that were of low risk of bias were included.

Author's conclusions
"Six of the 13 included RCTs showed that NSAIDs are more effective than placebo regarding pain intensity. NSAIDs are slightly more effective than placebo regarding disability. However, the magnitude of the effects is small, and the level of evidence was low. When we only included RCTs at low risk of bias, differences in effect between NSAIDs and placebo were reduced. We identified no difference in efficacy between different NSAID types, including

selective versus non-selective NSAIDs. Due to inclusion of RCTs only, the relatively small sample sizes and relatively short follow-up in most included trials, we cannot make firm statements about the occurrence of adverse events or whether NSAIDs are safe for long-term use."

14.16 COX-2-selective NSAID vs nonselective NSAID in chronic low back pain

Meta-analysis: Cochrane Enthoven 2016(98): "Non-steroidal anti-inflammatory drugs from chronic low back pain"

Inclusion criteria: RCTs of NSAIDs (including acetylsalicylic acid) for non-specific chronic low back pain, with exclusion of sciatica
Search strategy: CENTRAL,MEDLINE, EMBASE, PubMed and two clinical trials registry databases were searched up until June 2015.
Assessment of quality of included trials: yes

Remarks
1 RCT was found comparing etoricoxib with diclofenac. It did not meet our inclusion criteria (duration).

14.17 NSAID for sciatica

Meta-analysis: Cochrane Rasmussen-Barr 2017(105): “Non-steroidal anti-inflammatory drugs for sciatica”

Inclusion criteria: RCT’s comparing NSAID (including acetylsalicylic acid) to placebo, to other NSAIDs, or to other medication for sciatica.
Search strategy: Cochrane Central Register of Controlled Trials (CENTRAL),MEDLINE, EMBASE, PubMed, and two trials registers were searched up until June 2015.
Assessment of quality of included trials: yes

Remarks
No RCTs comparing acetylsalicylic acid vs placebo were found.

Remarks
No RCTs comparing COX-2-selective NSAID to placebo were found.

Remarks
No RCTs comparing COX-2-selective NSAID to nonselective NSAID were found.

Remarks
None of the four trials that compared nonselective NSAID to placebo met our inclusion criteria (duration).

Author’s conclusions

"This updated systematic review including 10 trials evaluating the efficacy of NSAIDs versus placebo or other drugs in people with sciatica reports low- to very low-level evidence using the GRADE criteria. The efficacy of NSAIDs for pain reduction was not significant. NSAIDs showed a better global improvement compared to placebo. These findings must be interpreted with caution, as the level of evidence according to the GRADE classification was very low for the outcome pain reduction and low for global improvement due to small study samples, inconsistent results, imprecision, and a high risk of bias in the included trials. While the trials included in the analysis were not powered to detect potential rare side effects, we found an increased risk for side effects in the short-term NSAIDs use. As NSAIDs are frequently prescribed, the risk-benefit ratio of prescribing the drug needs to be considered."

14.18 NSAID for neuropathic pain

Meta-analysis: Moore 2015(4): "Oral nonsteroidal anti-inflammatory drugs for neuropathic pain"

Inclusion criteria: RCTs comparing any oral NSAID with placebo or another active treatment in chronic neuropathic pain.
Search strategy: CENTRAL, MEDLINE, and EMBASE were searched from inception to May 2015.
Assessment of quality of included trials: yes

Remarks
No RCTs that met our inclusion criteria were found.

14.19 NSAID for cancer pain

Meta-analysis: Derry 2017(106): “Oral nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer pain in adults”

Inclusion criteria: RCTs comparing any oral NSAID alone with placebo or another NSAID, or a combination of NSAID plus opioid with the same dose of the opioid alone, for cancer pain of any pain intensity.
Search strategy: the Cochrane Central Register of Controlled Trials (CENTRAL),MEDLINE, and Embase were searched up to April 2017.
Assessment of quality of included trials: yes

Remarks
No RCT comparing NSAID with placebo was found.

Remarks
One RCT comparing celecoxib to diclofenac was found, but it did not meet our inclusion criteria (sample size).

14.20 Dexketoprofen

As dexketoprofen was not included in the search of the systematic reviews used as source material, we conducted a separate search for dexketoprofen without date limitations. It yielded no SRs or RCTs meeting our inclusion criteria.

15 Appendix. Evidence tables. Adjuvant analgesics

15.1 Duloxetine vs placebo for osteoarthritis

Meta-analysis: Osani 2019(107) "Efficacy and safety of duloxetine in osteoarthritis: a systematic review and meta-analysis"

Inclusion criteria: RCTs evaluating duloxetine vs placebo in osteoarthritis patients
Search strategy: MEDLINE, EMBASE, Web of Science, Google Scholar, and the Cochrane Database was searched up to December 2018.
Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result
Osani 2019(107) Design: SR + MA Search date: December 2018	Duloxetine Vs placebo	N= 5 n= 1713 (Chappel 2009, Chappel 2011, Frakes 2011, Uchio 2018, Wang 2017)	Pain	I^2= 5% **SMD -0.38 (-0.48 to -0.28)** **SS more improvement of pain with duloxetine**
		N= 5 n= 1695 (Chappel 2009, Chappel 2011, Frakes 2011, Uchio 2018, Wang 2017)	Function	I^2= 23% **SMD -0.35 (-0.46 to -0.24)** **SS more functional improvement with duloxetine**
		N= 3 n= 826 (Chappel 2009, Chappel 2011, Uchio 2018)	Quality of life	I^2= 0% **SMD 0.40 (0.26 to 0.53)** **SS more QoL improvement with duloxetine**
		N= 5 n= 1772 (Chappel 2009, Chappel 2011,	Discontinuation due to adverse events	Duloxetine: 12.4% Placebo: 5.5% I^2= 0%

		Frakes 2011, Uchio 2018, Wang 2017)		**RR 2.17 (1.57 to 3.01)** **SS more discontinuation due to adverse events with duloxetine**
		N= 5 n= 1762 (Chappel 2009, Chappel 2011, Frakes 2011, Uchio 2018, Wang 2017)	Treatment-emergent adverse events	Duloxetine: 55.1% Placebo: 37.4% %I^2= 77% **RR 1.53 (1.21 to 1.92)** **SS more treatment-emergent adverse events with duloxetin**
		N= 5 n= 1762 (Chappel 2009, Chappel 2011, Frakes 2011, Uchio 2018, Wang 2017)	Serious adverse events	Duloxetine: 1.1% Placebo: 1.2% I^2= 0% RR 1.03 (0.42 to 2.54) NS
		N= 5 n= 1762 (Chappel 2009, Chappel 2011, Frakes 2011, Uchio 2018, Wang 2017)	Gastrointestinal adverse events	Duloxetine: 35.5% Placebo: 7.7% I^2= 4% **RR 4.43 (3.45 to 5.69)** **SS more gastrointestinal adverse events with duloxetine**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (risk of bias) As assessed by Osani 2019
Chappel 2009(108)	231	Knee osteoarthritis	13 weeks	Duloxetine 60-120 mg/day	RANDO:

				Vs placebo	low ALLOCATION CONC: Low BLINDING PARTICIPANTS AND PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low INCOMPLETE OUTCOME DATA: High (High discontinuation rates) SELECTIVE REPORTING: low OTHER BIAS: unclear
Chappel 2011(109)	256	Knee osteoarthritis	13 weeks	Duloxetine 60-120 mg/day Vs placebo	RANDO: low ALLOCATION CONC: Low BLINDING PARTICIPANTS AND PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low INCOMPLETE OUTCOME DATA: High (high discontinuation rates, differential discontinuation rates/reasons in different groups) SELECTIVE REPORTING: low OTHER BIAS: unclear
Frakes 2011(110)	524	Knee osteoarthritis	12 weeks	Duloxetine 60-120 mg/day + NSAID	RANDO: Unclear (method not described)

				Vs Placebo + NSAID	ALLOCATION CONC: unclear(method not described) BLINDING PARTICIPANTS AND PERSONNEL: low BLINDING OUTCOME ASSESSMENT: Unclear (method not described) INCOMPLETE OUTCOME DATA: High (high discontinuation rates, differential discontinuation rates/reasons in different groups) SELECTIVE REPORTING: low OTHER BIAS: Unclear (insufficient detail in reporting)
Uchio 2018(111)	353	Knee osteoarthritis	14 weeks	Duloxetine 60 mg/day Vs placebo	RANDO: low ALLOCATION CONC: Low BLINDING PARTICIPANTS AND PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER BIAS: unclear
Wang 2017(112)	407	Knee osteoarthritis	13 weeks	Duloxetine 60 mg/day	RANDO: low

				Vs placebo	ALLOCATION CONC: Low BLINDING PARTICIPANTS AND PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER BIAS: unclear

Author's conclusions
"The results of our study indicate that duloxetine may be an effective treatment option for individuals with OA, but that use of the drug is associated with a significantly higher risk of adverse events. Patient preferences, cost considerations, and clinicians' judgment must be taken into account before the initiation of a duloxetine regimen."

15.2 Amitriptyline vs placebo for musculoskeletal pain

Amitriptyline vs placebo for musculoskeletal pain

Meta-analysis: van den Driest 2017(113) “Amitriptyline for musculoskeletal complaints: a systematic review”

Inclusion criteria: RCTs on the use of amitriptyline (compared to placebo, usual care or standard analgesic use) for musculoskeletal disorders
Search strategy: Medline, Embase, Web of Science and Cochrane were searched up to April 2016.
Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result
van den Driest 2017(113) Design: SR, no MA Search date: April 2016	Amitriptyline Vs placebo	N= 1 n= 118 (Goldman 2010)	Pain reduction (numeric rating scale for pain)	Amitriptyline: -0.7 Placebo: -0.4 Difference -0.3 (-0.19 to 0.10) NS
		N= 1 n= 118 (Goldman 2010	Function (improvement)	Amitriptyline: -3.9 Placebo: -0.8 **Difference -3.1 (-5.67 to -0.44)** **SS in favour of amitriptyline**
		N= 1 n= 118 (Goldman 2010	Adverse events	Amitriptyline: 31% Placebo: 22% P=0.30 NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (risk of bias) As assessed by van den Driest 2017
Goldman 2010(114)	118	Persistent arm pain due to repetitive use	6 weeks	Amitriptyline 25 mg	RANDO: Low

				Vs placebo	ALLOCATION CONC: Low BLINDING : Low DROP-OUT: Low ITT: yes SELECTIVE OUTCOME REPORTING: Unclear FUNDING: Low

Remarks
7 RCTs were found; 4 studies evaluated amitriptyline in low back pain, 2 in rheumatoid arthritis and one in persistent arm pain due to repetitive use. Only one study (comparing amitriptyline to placebo for persistent arm pain) met our inclusion criteria.

Author's conclusions
"Few studies have evaluated the use of amitriptyline in musculoskeletal complaints. Although amitriptyline may be effective in musculoskeletal complaints, more studies are required to establish for whom amitriptyline works better than other analgesics."

15.3 Antidepressants vs placebo for low back pain

Meta-analysis: Chou 2016(35) "Noninvasive treatments for low back pain"

Inclusion criteria: systematic reviews of randomized trials of pharmacological treatments and nonpharmacological treatments for nonradicular or radicular low back pain that addressed effectiveness or harms versus placebo, no treatment, usual care, a sham therapy, an inactive therapy, or another active therapy. Also included: randomized trials that were not in systematic reviews.
Search strategy: A prior systematic review (searches through October 2008), electronic databases (Ovid MEDLINE® and the Cochrane Libraries, January 2008 to April 2015), reference lists, and clinical trials registries.
Assessment of quality of included trials: yes

SR Chou 2016 Chou 2016(35) found a Cochrane systematic review (Uruqhart 2010) that made meta-analyses comparing antidepressants, TCA and SSRI to placebo for low back pain. Uruqhart did not include RCTs evaluating duloxetine.

Three additional RCTs, comparing duloxetine to placebo, were found by Chou 2016.

Meta-analysis: Uruqhart 2010(115) "Antidepressants for non-specific low back pain"

Inclusion criteria: RCTs that compared antidepressants to placebo for non-specific low back pain in adults
Search strategy: MEDLINE, EMBASE and PsycINFO, the Cochrane Central Register of Controlled Trials were searched up until November 2008
Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result

Uruqhart 2010(115) Design: SR+MA Search date: November 2008	Antidepressants vs placebo	N= 9 n= 376 (Atkinson 1999a, Atkinson 1999b, Atkinson 2007a, Atkinson 2007b, Atkinson 2007c, Dickens 2000, Goodkin 1990, Jenkins 1976, Katz 2005)	Pain	I^2= 0% Std. MD -0.04 (-0.25 to 0.17) NS
		N= 2 n= 132 (Dickens 2000, Goodkin 1990)	Specific functional status	I^2= 0% Std. MD -0.06 (-0.40 to 0.29) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (risk of bias) As assessed by Cochrane Uruqhart 2010
Atkinson 1999a(116)	69	Chronic low back pain	8 weeks	Maprotiline 50 mg vs placebo	RCT does not meet our inclusion criteria (sample size)
Atkinson 1999b(116)	70	Chronic low back pain	8 weeks	Paroxetine 10 -30 mg vs placebo	RCT does not meet our inclusion criteria (sample size)

Atkinson 2007a(117)	78	Chronic low back pain	12 weeks	Desipramine low dose vs placebo	RCT does not meet our inclusion criteria (sample size)
Atkinson 2007b(117)	78	Chronic low back pain	12 weeks	Desipramine high dose vs placebo	RCT does not meet our inclusion criteria (sample size)
Atkinson 2007c(117)	69	Chronic low back pain	12 weeks	Fluoxetine vs placebo	RCT does not meet our inclusion criteria (sample size)
Dickens 2000(118)	98	Chronic low back pain and depressive symptoms	8 weeks	Paroxetine 20 mg 1x/day vs placebo	RANDO: low ALLOCATION CONC: low BLINDING : low INCOMPLETE OUTCOME DATA: unclear (unclear from text)
Goodkin 1990(119)	59	Chronic low back pain	6 weeks	Trazodone vs placebo	RCT does not meet our inclusion criteria (sample size)
Jenkins 1976(120)	59	Chronic low back pain	4 weeks	Imipramine vs placebo	RCT does not meet our inclusion criteria (sample size)
Katz 2005(121)	54	Chronic low back pain	6 weeks	Bupropion vs placebo	RCT does not meet our inclusion criteria (sample size)

Remarks
No studies comparing amitriptyline, nortriptyline, duloxetine or venlafaxine to placebo were found.

Author's conclusions

"There is no clear evidence that antidepressants are more effective than placebo in the management of patients with chronic low back pain. These findings do not imply that severely depressed patients with back pain should not be treated with antidepressants; furthermore, there is evidence for their use in other forms of chronic pain."

15.4 TCA vs placebo for low back pain

Meta-analysis: Uruqhart 2010(115) "Antidepressants for non-specific low back pain"

Inclusion criteria: RCTs that compared antidepressants to placebo for non-specific low back pain in adults
Search strategy: MEDLINE, EMBASE and PsycINFO, the Cochrane Central Register of Controlled Trials were searched up until November 2008
Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result
Uruqhart 2010(115) Design: SR+MA Search date:	TCA vs placebo	N= 4 n= 148 (Atkinson 1999a, Atkinson 2007a, Atkinson 2007b, Jenkins 1976)	Pain	I^2= 32% Std. MD -0.10 (-0.51 to 0.31) NS

November 2008				

Ref + design	n	Population	Duration	Comparison	Methodology (risk of bias) As assessed by Cochrane Uruqhart 2010
Atkinson 1999a(116)	69	Chronic low back pain	8 weeks	Maprotiline 50 mg vs placebo	RCT does not meet our inclusion criteria (sample size)
Atkinson 2007a(117)	78	Chronic low back pain	12 weeks	Desipramine low dose vs placebo	RCT does not meet our inclusion criteria (sample size)
Atkinson 2007b(117)	78	Chronic low back pain	12 weeks	Desipramine high dose vs placebo	RCT does not meet our inclusion criteria (sample size)
Jenkins 1976(120)	59	Chronic low back pain	4 weeks	Imipramine vs placebo	RCT does not meet our inclusion criteria (sample size)

Remarks
No studies comparing amitriptyline, nortriptyline, duloxetine or venlafaxine to placebo were found.

Author's conclusions
"There is no clear evidence that antidepressants are more effective than placebo in the management of patients with chronic low back pain. These findings do not imply that severely depressed patients with back pain should not be treated with antidepressants; furthermore, there is evidence for their use in other forms of chronic pain."

15.5 SSRI vs placebo for low back pain

Meta-analysis: Uruqhart 2010(115) "Antidepressants for non-specific low back pain"

Inclusion criteria: RCTs that compared antidepressants to placebo for non-specific low back pain in adults
Search strategy: MEDLINE, EMBASE and PsycINFO, the Cochrane Central Register of Controlled Trials were searched up until November 2008
Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result
Uruqhart 2010(115) Design: SR+MA Search date: November 2008	SSRI vs placebo	N= 3 n= 199 (Atkinson 1999b, Atkinson 2007c, Dickens 2000)	Pain	I^2= 0% Std. MD 0.11 (-0.17 to 0.39) NS

Ref + design	n	Population	Duration	Comparison	Methodology (risk of bias)

					As assessed by Cochrane Uruqhart 2010
Atkinson 1999b(116)	70	Chronic low back pain	8 weeks	Paroxetine 10 -30 mg vs placebo	RCT does not meet our inclusion criteria (sample size)
Atkinson 2007c(117)	69	Chronic low back pain	12 weeks	Fluoxetine vs placebo	RCT does not meet our inclusion criteria (sample size)
Dickens 2000(118)	98	Chronic low back pain and depressive symptoms	8 weeks	Paroxetine 20 mg 1x/day vs placebo	RANDO: low ALLOCATION CONC: low BLINDING : low INCOMPLETE OUTCOME DATA: unclear (unclear from text)

Remarks
No studies comparing amitriptyline, nortriptyline, duloxetine or venlafaxine to placebo were found.

Author's conclusions
"There is no clear evidence that antidepressants are more effective than placebo in the management of patients with chronic low back pain. These findings do not imply that severely depressed patients with back pain should not be treated with antidepressants; furthermore, there is evidence for their use in other forms of chronic pain."

15.6 Duloxetine vs placebo for low back pain

Meta-analysis: Chou 2016(35) “Noninvasive treatments for low back pain”

Inclusion criteria: systematic reviews of randomized trials of pharmacological treatments and nonpharmacological treatments for nonradicular or radicular low back pain that addressed effectiveness or harms versus placebo, no treatment, usual care, a sham therapy, an inactive therapy, or another active therapy. Also included: randomized trials that were not in systematic reviews.
Search strategy: A prior systematic review (searches through October 2008), electronic databases (Ovid MEDLINE® and the Cochrane Libraries, January 2008 to April 2015), reference lists, and clinical trials registries.
Assessment of quality of included trials: yes

SR Chou 2016 Chou 2016(35) found a Cochrane systematic review (Uruqhart 2010) that made meta-analyses comparing antidepressants, TCA and SSRI to placebo for low back pain. Uruqhart did not include RCTs evaluating duloxetine.

Three additional RCTs, comparing duloxetine to placebo, were found by Chou 2016.

Ref	Comparison	N/n	Outcomes	Result

Chou 2016(35) Design: SR, no MA Search date: April 2015 a	Duloxetine Vs placebo	N= 3 n= 1041 (Skljarevski 2009, Skljarevski 2010a, Skljarevski 2010b)	Pain, BPI-S mean change from baseline	Duloxetine 20mg: -1.79 Duloxetine 60mg: -2.50 Duloxetine 120mg: -2.45 Placebo: -1.87 **Duloxetine 60 mg vs Placebo: p<0.05** **SS in favour of duloxetine 60 mg** **----------** Duloxetine 60mg: -2.25 Placebo: -1.65 **Duloxetine 60 mg vs Placebo: p=0.002** **SS in favour of duloxetine 60 mg** **----------** Duloxetine 60mg: -2.66 Placebo: -1.90 **Duloxetine 60 mg vs Placebo: p<0.05** **SS in favour of duloxetine 60 mg**

		N= 3 n= 1041 (Skljarevski 2009, Skljarevski 2010a, Skljarevski 2010b)	Function, BPI-I average mean change from baseline:	Duloxetine 20mg: -1.84 Duloxetine 60mg: -2.40 Duloxetine 120mg: -1.92 Placebo: -1.61 **Duloxetine 60 mg vs Placebo: p<0.05** **SS in favour of duloxetine 60 mg** --- Duloxetine 60mg: -2.01 Placebo: -1.43 **Duloxetine 60 mg vs Placebo: p<0.001** **SS in favour of duloxetine 60 mg** --- Duloxetine 60mg: -1.92 Placebo: -1.18 **Duloxetine 60 mg vs Placebo: p<0.01** **SS in favour of duloxetine 60 mg**

		N= 2 n= 640 (Skljarevski 2009, Skljarevski 2010b)	Quality of life, mean change SF-36 subscales - Bodily pain	Duloxetine 20mg: 1.51 Duloxetine 60mg: 1.95 Duloxetine 120mg: 2.11 Placebo: . 1.36 **Duloxetine 60 mg vs Placebo: p<0.05** **Duloxetine 120 mg vs Placebo: p<0.05** **SS in favour of duloxetine 60 mg and duloxetine 120 mg** **----------** **Duloxetine 60 mg vs Placebo: p=0.04** **SS in favour of duloxetine 60 mg**
		N= 3 n= 1041 (Skljarevski 2009, Skljarevski 2010a, Skljarevski 2010b)	Serious adverse events	NS
		N= 3 n= 1041 (Skljarevski 2009, Skljarevski 2010a, Skljarevski 2010b)	Withdrawal due to adverse events	**I^2= 0%** **OR 2.52 (1.58 to 4.03)** **SS more withdrawals due to adverse events with duloxetine**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology As assessed by Chou 2016
Skljarevksi 2009(122)	404	Chronic low back pain with or without sciatica	13 weeks	Duloxetine 20 mg/day Vs Duloxetine 60 mg/day Vs Duloxetine 120 mg/day Vs Placebo	Overall: good RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: Adequate Personnel: Adequate Assessors: Adequate ATTRITION: Adequate ITT: No SELECTIVE OUTCOME REPORTING: Unclear
Skljarevksi 2010a(123)	401	Chronic low back pain Radicular compression excluded	12 weeks	Duloxetine 60 mg/day Vs Placebo	Overall: fair RANDO: Unclear ALLOCATION CONC: Unclear BLINDING : Participants: Adequate Personnel: Unclear Assessors: Adequate ATTRITION: Adequate ITT: No SELECTIVE OUTCOME REPORTING: Unclear
Skljarevksi 2010b(124)	236	Chronic low back pain Radicular compression excluded	13 weeks	Duloxetine 60 mg/day; titration to 120 mg/day in nonresponders after week 7 Vs	Overall: fair RANDO: Unclear ALLOCATION CONC: Unclear

				Placebo/ sham titration in nonresponders	BLINDING : Participants: Adequate Personnel: Unclear Assessors: Adequate ATTRITION: Adequate ITT: No SELECTIVE OUTCOME REPORTING: Unclear

Duloxetine vs placebo for chronic low back pain

Study details	n/Population	Comparison	Outcomes		Methodological
RCT Konno 2016(125) Design: RCT DB, PG Duration of follow-up: 14 weeks	n= 458 Mean age: 58-60 y Previous pain intervention: NSAID Other interventions for pain allowed during study: no concomitant use of analgesic drugs was allowed <u>Inclusion</u>	Duloxetine 60 mg Vs placebo	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 0% Drop-out and Exclusions: 11% • Described: yes • Balanced across groups: yes ITT:
			BPI average pain score (PO) (scale 0 (no pain) -10 (worst pain imaginable))	Duloxetine: -2.43 Placebo: -1.96 **LS Mean changes** **p=0.0026** **SS in favour of duloxetine**	
			QoL EQ-5D	Duloxetine: 0.08 Placebo: 0.09 LS Mean changes p= 0.5237 NS	
			Safety		
			Serious adverse events	Duloxetine: 4	

	Age 20 to <80 y Low back pain at least 6 months Had used NSAIDs for at least 14 days per month <u>Exclusion</u> Radiculopathy symptoms Specific low back diseases History of low back surgery Diagnosed with major depressive disorders			Placebo: 4	No (4 randomized and allocated to duloxetine not included in full analysis set) SELECTIVE REPORTING: yes; no reporting of total adverse events Other important methodological remarks : *in a pretreatment period, patients were withdrawn from all analgesics and other therapeutic drugs for chronic low back pain *QoL calculated with LOCF analysis Sponsor: Eli Lilly, Shionogi & Co. Ltd.
			Discontinuation because of adverse events	Duloxetine: 16 Placebo: 8	

15.7 Pregabaline vs placebo for low back pain

Meta-analysis: Shanthanna 2017(126) "Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials"
Inclusion criteria: RCTs reporting use of gabapentin or pregabalin for the treatment of chronic low back pain (with or without leg pain) in adult patients
Search strategy: MEDLINE, EMBASE, and Cochrane were searched up to December 2016
Assessment of quality of included trials: yes

No RCTs were found that compared pregabalin to placebo and that met our inclusion criteria.

15.8 Gabapentine vs placebo for low back pain

Meta-analysis: Shanthanna 2017(126) "Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials"
Inclusion criteria: RCTs reporting use of gabapentin or pregabalin for the treatment of chronic low back pain (with or without leg pain) in adult patients
Search strategy: MEDLINE, EMBASE, and Cochrane were searched up to December 2016
Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result
Shanthanna 2017(126) Design: SR+ MA Search date: December 2016	Gabapentin Vs placebo	N= 3 n= 185 (Atkinson 2016, McCleane 2000, McCleane 2001)	Pain relief (mean differences)	I^2=0% Std. Mean Difference: -0.22 (-0.51 to 0.07) NS
		N= 2	Pain relief (success)	Gabapentin: 20/60

		n= 120 (Atkinson 2016, McCleane 2000)		Placebo:21/60 I^2=69% RR 0.95 (0.61 to 1.499) NS
		N= 3 n= 221 (Atkinson 2016, McCleane 2000, McCleane 2001)	Dizziness	Gabapentin: 29/110 Placebo: 14/111 I^2= 49% **RR 1.99 (1.17 to 3.37)** **SS more dizziness with gabapentin**
		N= 3 n= 221 (Atkinson 2016, McCleane 2000, McCleane 2001)	Fatigue or lethargy	Gabapentin: 29/110 Placebo: 15/111 I^2= 0% **RR 1.85 (1.12 to 3.05)** **SS more lethargy with gabapentin**
		N= 3 n= 221 (Atkinson 2016, McCleane 2000, McCleane 2001)	Visual disturbances	Gabapentin: 20/110 Placebo: 3/111 I^2= 0% **RR 5.72 (1.94 to 16.91)** **SS more visual disturbances with gabapentin**
		N= 3 n= 221	Difficulties with mentation	Gabapentin: 23/110 Placebo: 6/111 I^2= 0%

		(Atkinson 2016, McCleane 2000, McCleane 2001)		**RR 3.34 (1.54 to 7.25)** **SS more difficulties with mentation with gabapentin**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Atkinson 2016(127)	116	Chronic low back pain >6 months	12 weeks	Gabapentin 300 up to 1200 mg/day Vs placebo	RANDO: Low ALLOCATION CONC: Low BLINDING : Low INCOMPLETE OUTCOME DATA: Low SELECTIVE REPORTING: Low
McCleane 2000(128)	48		8 weeks		RCT did not meet our inclusion criteria (sample size)
McCleane 2001(129)	65		6 weeks		RCT did not meet our inclusion criteria (sample size)

Author's conclusions
"Existing evidence on the use of gabapentinoids in CLBP is limited and demonstrates significant risk of adverse effects without any demonstrated benefit. Given the lack of efficacy, risks, and costs associated, the use of gabapentinoids for CLBP merits caution. There is need for large high-quality trials to more definitively inform this issue."

15.9 Carbamazepine vs placebo for low back pain

Meta-analysis: Chou 2016(35) “Noninvasive treatments for low back pain”

Inclusion criteria: systematic reviews of randomized trials of pharmacological treatments and nonpharmacological treatments for nonradicular or radicular low back pain that addressed effectiveness or harms versus placebo, no treatment, usual care, a sham therapy, an inactive therapy, or another active therapy. Also included: randomized trials that were not in systematic reviews.
Search strategy: A prior systematic review (searches through October 2008), electronic databases (Ovid MEDLINE® and the Cochrane Libraries, January 2008 to April 2015), reference lists, and clinical trials registries.
Assessment of quality of included trials: yes

Remarks
No RCTs were found that evaluated carbamazepine for low back pain.

15.10 Amitriptyline vs placebo for chronic neck pain

Study details	n/Population	Comparison	Outcomes	Methodological
	n= 332 randomized;		Efficacy	RANDO:

Maarrawi 2018(130) Design: RCT DB PG Duration of follow-up: 2 months	212 analysed Mean age: 44y Previous pain intervention: exclusion of patients taking medication other than paracetamol or NSAID for neck pain 1 month prior to enrollment Other interventions for pain allowed during study: no <u>Inclusion</u> Chronic neck pain without previous trauma and any other neurologic disorder Age 18 to 75y	Amitriptyline 25 mg 1x/day Vs placebo	Pain VAS (PO)	Amitriptyline: 3.34 Placebo: 6.12 MD 2.78 (2.46 to 3.11) SS in favour of amitriptyline	Adequate ALLOCATION CONC: Unclear (method not described) BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 11.4 % Drop-out and Exclusions: 25 % • Described: limited • Balanced across groups: yes ITT: No, per protocol analysis SELECTIVE REPORTING: yes; no reason/ description given for 62 participants excluded from analysis; unclear reporting of adverse events Sponsor: Council of Research of the Saint Joseph University of Beirut - Lebanon
			Safety		
			Discontinuation due to adverse events	Amitriptyline: 8/220 Placebo: 0/220	

	English-educated patients <u>Exclusion</u> Presence of neurologic disorder, major depressive disorder, analgesic abuse, current psychiatric abnormalities, medications for chronic neck pain other than NSAID or paracetamol taken during last month, pregnancy,…				

15.11 Amitriptyline vs placebo for neuropathic pain

Meta-analysis: Cochrane Moore 2015(131) “Amitriptyline for neuropathic pain in adults” <u>Inclusion criteria:</u> double blind RCTs, ≥4 weeks duration, comparing amitriptyline to placebo or an active comparator, for neuropathic pain. Excluded were studies using amitriptyline to treat pain resulting from the use of other drugs. <u>Search strategy</u>: CENTRAL, MEDLINE, and EMBASE were searched up to March 2015. <u>Assessment of quality of included trials</u>: yes

Ref	Comparison	N/n	Outcomes	Result
Cochrane Moore 2015(131) Design: SR+ MA Search date: (March 2015)	Amitriptyline Vs placebo	N= 1 n= 169 (Anon 2000)	Efficacy Painful diabetic neuropathy	Amitriptyline: 37/88 Placebo: 24/81 RR 1.42 (0.94 to 2.15) NS
		N= 6 n= 519 (Anon 2000, Cardenas 2002, Kautio 2008, Leijon 1989, Shlay 1998, Vrethem 1997)	At least one adverse event	Amitriptyline: 148/269 Placebo: 89/250 I^2= 89% **RR 1.54 (1.32 to 1.81)** **SS more participants with at least one adverse event with amitriptyline**
		N= 3 n= 303 (Anon 2000, Max 1988, Rintala 2007)	Adverse event withdrawal	Amitriptyline: 25/159 Placebo: 10/144 I^2= 0% **RR 2.23 (1.11 to 4.45)** **SS more withdrawals because of an adverse event with amitriptyline**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (risk of bias) As assessed by Moore 2015
Anon 2000 (132)	254	PDN	9 weeks	Amitriptyline 75 mg/day Pregabalin 600 mg/day Placebo	RANDO: Unclear (method not reported) ALLOCATION CONC: Unclear (method not reported) BLINDING : low INCOMPLETE OUTCOME DATA: Unclear (method not reported)
Cardenas 2002(133)	84	Spinal cord injury	6 weeks	Amitriptyline 25 to 125 mg/day Placebo	RANDO: Unclear (method not reported) ALLOCATION CONC: low BLINDING : low INCOMPLETE OUTCOME DATA: Unclear (method not reported)
Kautio 2008(134)	42		8 weeks		RCT did not meet our inclusion criteria (sample size)
Leijon 1989 (135)	15		3 x 4weeks		RCT did not meet our inclusion criteria (sample size)
Max 1988(136)	62	PHN	2x 6 weeks		RCT did not meet our inclusion criteria (sample size)
Rintala 2007(137)	38		3x 9 weeks		RCT did not meet our inclusion criteria (sample size)
Shlay 1998(138)	125		4 weeks		RCT did not meet our inclusion criteria (duration)

Vrethem 1997(139)	37		3x 4 weeks		RCT did not meet our inclusion criteria (sample size)

Remarks
We did not report the meta-analyses of efficacy of amitriptyline in postherpetic neuralgia, mixed neuropathic pain, cancer-related neuropathic pain or post-stroke pain because of insufficient sample size of the pooled groups. We did not report the meta-analyses of efficacy of amitriptyline in HIV-related neuropathy because of insufficient duration of follow-up.

Author's conclusions
"Amitriptyline has been a first-line treatment for neuropathic pain for many years. The fact that there is no supportive unbiased evidence for a beneficial effect is disappointing, but has to be balanced against decades of successful treatment in many people with neuropathic pain. There is no good evidence of a lack of effect; rather our concern should be of overestimation of treatment effect. Amitriptyline should continue to be used as part of the treatment of neuropathic pain, but only a minority of people will achieve satisfactory pain relief. Limited information suggests that failure with one antidepressant does not mean failure with all."

Amitrtiptyline vs placebo for painful HIV-associated sensory neuropathy

Study details	n/Population	Comparison	Outcomes	Methodological
	n= 124	Amitriptyline	Efficacy	RANDO:

Dinat 2015(140) Design: RCT DB, CO Duration of follow-up: 6 weeks	Mean age: 38 y Other interventions for pain allowed during study: y, prespecified rescue medication permitted (paracetamol, NSAIDs, codeine phosphate) <u>Inclusion</u> ≥ 18 y Confirmed HIV infection Current symptomatic HIV-SN On stable antiretroviral therapy or therapy naïve <u>Exclusion</u> Severe pain from HIV-SN that warranted a change in treatment regimen	(individualized dose escalation to tolerance or effect every three days; 25 mg – 50 mg – 75 mg – 100 mg – 150 mg) Vs Placebo (individualized dose escalation to tolerance or effect every three days; 1 – 6 tablets)	Pain (PO) Safety Unclear reporting	Per protocol population Amitriptyline: 2.7 SD 3.2 Placebo: 2.4 SD 3.2 P=0.47 NS	Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 0% Drop-out and Exclusions: 1.6 % • Described: yes • Balanced across groups: yes ITT: Primary analysis per protocol SELECTIVE REPORTING: unclear; not clear if all adverse events were reported (the three most common adverse events reported) Other important methodological remarks: cross-over: 2 x 6 weeks with 3 weeks washout inbetween; baseline period 2 (week 9) pain scores were

	Already taking amitriptyline Limb amputation Kaposi sarcoma of the lower limbs Current post-herpetic neuralgia or herpes zoster, Pregnancy, Treatment for tuberculosis, Malignancy, Major psychiatric disorders, …				significantly less than those of week 1 Sponsor: grant from the Diana Princess of Wales Memorial Fund.

15.12 Nortriptyline vs placebo for neuropathic pain

Meta-analysis: Cochrane Derry 2015(141)

Inclusion criteria: double-blind RCTs comparing nortriptyline with placebo or another active treatment in adults with chronic neuropathic pain.
Search strategy: the Cochrane Central Register of Controlled Trials (CENTRAL),MEDLINE, and EMBASE were searched up until January 2015.
Assessment of quality of included trials: yes

Remarks
Cochrane Derry 2015 found 3 small cross-over RCTs comparing nortriptyline with placebo. None met our inclusion criteria (duration).

Author's conclusions
"We found little evidence to support the use of nortriptyline to treat the neuropathic pain conditions included in this review. There were no studies in the treatment of trigeminal neuralgia. The studies were methodologically flawed, largely due to small size, and potentially subject to major bias. The results of this review do not support the use of nortriptyline as a first line treatment. Effective medicines with much greater supportive evidence are available, such as duloxetine and pregabalin."

15.13 Duloxetine vs placebo for neuropathic pain

Meta-analysis: Cochrane Lunn 2014(142)"Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia"

Inclusion criteria: randomised or quasi-randomised trials of duloxetine for the treatment of painful peripheral neuropathy or chronic pain in adults.
Search strategy: The Cochrane Neuromuscular Group Specialized Register, CENTRAL, DARE, HTA, NHSEED,MEDLINE, and EMBASE were searched up to November 2013.
Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result
Cochrane Lunn 2014(142)	Duloxetine vs placebo	N= 5 n= 1655	Number of participants with ≥50% improvement of pain at 12 weeks or less	Duloxetine: 489/1059 Placebo: 180/596 I^2= 62%

Design: SR + MA Search date: (November 2013)		(Gao 2010, Goldstein 2005, Raskin 2005, Wernicke 2006, Yasuda 2010)		**RR 1.53 (1.21 to 1.92)** **SS in favour of duloxetine**
		N= 4 n= 1220 (Gao 2010, Raskin 2005, Wernicke 2006, Yasuda 2010)	Number of participants with ≥30% improvement of pain at 12 weeks or less	Duloxetine: 458/725 Placebo: 220/495 I^2= 60% **RR 1.45 (1.30 to 1.63)** **SS in favour of duloxetine**
		N= 1 n= 200 (Goldstein 2005)	Mean improvement in SF-36 Physical Subscore at 12 weeks or less (Duloxetin 20 mg daily)	I^2= not applicable MD -0.27 (-2.42 to 1.88) NS
		N= 3 n= 541 (Goldstein 2005, Rowbotham 2012, Wernicke 2006)	Mean improvement in SF-36 Physical Subscore at 12 weeks or less (Duloxetin 60 mg daily)	I^2= 0% **MD 2.65 (1.38 to 3.92)** **SS in favour of duloxetine**
		N= 2 n= 409 (Goldstein 2005,	Mean improvement in SF-36 Physical Subscore at 12 weeks or less (Duloxetin 120 mg daily)	I^2= 26% **MD 2.80 (1.04 to 4.55)** **SS in favour of duloxetine**

		Wernicke 2006)		
		N= 14 n= 5258 (Arnold 2004, Arnold 2005, Arnold 2010, Arnold 2012, Brecht 2007, Chappell 2008, Gao 2010, Gaynor 2011a, Gaynor 2011b, Raskin 2005, Rowbotham 2012, Tesfaye 2013, Wernicke 2006, Yasuda 2010)	Adverse events during first 12 weeks of treatment	Duloxetine: 2033/2796 Placebo: 1530/2462 I^2= 9% **RR 1.15 (1.11 to 1.20)** **SS more adverse events with duloxetine**
		N= 17 n= 6285 (Arnold 2004, Arnold 2005, Arnold 2010, Arnold 2012, Brecht 2007, Chappell 2008, Gao 2010,	Adverse events leading to cessation	Duloxetine: 447/3540 Placebo:158/2745 I^2= 0% **RR 1.99 (1.67 to 2.37)** **SS more adverse events leading to cessation with duloxetine**

		Gaynor 2011a, Gaynor 2011b, Goldstein 2005, Raskin 2005, Rowbotham 2012, Russel 2008, Tesfaye 2013, Vranken 2011, Wernicke 2006, Yasuda 2010)		
		N= 14 n= 4976 (Arnold 2005, Arnold 2010, Arnold 2012, Brecht 2007, Chappell 2008, Gao 2010, Gaynor 2011a, Gaynor 2011b, Goldstein 2005, Raskin 2005, Russel 2008, Vranken 2011, Wernicke 2006, Yasuda 2010)	Serious adverse events	Duloxetine: 42/2785 Placebo: 39/2191 I^2= 0% RR 0.81 (0.53 to 1.25) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (risk of bias) As assessed by Lunn 2014
Arnold 2004(143)		fibromyalgia	12 weeks		RCT did not meet our inclusion criteria (population)
Arnold 2005(144)		fibromyalgia	12 weeks		RCT did not meet our inclusion criteria (population)
Arnold 2010(145)		fibromyalgia	24 weeks		RCT did not meet our inclusion criteria (population)
Arnold 2012(146)		fibromyalgia	12 weeks		RCT did not meet our inclusion criteria (population)
Brecht 2007(147)		Major depressive disorder	8 weeks		RCT did not meet our inclusion criteria (population)
Chappell 2008(148)		fibromyalgia	26 weeks		RCT did not meet our inclusion criteria (population)
Gao 2010(149)	215	PDN	12 weeks	Duloxetine 60 mg daily placebo	RANDO: Unclear (method not described) ALLOCATION CONC: low BLINDING : Low INCOMPLETE OUTCOME DATA: Low SELECTIVE REPORTING: Low OTHER BIAS:

					Low
Gaynor 2011a(150)		Major depressive disorder	8 weeks		RCT did not meet our inclusion criteria (population)
Gaynor 2011b(151)		Major depressive disorder	8 weeks		RCT did not meet our inclusion criteria (population)
Goldstein 2005(152)	457	PDN	8 weeks	Duloxetine 20, 60 or 120 mg daily placebo	RANDO: low ALLOCATION CONC: low BLINDING : Low INCOMPLETE OUTCOME DATA: High (dropout 25% and significantly more in the higher dose treatment groups) SELECTIVE REPORTING: Unclear OTHER BIAS: Low
Raskin 2005(153)	348	PDN	12 weeks	Duloxetine 60 or 120 mg daily placebo	RANDO: low ALLOCATION CONC: low BLINDING : Low INCOMPLETE OUTCOME DATA: Low SELECTIVE REPORTING: Low OTHER BIAS: Low
Rowbotham 2012(154)	108	PDN	8 weeks	ABT-894 1 mg, 2 mg, 4 mg daily	RANDO: low

				Duloxetine 60 mg daily placebo	ALLOCATION CONC: low BLINDING : Low INCOMPLETE OUTCOME DATA: Low SELECTIVE REPORTING: Low OTHER BIAS: Low
Russel 2008(155)		fibromyalgia	26 weeks		RCT did not meet our inclusion criteria (population)
Tesfaye 2013(156)	401	PDN	8 weeks	Pregabalin 150 mg 2x/day Duloxetine 60 mg 1x/day Placebo	RANDO: low ALLOCATION CONC: Unclear (method not described) BLINDING : Low INCOMPLETE OUTCOME DATA: Unclear (dropout 17%, 9% with adverse events; no statement as to whether LOCF or BOCF was used) SELECTIVE REPORTING: High (partial reporting of some outcomes, differences of reporting between phase II and phase III) OTHER BIAS: High: Designed, interpreted, written and submitted by Lilly. Ghost written by professional writer for company.
Vranken 2011(157)	48	Central neuropathic pain	8 weeks		RCT did not meet our inclusion criteria (sample size)

Wernicke 2006(158)	334	PDN	12 weeks	Duloxetine 60 or 120 mg daily placebo	RANDO: low ALLOCATION CONC: low BLINDING : Low INCOMPLETE OUTCOME DATA: High (dropout 25%, 30% and 21% in duloxetine 60 mg, 120 mg, and placebo groups respectively) SELECTIVE REPORTING: Unclear (modified ITT) OTHER BIAS: Low
Yasuda 2010(159)	339	PDN	12 weeks	Duloxetine 40 or 60 mg daily placebo	RANDO: low ALLOCATION CONC: Unclear (method not described) BLINDING : Unclear (method not described) INCOMPLETE OUTCOME DATA: Low SELECTIVE REPORTING: Low OTHER BIAS: Low

Author's conclusions
"There is adequate amounts of moderate quality evidence from eight studies performed by the manufacturers of duloxetine that doses of 60 mg and 120 mg daily are efficacious for treating pain in diabetic peripheral neuropathy but lower daily doses are not. Further trials are not required."

"Minor side effects are common and more common with duloxetine 60 mg and particularly with 120 mg daily, than 20 mg daily, but serious side effects are rare."

Duloxetine vs placebo for diabetic peripheral neuropathic pain

Study details	n/Population	Comparison	Outcomes		Methodological
RCT Gao 2015(160) Design: RCT DB PG Duration of follow-up: 12 weeks	n= 405 Mean age: 61y Other interventions for pain allowed during study: rescue treatment with paracetamol up to 3g/day was allowed. Episodic use of analgesic agents allowed for pain unrelated to diabetic neuropathy.	Duloxetine 60 mg/day Vs Placebo	Efficacy		RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (method not described) BLINDING : Participants: yes Personnel: yes Assessors: unclear Remarks on blinding method: Described as "double blind" FOLLOW-UP: Lost-to follow-up: 0.2% Drop-out and Exclusions: 14% • Described: yes • Balanced across groups: yes
			Pain severity reduction (PO) (0-10 no pain- worst pain)	Duloxetine: -2.40 Placebo: -1.97 **LS MD: -0.43 (-0.82 to -0.044)** **P=0.030** **SS in favour of duloxetine**	
			Safety		
			Patients with at least one adverse event	Duloxetine: 94 (46.5%) Placebo: 72 (35.6%) P= 0.034 **SS more patients with an adverse event with duloxetine**	

	<u>Inclusion</br></u>Age ≥18y Bilateral PDN <u>Exclusion</br></u>Any medical or other condition that could have compromised participation in the study (unstable glycemic control, major depressive disorder, anxiety disorders, alcohol or eating disorders, serious or unstable cardiovascular, hepatic, renal, respiratory illness, …)		Discontinuations because of adverse events	Duloxetine: 3 (1.5%) Placebo: 2 (1.0%) No statistical testing	ITT: Modified ITT: all randomised patients with a baseline and at least one postbaseline observation (for efficacy variables) SELECTIVE REPORTING: no Sponsor: Eli Lilly
			Serious adverse events	Duloxetine: 17 (8.4%) Placebo: 8 (4.0%) P: 0.097 NS	

15.14 Venlafaxine vs placebo for neuropathic pain

Meta-analysis: Cochrane Gallagher 2015(161)

Inclusion criteria: RCTs comparing venlafaxine with placebo or another active treatment in neuropathic pain in adults.
Search strategy: the Cochrane Central Register of Controlled Trials (CENTRAL) via The Cochrane Library, MEDLINE and EMBASE were searched up to August 2014.
Assessment of quality of included trials: yes

Remarks

Cochrane Gallagher found 5 RCTs that compared venlafaxine to placebo. Four RCTs did not meet our inclusion criteria (sample size and/or duration). No meta-analysis was performed. Only one RCT (Rowbotham 2004) did meet our inclusion criteria.

We will report RCT Rowbotham 2004 below.

Author's conclusions

"We found little compelling evidence to support the use of venlafaxine in neuropathic pain. While there was some third-tier evidence of benefit, this arose from studies that had methodological limitations and considerable risk of bias. Placebo effects were notably strong in several studies. Given that effective drug treatments for neuropathic pain are in current use, there is no evidence to revise prescribing guidelines to promote the use of venlafaxine in neuropathic pain. Although venlafaxine was generally reasonably well tolerated, there was some evidence that it can precipitate fatigue, somnolence, nausea, and dizziness in a minority of people."

Venlafaxine versus placebo in painful diabetic neuropathy

Study details	n/Population	Comparison	Outcomes	Methodological
	n= 244		Efficacy	RANDO:

Rowbotham 2004(162) Design: RCT (DB, PG) Duration of follow-up: 6 weeks	Mean age: 58-60 y Other interventions for pain allowed during study: Tramadol was prohibited during study; Other opioids and analgesics were allowed within the limit of 1 dose of 1 type of analgesic per day.	Venlafaxine extended release 75 mg or Venlafaxine extended release 150-225 mg Vs Placebo	VAS-Pain Intensity reductions (PO)	Venlafaxine XR 75 mg: 22.4 mm Venlafaxine XR 150-225 mg: 33.8 mm Placebo : 18.7 mm Venlafaxine 75 vs placebo NS **Venlafaxine 150-225 vs placebo** **P<0.001** **SS in favour of venlafaxine 150-255** **Venlafaxine 75 vs Venlafaxine 150-225** **P=0.006** **SS in favour of venlafaxine 150-255**	Unclear (method not described) ALLOCATION CONC: Unclear (no described) BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Drop-out and Exclusions: 17% • Described: yes • Balanced across groups: unclear (12 drop-outs in both placebo and venla 75 groups, 18 in venla 150/225)

	<u>Inclusion</u> Painful diabetic neuropathy Metabolically stable type 1 or 2 diabetes mellitus Age ≥18 y Baseline pain >40 mm on VAS-pain intensity scale <u>Exclusion</u> Presence of clinically important psychiatric disorders or recent drug or alcohol abuse; Major depressive disorder within 6 months of study initiation; Clinically significant comorbidity or clinically significant laboratory or physical examination results.		VAS-Pain relief (PO)	Venlafaxine XR 75 mg: 51.0 mm Venlafaxine XR 150-225 mg: 59.9 mm Placebo : 43.6 mm Venlafaxine 75 vs placebo NS **Venlafaxine 150-225 vs placebo** **P<0.001** **SS in favour of venlafaxine 150-255** Venlafaxine 75 vs Venlafaxine 150-225 P=0.07 NS	ITT: Modified ITT: All randomized participants who received at least 1 dose of assigned treatment and had a baseline evaluation and at least 1 score during therapy or within 3 days of the last dose. SELECTIVE REPORTING: unclear: not all quantitative data clearly reported Other important methodological remarks : On study completion or discontinuation, medication was tapered for up to 2 weeks. Last observation carried forward analysis. Sponsor: Wyeth
			Safety		
			Treatment-emergent adverse events	Venlafaxine XR 75 mg: 88% Venlafaxine XR 150-225 mg: 89% Placebo : 75% NS	
			Serious adverse events	Venlafaxine XR 75 mg: 9% Venlafaxine XR 150-225 mg: 12% Placebo : 10% NS	

			Adverse events leading to study withdrawal	Venlafaxine XR 75 mg: 7% Venlafaxine XR 150-225 mg: 10% Placebo : 4% NS between 3 groups	

15.15 Direct comparisons of antidepressants for neuropathic pain

Meta-analysis: Cochrane Moore 2015(131) "Amitriptyline for neuropathic pain in adults"

Inclusion criteria: double blind RCTs, ≥4 weeks duration, comparing amitriptyline to placebo or an active comparator, for neuropathic pain. Excluded were studies using amitriptyline to treat pain resulting from the use of other drugs.
Search strategy: CENTRAL, MEDLINE, and EMBASE were searched up to March 2015.
Assessment of quality of included trials: yes

Remarks

SR Moore 2015 found one RCT comparing amitriptyline to nortriptyline. It did not meet our inclusion criteria (sample size).
SR Moore 2015 found one RCT comparing amitriptyline to duloxetine. It did not meet our inclusion criteria (sample size).
SR Moore 2015 did not find RCTs comparing amitriptyline to venlafaxine.

Meta-analysis: Cochrane Derry 2015(141)

Inclusion criteria: double-blind RCTs comparing nortriptyline with placebo or another active treatment in adults with chronic neuropathic pain.
Search strategy: the Cochrane Central Register of Controlled Trials (CENTRAL),MEDLINE, and EMBASE were searched up until January 2015.
Assessment of quality of included trials: yes

Remarks

Cochrane Derry 2015 found 1 RCT comparing nortriptyline to amitriptyline. It did not meet our inclusion criteria (sample size & duration).

Meta-analysis: Cochrane Lunn 2014(142) "Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia"

Inclusion criteria: randomised or quasi-randomised trials of duloxetine for the treatment of painful peripheral neuropathy or chronic pain in adults.
Search strategy: The Cochrane Neuromuscular Group Specialized Register, CENTRAL, DARE, HTA, NHSEED,MEDLINE, and EMBASE were searched up to November 2013.
Assessment of quality of included trials: yes

Remarks

Cochrane Lunn(142) found one RCT comparing duloxetine to amitriptyline: Kaur 2011. We will report this RCT below.

No RCTs comparing duloxetine to nortriptyline or venlafaxine were found.

Remarks
Cochrane Gallagher 2015(161) found no RCTs that compared venlafaxine to nortriptyline, amitriptyline or duloxetine.

Duloxetine vs amitriptyline for painful diabetic neuropathy

Study details	n/Population	Comparison	Outcomes		Methodological
Kaur 2011(163) Design: RCT DB, CO	n= 65 randomized Mean age: 53 y Previous pain intervention: pregabalin 20%, amitriptyline 8%, duloxetine 2%, gabapentin 2%	Duloxetine (20, 40 or 60 mg 1x/day) Vs Amitriptyline (10, 25 or 50 mg 1x/day) Assessments every 2 weeks	Efficacy		RANDO: Adequate ALLOCATION CONC: Unclear (unclear, method not described) BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: % Drop-out and Exclusions: 11% • Described: no
			Overall pain relief >30%	Duloxetine: 64% Amitriptyline: 62% NS difference	
			Overall pain relief >50%	Duloxetine: 59% Amitriptyline: 55% NS difference	
			Safety		
			Treatment-emergent adverse events	Duloxetine: 112 Amitriptyline: 111 No statistical test	

Duration of follow-up: Crossover: 2 x 6 weeks with 2 weeks wash-out	Other interventions for pain allowed during study: paracetamol 3 g/day as a rescue medication; no other pain medication allowed <u>Inclusion</u> Age between 18-75y Stable glucose-lowering medications Painful diabetic neuropathy at least 1 month <u>Exclusion</u> Clinically significant or unstable medical or psychiatric illnesses; Other causes of neuropathy Pregnancy or lactation	with optional uptitration	Moderate to severe treatment-emergent adverse events	Duloxetine: 24% Amitriptyline: 51% **P<0.01** **SS more moderate to severe treatment-emergent adverse events with amitriptyline**	• Balanced across groups: unclear ITT: Modified ITT: patients who received at least one dose of randomized study medication and had at least one postbaseline efficacy assessment. SELECTIVE REPORTING: yes; limited quantitative reporting of results/ analyses; unclear what primary endpoint result was Other important methodological remarks: 2-week run-in during which patients were withdrawn from any existing medication for PDN Sponsor: unclear Free samples provided by Wockhardt Limited andSun Pharmaceutical Industries Limited

15.16 Pregabaline vs placebo for neuropathic pain

Meta-analysis: Cochrane Derry 2019(164) "Pregabalin for neuropathic pain in adults"

Inclusion criteria: double-blind RCTs; of pregabalin compared to placebo or active comparator, in adults with one or more chronic neuropathic conditions and at least moderate pain intensity at baseline.
Search strategy: CENTRAL, MEDLINE, and Embase were searched from January 2009 to April 2018 (update of previous Cochrane Review published in 2009)
Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result
Cochrane Derry 2019{Derry, 2019 #82 Design: SR+MA Search date: April 2018	Pregabalin 150 mg Vs placebo	N= 1 n= 180 (van Seventer 2006)	At least 30% pain intensity reduction	Pregabalin: 34/87 Placebo: 16/93 I^2= not applicable **RR 2.27 (1.35 to 3.81)** **SS in favour of pregabalin**
		N= 4 n= 699 (1008-030, Ogawa 2010, Sabatowski 2004, van Seventer 2006)	At least 50% pain intensity reduction Postherpetic neuralgia	Pregabalin: 83/339 Placebo: 45/360 I^2= 42% **RR 1.96 (1.41 to 2.74**) **SS in favour of pregabalin**
		N= 2 n= 359	At least 50% pain intensity reduction Painful diabetic neuropathy	Pregabalin: 48/178 Placebo: 42/181 I^2= 0%

		(Richter 2005, Tölle 2008)		RR 1.14 (0.80 to 1.63) NS
		N= 6 n= 1058 (1008-030, Ogawa 2010, Sabatowski 2004, van Seventer 2006, Richter 2005, Tölle 2008)	Withdrawal because of adverse event	Pregabalin: 34/517 Placebo: 31/541 I^2= 0% RR 1.15 (0.72 to 1.83) NS
		N= 1 n= 185 (Ogawa 2010)	Participants experiencing any adverse event	Pregabalin: 65/87 Placebo: 62/98 I^2= not applicable RR 1.18 (0.97 to 1.43) NS
		N= 3 n= 542 (Ogawa 2010, Sabatowski 2004, Tölle 2008)	Participants experiencing any serious adverse event	Pregabalin: 11/267 Placebo: 11/275 I^2= 28% RR 1.03 (0.45 to 2.38) NS
		N= 5 n= 886 (Ogawa 2010, Sabatowski 2004, van Seventer 2006,	Somnolence	Pregabalin: 48/433 Placebo: 23/453 I^2= 0% **RR 2.22 (1.38 to 3.57)** **SS more participants with somnolence with pregabalin**

		Richter 2005, Tölle 2008)		
		N= 5 n= 886 (Ogawa 2010, Sabatowski 2004, van Seventer 2006, Richter 2005, Tölle 2008)	Dizziness	Pregabalin: 45/433 Placebo: 32/453 I^2=2% RR 1.48 (0.97 to 2.27) NS

* Characteristics of included studies: see below

Ref	Comparison	N/n	Outcomes	Result
Cochrane Derry 2019{Derry, 2019 #82 Design: SR+MA Search date: April 2018	Pregabalin 300 mg Vs placebo	N= 3 n= 589 (Liu 2017, Stacey 2008, van Seventer 2006)	At least 30% pain intensity reduction Postherpetic neuralgia	Pregabalin: 149/297 Placebo: 72/292 I^2= 0% **RR 2.05 (1.63 to 2.57)** **SS in favour of pregabalin**
		N= 8 n= 2320 (A0081071, Lesser 2004, Mu 2018, Raskin 2016, Rauck 2013, Smith 2014, Vinik 2014, Ziegler 2015)	At least 30% pain intensity reduction Painful diabetic neuropathy	Pregabalin: 514/1105 Placebo: 510/1215 I^2= 54% **RR 1.11 (1.01 to 1.21)** **SS in favour of pregabalin**
		N= 4	At least 50% pain intensity reduction	Pregabalin: 114/351

		n= 713 (Ogawa 2010, Sabatowski 2004, Stacey 2008, van Seventer 2006)	Postherpetic neuralgia	Placebo: 47/362 I^2=0% **RR 2.52 (1.86 to 3.42)** **SS in favour of pregabalin**
		N= 11 n= 2931 (A0081071, Lesser 2004, Mu 2018, Raskin 2016, Rauck 2013, Rosenstock 2004, Satoh 2011, Smith 2014, Tölle 2008, Vinik 2014, Ziegler 2015)	At least 50% pain intensity reduction Painful diabetic neuropathy	Pregabalin: 434/1415 Placebo: 358/1516 I^2=48% **RR 1.30 (1.15 to 1.46)** **SS in favour of pregabalin**
		N= 18 n= 4317 (Liu 2017, Ogawa 2010, Sabatowski 2004, Stacey 2008, van Seventer 2006, A0081071, Huffman 2015, Lesser 2004,	Withdrawal because of adverse event	Pregabalin: 199/2133 Placebo: 112/2148 I^2= 0% **RR 1.86 (1.49 to 2.33)** **SS more withdrawals because of advere events with pregabalin**

		Mu 2018, NCT00785577, Raskin 2016, Rauck 2013, Rosenstock 2004, Satoh 2011, Smith 2014, Tölle 2008, Vinik 2014, Ziegler 2015)		
		N= 15 n= 3697 (A0081071, A9011015, Holbech 2015, Huffman 2015, Liu 2017, Mu 2018, NCT00785577, Ogawa 2010, Raskin 2016, Rauck 2013, Rosenstock 2004, Satoh 2011, Smith 2014, Stacey 2008, Ziegler 2015)	Participants experiencing any adverse event	Pregabalin: 1085/1811 Placebo: 954/1886 I^2= 44% **RR 1.21 (1.15 to 1.28)** **SS more participants experiencing an adverse event with pregabalin**

		N= 17 n= 4112 (A0081071, A9011015, Huffman 2015, Lesser 2004, Liu 2017, Mu 2018, NCT00785577, Ogawa 2010, Raskin 2016, Rauck 2013, Sabatowski 2004, Satoh 2011, Smith 2014, Stacey 2008, Tölle 2008, Vinik 2014, Ziegler 2015)	Participants experiencing any serious adverse event	Pregabalin: 61/1979 Placebo: 54/2133 I^2= 0% RR 1.19 (0.83 to 1.70) NS
		N= 17 n= 4248 (Liu 2017, Ogawa 2010, Sabatowski 2004, Stacey 2008, van Seventer 2006, A0081071, Huffman 2015, Lesser 2004, Mu 2018,	Somnolence	Pregabalin: 245/2048 Placebo: 79/2200 I^2= 0% **RR 3.34 (2.62 to 4.26)** **SS more participants with somnolence with pregabalin**

		NCT00785577, Raskin 2016, Rauck 2013, Rosenstock 2004, Satoh 2011, Smith 2014, Tölle 2008, Vinik 2014)		
		N= 17 n= 4248 (Liu 2017, Ogawa 2010, Sabatowski 2004, Stacey 2008, van Seventer 2006, A0081071, Huffman 2015, Lesser 2004, Mu 2018, NCT00785577, Raskin 2016, Rauck 2013, Rosenstock 2004, Satoh 2011, Smith 2014, Tölle 2008, Vinik 2014)	Dizziness	Pregabalin: 348/2048 Placebo: 104/2200 I^2= 0% **RR 3.53 (2.86 to 4.35)** **SS more participants with dizziness with pregabalin**

* Characteristics of included studies: see below

Ref	Comparison	N/n	Outcomes	Result
Cochrane Derry 2019{Derry, 2019 #82 Design: SR+MA Search date: April 2018	Pregabalin 600 mg Vs placebo	N= 3 n= 546 (Dworkin 2003, Stacey 2008, van Seventer 2006)	At least 30% pain intensity reduction Postherpetic neuralgia	Pregabalin: 167/270 Placebo: 65/267 I^2= 0% **RR 2.53 (2.01 to 3.18)** **SS in favour of pregabalin**
		N= 3 n= 789 (A0081071, Guan 2011, Lesser 2004)	At least 30% pain intensity reduction Painful diabetic neuropathy	Pregabalin: 277/439 Placebo: 164/350 I^2=75% **RR 1.33 (1.16 to 1.51)** **SS in favour of pregabalin**
		N= 4 n= 1367 (A0081279, Freynhagen 2005, Moon 2010, van Seventer 2010)	At least 30% pain intensity reduction Mixed neuropathic pain	Pregabalin: 402/834 Placebo: 192/533 I^2= 68% **RR 1.24 (1.08 to 1.43)** **SS in favour of pregabalin**
		N= 3 n= 562 (Cardenas 2013, Kim 2011, Siddall 2006)	At least 30% pain intensity reduction Central neuropathic pain	Pregabalin: 125/282 Placebo: 77/280 I^2= 60% **RR 1.62 (1.28 to 2.03)** **SS in favour of pregabalin**
		N= 2 n= 664	At least 30% pain intensity reduction HIV neuropathy	Pregabalin: 172/322 Placebo: 182/342

		(A0081244, Simpson 2010)		I^2= 0% RR 1.00 (0.87 to 1.16) NS
		N= 4 n= 732 (Dworkin 2003, Ogawa 2010, Stacey 2008, van Seventer 2006)	At least 50% pain intensity reduction Postherpetic neuralgia	Pregabalin: 151/367 Placebo: 56/365 I^2= 22% **RR 2.66 (2.04 to 3.48)** **SS in favour of pregabalin**
		N= 7 n= 1360 (1008-040, A0081071, Arezzo 2008, Lesser 2004, Richter 2005, Satoh 2011, Tölle 2008)	At least 50% pain intensity reduction Painful diabetic neuropathy	Pregabalin: 263/630 Placebo: 185/730 I^2= 66% **RR 1.61 (1.37 to 1.88)** **SS in favour of pregabalin**
		N= 4 n= 1367 (A0081279, Freynhagen 2005, Moon 2010, van Seventer 2010)	At least 50% pain intensity reduction Mixed neuropathic pain	Pregabalin: 287/834 Placebo: 109/533 I^2= 42% **RR 1.51 (1.23 to 1.85)** **SS in favour of pregabalin**
		N= 3 n= 562	At least 50% pain intensity reduction Central neuropathic pain	Pregabalin: 72/282 Placebo: 43/280

		(Cardenas 2013, Kim 2011, Siddal 2006)		I^2= 42% **RR 1.67 (1.19 to 2.34)** **SS in favour of pregabalin**
		N= 2 n= 674 (A0081244, Simpson 2010)	At least 50% pain intensity reduction HIV neuropathy	Pregabalin: 109/332 Placebo: 130/342 I^2= 0% RR 0.86 (0.70 to 1.06) NS
		N= 21 n= 5024 (Dworkin 2003, Ogawa 2010, Stacey 2008, van Seventer 2006, 1008-040, A0081071, Arezzo 2008, Guan 2011, Lesser 2004, Richter 2005, Satoh 2011, Tölle 2008, A0081279, Freyhagen 2005, Moon 2010, van Seventer 2010, Cardenas	Withdrawal because of adverse event	Pregabalin: 300/2666 Placebo: 119/2358 I^2= 51% **RR 2.18 (1.78 to 2.68)** **SS more withdrawals because of an adverse event with pregabalin**

		2013, Kim 2011, Siddal 2006, A0081244, Simpson 2010)		
		N= 15 n= 3963 (A0081071, A0081244, A0081279, Cardenas 2013, Dworkin 2003, Freynhagen 2005, Guan 2011, Kim 2011, Moon 2010, Ogawa 2010, Satoh 2011, Siddall 2006, Simpson 2010, Stacey 2008, van Seventer 2010)	Participants experiencing any adverse event	Pregabalin: 1475/2142 Placebo: 1030/1821 I^2= 55% **RR 1.30 (1.24 to 1.37)** **SS more participants experiencing an adverse event with pregabalin**
		N= 16 n= 3995 (A0081071, A0081244, A0081279, Arezzo 2008, Cardenas	Participants experiencing any serious adverse event	Pregabalin: 70/2045 Placebo: 66/1950 I^2= 11% RR 1.07 (0.77 to 1.48) NS

		2013, Guan 2011, Kim 2011, Lesser 2014, Moon 2010, Ogawa 2010, Satoh 2011, Siddall 2006, Simpson 2010, Stacey 2008, Tölle 2008, van Seventer 2010)		
		N= 20 n= 4856 (Dworkin 2003, Ogawa 2010, Stacey 2008, van Seventer 2006, A0081071, Arezzo 2008, Guan 2011, Lesser 2004, Richter 2005, Satoh 2011, Tölle 2008, A0081279, Freyhagen 2005, Moon 2010, van Seventer 2010, Cardenas	Somnolence	Pregabalin: 443/2579 Placebo: 118/2277 I^2= 0% **RR 3.68 (3.02 to 4.47)** **SS more participants with somnolence with pregabalin**

		2013, Kim 2011, Siddal 2006, A0081244, Simpson 2010)		
		N= 21 n= 5240 (Dworkin 2003, Ogawa 2010, Stacey 2008, van Seventer 2006, A0081071, Arezzo 2008, Guan 2011, Huffman 2015, Lesser 2004, Richter 2005, Satoh 2011, Tölle 2008, A0081279, Freyhagen 2005, Moon 2010, van Seventer 2010, Cardenas 2013, Kim 2011, Siddal 2006, A0081244, Simpson 2010)	Dizziness	Pregabalin: 659/2777 Placebo: 152/2463 I^2= 68% **RR 3.95 (3.34 to 4.68)** **SS more participants with dizziness with pregabalin**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (risk of bias) As assessed by Derry 2019
1008-030(165)	256		5 weeks		RCT did not meet our inclusion criteria (duration)
1008-040(166)	256	Painful diabetic neuropathy	6 weeks	Pregabalin 600 mg Amitriptyline 75 mg Placebo	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (method not described) BLINDING : Unclear (method not described) INCOMPLETE OUTCOME DATA: Unclear (imputation method not described- probably LOCF)
A0081071(167)	456	Painful diabetic neuropathy	14 weeks	Pregabalin 300 mg Pregabalin 600 mg Placebo	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (method not described) BLINDING : low INCOMPLETE OUTCOME DATA: Unclear (imputation LOCF)
A0081244(168)	375	HIV neuropathy	17 weeks	Pregabalin to 450 mg daily Placebo	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (method not described) BLINDING : low INCOMPLETE OUTCOME DATA: Unclear (imputation LOCF/modified BOCF)

A0081279(169)	539	Post-traumatic peripheral neuropathic pain	16 weeks	Pregabalin 150 to 600 mg daily Placebo	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (method not described) BLINDING : Unclear (not reported) INCOMPLETE OUTCOME DATA: low (BOCF for particpants who discontinued due to adverse events or lack of efficacy)
A9011015(170)	31				RCT did not meet our inclusion criteria (sample size)
Arezzo 2008(171)	167	Painful diabetic neuropathy	13 weeks	Pregabalin 600 mg daily Placebo	RANDO: low ALLOCATION CONC: low BLINDING : low INCOMPLETE OUTCOME DATA: Unclear (not clearly stated)
Cardenas 2013(172)	219	Spinal cord injury	17 weeks	Pregabalin 150 to 600 mg daily Placebo	RANDO: low ALLOCATION CONC: low BLINDING : low INCOMPLETE OUTCOME DATA: Unclear (modified BOCF for mean pain score, LOCF for other analyses)
Dworkin 2003(173)	173	Postherpetic neuropathy	9 weeks	Pregabalin 600 mg daily Placebo	RANDO: low ALLOCATION CONC: low

					BLINDING : low INCOMPLETE OUTCOME DATA: Unclear (LOCF imputation and large difference in withdrawals between groups)
Freynhagen 2005(174)	338	Chronic neuropathic pain (PHN, PDN)	12 weeks	Pregabalin flexible dose Placebo	RANDO: Unclear (method not reported) ALLOCATION CONC: Unclear (method not reported) BLINDING : low INCOMPLETE OUTCOME DATA: Unclear (method not reported)
Guan 2011(175)	309	PDN	8 weeks	Pregabalin up to 600 mg daily Placebo	RANDO: Unclear (method not reported) ALLOCATION CONC: Unclear (method not reported) BLINDING : low INCOMPLETE OUTCOME DATA: Unclear (LOCF imputation)
Holbech 2015(176)	69		Crossover 4x5 weeks		RCT did not meet our inclusion criteria (duration)
Huffman 2015(177)	203	PDN	Crossover 2x6 weeks	Pregabalin 150 to 300mg daily Placebo	RANDO: low ALLOCATION CONC: Unclear (method not reported) BLINDING : low INCOMPLETE OUTCOME DATA: Unclear (LOCF imputation)

Kim 2011(178)	219	Central post-stroke pain	14 weeks	Pregabalin 150 to 600 mg daily Placebo	RANDO: low ALLOCATION CONC: low BLINDING : low INCOMPLETE OUTCOME DATA: Unclear (LOCF imputation)
Lesser 2004(179)	337		5 weeks		RCT did not meet our inclusion criteria (duration)
Liu 2017(180)	220	PHN	9 weeks	Pregabalin 300 mg daily Placebo	RANDO: low ALLOCATION CONC: low BLINDING : low INCOMPLETE OUTCOME DATA: Unclear (LOCF imputation)
Moon 2010(181)	240	Peripheral neuropathic pain Post-traumatic neuropathic pain	10 weeks	Pregabalin 150 to 600 mg daily Placebo	RANDO: low ALLOCATION CONC: low BLINDING : low INCOMPLETE OUTCOME DATA: Unclear (LOCF imputation)
Mu 2018(182)	623	PDN	10 weeks	Pregabalin 300 mg daily Placebo	RANDO: low ALLOCATION CONC: low BLINDING : low INCOMPLETE OUTCOME DATA:

					Unclear (LOCF imputation)
NCT00785577(183)	273	PDN	6 weeks	Pregabalin 300 mg daily Placebo	RANDO: Unclear (method not reported) ALLOCATION CONC: Unclear (method not reported) BLINDING : low INCOMPLETE OUTCOME DATA: Unclear (method not reported)
Ogawa 2010(184)	371	PDN	13 weeks	Pregabalin 150 mg daily Pregabalin 300 mg daily Pregabalin 600 mg daily Placebo	RANDO: Unclear (method not reported) ALLOCATION CONC: Unclear (method not reported) BLINDING : Unclear (method not reported) INCOMPLETE OUTCOME DATA: Unclear (LOCF and between group differences in withdrawal)
Raskin 2016(185)	301	PDN	Crossover 2x6weeks	Pregabalin 150 to 300 mg daily Placebo	RANDO: Unclear (method not reported) ALLOCATION CONC: Unclear (method not reported) BLINDING : Unclear (method not reported) INCOMPLETE OUTCOME DATA: Unclear (LOCF)
Rauck 2013(186)	420	PDN	14 weeks	Pregabalin 300 mg daily Gabapentin 1200 mg daily Gabapentin 2400 mg daily Gabapentin 3600 mg daily Placebo	RANDO: low ALLOCATION CONC: Unclear (method not reported) BLINDING : low INCOMPLETE OUTCOME DATA:

					Unclear (LOCF)
Richter 2005(187)	246	PDN	6 weeks	Pregabalin 150 mg daily Pregabalin 600 mg daily Placebo	RANDO: low ALLOCATION CONC: Unclear (method not reported) BLINDING : low INCOMPLETE OUTCOME DATA: Unclear (patients with missing data excluded from analysis)
Rosenstock 2004(188)	146	PDN	8 weeks	Pregabalin 300 mg daily Placebo	RANDO: low ALLOCATION CONC: low BLINDING : Unclear (method not reported) INCOMPLETE OUTCOME DATA: Unclear (method not reported)
Sabatowski 2004(189)	238	PHN	8 weeks	Pregabalin 150 mg daily Pregabalin 300 mg daily Placebo	RANDO: low ALLOCATION CONC: Unclear (method not reported) BLINDING : low INCOMPLETE OUTCOME DATA: Unclear (method not reported)
Satoh 2011(190)	314	PDN	13 weeks	Pregabalin 300 mg daily Pregabalin 600 mg daily Placebo	RANDO: low ALLOCATION CONC: Unclear (method not reported) BLINDING : Unclear (method not reported) INCOMPLETE OUTCOME DATA:

					Unclear (LOCF)
Siddal 2006(191)	137	Spinal cord injury	12 weeks	Pregabalin up to 600 mg daily Placebo	RANDO: low ALLOCATION CONC: low BLINDING : low INCOMPLETE OUTCOME DATA: Unclear (LOCF)
Simpson 2010(192)	302	HIV neuropathy	14 weeks	Pregabalin150 to 300 mg daily Placebo	RANDO: low ALLOCATION CONC: low BLINDING : low INCOMPLETE OUTCOME DATA: Unclear (LOCF)
Smith 2014(193)	386	PDN	15 weeks	Pregabalin 300 mg daily Carisbamate 800 mg daily Carisbamate 1200 mg daily Placebo, n = 95	RANDO: Unclear (method not reported) ALLOCATION CONC: Unclear (method not reported) BLINDING : low INCOMPLETE OUTCOME DATA: Unclear (LOCF)
Stacey 2008(194)	269	PHN	4 weeks	Pregabalin flexible dose (150 to 600 mg daily) pregabalin 300 mg Placebo	RCT did not meet our inclusion criteria (duration)
Tölle 2008(195)	395	PDN	12 weeks	Pregabalin 150 mg daily Pregabalin 300 mg daily Pregabalin 600 mg daily Placebo	RANDO: Unclear (method not reported) ALLOCATION CONC: Unclear (method not reported)

					BLINDING : Unclear (method not reported) INCOMPLETE OUTCOME DATA: Unclear (method not reported)
van Seventer 2006(196)	368	PHN	13 weeks	Pregabalin 150 mg daily Pregabalin 300 mg daily Pregabalin 600 mg daily Placebo	RANDO: Unclear (method not reported) ALLOCATION CONC: Unclear (method not reported) BLINDING : Unclear (method not reported) INCOMPLETE OUTCOME DATA: Unclear (method not reported)
van Seventer 2010(197)	254	Post-traumatic peripheral neuropathic pain	8 weeks	Pregabalin 150 to 600 mg daily Placebo	RANDO: low ALLOCATION CONC: low BLINDING : low INCOMPLETE OUTCOME DATA: Unclear (method not reported)
Vinik 2014(198)	452		5 weeks		RCT did not meet our inclusion criteria (duration)
Ziegler 2015(199)	194	PDN	6 weeks	Pregabalin 300 mg daily ABT-639 200 mg daily Placebo	RANDO: low ALLOCATION CONC: low BLINDING : low INCOMPLETE OUTCOME DATA: Unclear (missing data not imputed)

Author's conclusions
"Evidence shows efficacy of pregabalin in postherpetic neuralgia, painful diabetic neuralgia, and mixed or unclassified post-traumatic neuropathic pain, and absence of efficacy in HIV neuropathy; evidence of efficacy in central neuropathic pain is inadequate. Some people will derive substantial benefit with pregabalin; more will havemoderate benefit, butmany will have no benefit or will discontinue treatment."

Pregabalin vs placebo for post-traumatic peripheral neuropathic pain

Study details	n/Population	Comparison	Outcomes		Methodological
Markman 2018(200) Design: RCT DB PG Duration of follow-up:	n= 542 randomized 539 analysed Mean age: 53y Other interventions for pain allowed during study: prohibited medications included opioids, local anesthetics, topical and intraspinal	Pregabalin (150, 300, 450 or 600 mg/day) (individualized titration) Vs placebo	Efficacy		RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (method not described) BLINDING : Participants: yes Personnel: unclear Assessors: unclear FOLLOW-UP: Lost-to follow-up: 3 % Drop-out and Exclusions: 15 % • Described: yes • Balanced across groups: unclear 15% pregabalin vs 20% placebo
			Pain (mean pain week 15) (PO)	pregabalin: -2.12 (-2.42 to -1.82) placebo: -1.90 (-2.21 to -1.60) MD -0.22 (0.54 to 0.10) P= 0.18 NS	
			Safety		
			Patients experiencing at least one adverse event	pregabalin: 50.4% placebo: 40.0%	
			Patients with serious adverse event	pregabalin: 0.7% placebo: 2.6%	

15 weeks	steroids, antiepileptics and antipsychotics; Allowed medications included NSAID, non-opioid analgesics, antidepressants, tramadol and triptans, sleep medication. Paracetamol ≤3g/day allowed as rescue medication <u>Inclusion</u> Age ≥18y Post-traumatic peripheral neuropathic pain for ≥6 monhs after a surgical or non-surgical traumatic event <u>Exclusion</u> Neuropathic pain due to postherpetic pain, diabetic peripheral neuropathy, complex regional pain		Discontinuations because of adverse events	pregabalin: 19.3% placebo: 6.0%	ITT: Modified ITT, defined as all randomized patients who received at least one dose of study drug SELECTIVE REPORTING:no Sponsor: Pfizer Inc.

	syndrome and other conditions; nonpharmacological treatments for pain; severe or acute medical or psychiatric conditions; clinically significant laboratory abnormalities				

15.17 Gabapentin vs placebo for neuropathic pain

Meta-analysis: Cochrane Wiffen 2017(201) "Gabapentin for chronic neuropathic pain in adults"
Inclusion criteria: RCTs comparing gabapentin and placebo or another active treatment for neuropathic pain, with participant-reported pain assessment.
Search strategy: CENTRAL, MEDLINE, and Embase were searched from January 2014 up until January 2017. (update of Cochrane review Moore 2014)
Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result
Cochrane Wiffen 2017(201) Design: SR+MA	Gabapentin Vs placebo	N= 7 n= 2031 (Backonja 2011, Gong 2008, Irving 2009, Rice 2001, Sang	Participant-reported pain intensity reduction of 50% or greater For postherpetic neuralgia	Gabapentin: 415/1252 Placebo: 146/779 I^2= 62% **RR 1.69 (1.46 to 2.00)** **SS in favour of gabapentin**

Search date: January 2017		2013, Wallace 2010, Zhang 2013)		
		N= 6 n= 1277 (Backonja 1998, CTR 945-1008, CTR 945-224, Perez 2000, Rauck 2013a, Sandercock 2012)	Participant-reported pain intensity reduction of 50% or greater For painful diabetic neuropathy	Gabapentin: 304/798 Placebo: 101/479 I^2=43% **RR 1.86 (1.53 to 2.27)** **SS in favour of gabapentin**
		N= 1 n= 305 (Serpell 2002)	Participant-reported pain intensity reduction of 50% or greater For mixed neuropathic pain	Gabapentin: 32/153 Placebo: 22/152 I^2= not applicable RR 1.45 (0.88 to 2.37) NS
		N= 18 n= 4279 (not reported)	Participants experiencing at least one adverse event	Gabapentin: 630/1000 Placebo: 490/1000 I^2= **RR 1.3 (1.2 to 1.4)** **SS more participants experiencing at least one adverse event with gabapentin**

		N= 22 n= 4346 (not reported)	Adverse event withdrawals	Gabapentin: 110/1000 Placebo: 82/1000 **RR 1.4 (1.1 to 1.7)** **SS more adverse event withdrawals with gabapentin**
		N= 19 n= 3948 (not reported)	Serious adverse events	Gabapentin: 32/1000 Placebo: 28/1000 RR 1.2 (0.8 to 1.7) NS
		Not calculated	Death	Gabapentin: 3/ max 3603 exposed Placebo: 5/ max 2377 exposed RR not calculated

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (risk of bias) As assessed by Wiffen 2017
Backonja 1998(202)	165	Painful diabetic neuropathy	8 weeks	Gabapentin 3600 mg /day (max) Vs placebo	RANDO: low ALLOCATION CONC: unclear (not reported) BLINDING : low INCOMPLETE OUTCOME DATA: unclear (LOCF imputation)

Backonja 2011(203)	102	Postherpetic neuralgia	3 weeks	Gabapentin 1200 mg /day (max) Vs placebo	RCT did not meet our inclusion criteria (duration)
CTR 945-1008(204)	389	Painful diabetic neuropathy	12 weeks	Gabapentin 3600 mg /day (max) Vs placebo	RANDO: unclear (not described) ALLOCATION CONC: unclear (not reported) BLINDING : low INCOMPLETE OUTCOME DATA: unclear (LOCF imputation)
CTR 945-224(205)	325	Painful diabetic neuropathy	7 weeks	Gabapentin 600 mg /day Gabapentin 1200 mg /day Gabapentin 2400 mg /day Vs placebo	RANDO: low ALLOCATION CONC: low BLINDING : low INCOMPLETE OUTCOME DATA: unclear (probably LOCF imputation)
Gong 2008(206)	231	Postherpetic neuralgia	6 weeks	Gabapentin 1800 mg /day Vs placebo	RANDO: unclear (unclear description) ALLOCATION CONC: unclear (unclear description) BLINDING : low INCOMPLETE OUTCOME DATA: high (reasons for withdrawal not given per treatment group; no information about how data from withdrawals contributed to analyses)
Irving 2009(207)	158	Postherpetic neuralgia	4 weeks	Gabapentin 1800 mg /day Vs	RCT does not meet our inclusion criteria (duration)

				placebo	
Perez 2000(208)	32	Painful diabetic neuropathy	12 weeks	Gabapentin 1200 mg /day Vs placebo	RCT does not meet our inclusion criteria (sample size)
Rauck 2013a(186)	421	Painful diabetic neuropathy	12 weeks	Gabapentin 1200 mg /day Gabapentin 2400 mg /day Gabapentin 3600 mg /day Pregabalin 300 mg/day Vs placebo	RANDO: low ALLOCATION CONC: low BLINDING : low INCOMPLETE OUTCOME DATA: unclear (LOCF imputation)
Rice 2001(209)	334	Postherpetic neuralgia	7 weeks	Gabapentin 1800 mg /day Gabapentin 2400 mg /day Vs placebo	RANDO: low ALLOCATION CONC: low BLINDING : low INCOMPLETE OUTCOME DATA: unclear (LOCF imputation
Sandercock 2012(210)	147	Painful diabetic neuropathy	4 weeks	Gabapentin 3000 mg /day Vs placebo	RCT does not meet our inclusion criteria (duration)
Sang 2013(211)	452	Postherpetic neuralgia	10 weeks	Gabapentin 1800 mg /day Vs placebo	RANDO: low ALLOCATION CONC: unclear (not described) BLINDING : low INCOMPLETE OUTCOME DATA: low (BOCF imputation)
Serpell 2002(212)	305	Mixed neuropathic pain	8 weeks	Gabapentin 2400 mg /day	RANDO: low

				Vs placebo	ALLOCATION CONC: low BLINDING : low INCOMPLETE OUTCOME DATA: unclear (imputation not mentioned)
Wallace 2010(213)	405	Postherpetic neuralgia	10 weeks	Gabapentin 1800 mg /day Vs placebo	RANDO: unclear (not described) ALLOCATION CONC: low BLINDING : low INCOMPLETE OUTCOME DATA: low (imputation is BOCF)
Zhang 2013(214)	371	Postherpetic neuralgia	12 weeks	Gabapentin 1200 mg /day Gabapentin 2400 mg /day Gabapentin 3600 mg /day Pregabalin 300 mg/day Vs placebo	RANDO: low ALLOCATION CONC: low BLINDING : low INCOMPLETE OUTCOME DATA: unclear (LOCF imputation)

Author's conclusions
"Gabapentin at doses of 1800 mg to 3600 mg daily (1200 mg to 3600 mg gabapentin encarbil) can provide good levels of pain relief to some people with postherpetic neuralgia and peripheral diabetic neuropathy. Evidence for other types of neuropathic pain is very limited."

15.18 Carbamazepine vs placebo for neuropathic pain

Meta-analysis: Cochrane Wiffen 2014(215) "Carbamazepine for chronic neuropathic pain and fibromyalgia in adults" Inclusion criteria: double blind RCTs comparing carbamazepine with placebo or active control, for the treatment of neuropathic pain or fibromyalgia in adults. Search strategy: MEDLINE, EMBASE and CENTRAL were searched up until February 2014. Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result
Cochrane Wiffen 2014(215) Design: SR+ MA Search date: February 2014	Carbamazepine Vs placebo	N= 4 n= 188 (Nicol 1969, Killian 1968, Rull 1969, Leijon 1989)	Any pain improvement	Carbamazepine: 56/92 Placebo: 9/96 I^2= 50% **RR 6.46 (3.43 to 12.17)** **SS in favour of carbamazepine**
		N= 4 n= 346 (Campbell 1966, Lechin 1989, Leijon 1989, Wilton 1974)	At least 1 adverse event	Carbamazepine: 113/173 Placebo: 47/173 I^2= 65% **RR 2.40 (1.85 to 3.12)** **SS greater proportion of participants with at least 1 adverse event**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (risk of bias) As assessed by Wiffen 2014

Campbell 1966(216)	77	Trigeminal neuralgia	8 weeks (assessment at 2 weeks)	Carbamazepine vs placebo Crossover study	RCT does not meet our inclusion criteria (duration)
Killian 1968(217)	42	Trigeminal neuralgia Postherpetic neuralgia	10 days treatment (open follow-up range 2 weeks- 36 weeks)	Carbamazepine vs placebo partial cross-over study	RCT does not meet our inclusion criteria (open follow-up)
Lechin 1989(218)	59	Trigeminal neuralgia	24 weeks (assessment at 8 weeks)	Carbamazepine vs pimozide Cross-over	RCT does not meet our inclusion criteria (comparison)
Leijon 1989(135)	15	Central post stroke pain	14 weeks (assessment at 4 weeks)	Carbamazepine vs amitriptyline Cross-over	RCT does not meet our inclusion criteria (sample size)
Nicol 1969(219)	64	Trigeminal neuralgia	Treatment 2-42 months; follow-up 46 months	Carbamazepine vs placebo Partial cross-over	RCT does not meet our inclusion criteria (sample size)
Rull 1969(220)	30	Painful diabetic neuropathy	6 weeks (assessment at 2 weeks)	Carbamazepine vs placebo cross-over	RCT does not meet our inclusion criteria (sample size)
Wilton 1974(221)	40	Diabetic neuropathy	4 weeks (assessment at 2 weeks)	Carbamazepine vs placebo cross-over	RCT does not meet our inclusion criteria (duration)

Remarks

Three additional RCTs were included in the quantitative analysis of this systematic review. None of the remaining RCTs met our inclusion criteria.

Author's conclusions
Carbamazepine is probably effective in some people with chronic neuropathic pain, but with caveats. No trial was longer than four weeks, had good reporting quality, nor used outcomes equivalent to substantial clinical benefit. In these circumstances, caution is needed in interpretation, and meaningful comparison with other interventions is not possible.

15.19 Direct comparisons of anticonvulsants for neuropathic pain

Meta-analysis: Cochrane Derry 2019(164) "Pregabalin for neuropathic pain in adults"

Inclusion criteria: double-blind RCTs; of pregabalin compared to placebo or active comparator, in adults with one or more chronic neuropathic conditions and at least moderate pain intensity at baseline.
Search strategy: CENTRAL, MEDLINE, and Embase were searched from January 2009 to April 2018 (update of previous Cochrane Review published in 2009)
Assessment of quality of included trials: yes

Remarks
SR Derry 2019 found one RCT comparing pregabalin vs gabapentin. It did not meet our inclusion criteria (duration). SR Derry 2019 found no RCTs comparing pregabalin vs carbamazepin.

Meta-analysis: Cochrane Wiffen 2017(201) “Gabapentin for chronic neuropathic pain in adults” Inclusion criteria: RCTs comparing gabapentin and placebo or another active treatment for neuropathic pain, with participant-reported pain assessment. Search strategy: CENTRAL, MEDLINE, and Embase were searched from January 2014 up until January 2017. (update of Cochrane review Moore 2014) Assessment of quality of included trials: yes

Remarks
SR Wiffen 2017 found one RCT comparing gabapentin to pregabalin. It did not meet our inclusion criteria (duration).

Meta-analysis: Cochrane Wiffen 2014(215) “Carbamazepine for chronic neuropathic pain and fibromyalgia in adults” Inclusion criteria: double blind RCTs comparing carbamazepine with placebo or active control, for the treatment of neuropathic pain or fibromyalgia in adults. Search strategy: MEDLINE, EMBASE and CENTRAL were searched up until February 2014. Assessment of quality of included trials: yes

Remarks
No RCTs that met our inclusion criteria, and comparing carbamazepine to pregabalin or gabapentin, were found.

15.20 Adjuvant analgesics in cancer pain

Meta-analysis: Huang 2019(222) “Comparative efficacy of therapeutics for chronic cancer pain: a Bayesian network meta-analysis”

Inclusion criteria: RCTs comparing any systematic pharmaceutical intervention and/or combination in treating chronic cancer pain.
Search strategy: MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were searched from 1970 to August 2018.
Assessment of quality of included trials: yes

Remarks

Two RCT’s comparing amitriptyline vs placebo were found. They did not meet our inclusion criteria (duration).

One RCT comparing duloxetine vs placebo was found. It did not meet our inclusion criteria (duration).

No RCTs were found directly comparing amitriptyline, duloxetine, nortriptyline or venlafaxine.

Two RCT’s comparing gabapentin vs placebo were found. They did not meet our inclusion criteria (duration).

Two RCT’s comparing pregabalin vs placebo were found. They did not meet our inclusion criteria (duration).

One RCT was found comparing gabapentin vs pregabalin. It did not meet our inclusion criteria (duration).

16 Appendix. Evidence tables. Topical analgesics

16.1 Topical diclofenac versus topical placebo for chronic musculoskeletal pain

Meta-analysis: Derry 2016(223) Cochrane review. Topical NSAIDs for chronic musculoskeletal pain in adults (review)

Inclusion criteria: Randomised, double-blind, active or inert carrier (placebo) controlled trials in which treatments were administered to adults with chronic musculoskeletal pain of moderate or severe intensity; studies examining participants with neuropathic pain or fibromyalgia were excluded.
Search strategy: The Cochrane Central Register of Controlled Trials (CENTRAL),MEDLINE, EMBASE, and their own in-house database was searched;
the date of the last search was February 2016. The references lists of included studies and reviews were also searched. Unpublished studies were sought by asking personal contacts and searching online clinical trial registers and manufacturers' web sites; studies that stringent quality criteria; at least 10 participants in each treatment arm; with application of treatment at least once daily
Assessment of quality of included trials: yes (GRADE)
ITT analysis: wherever possible
Other methodological remarks: /

Ref	Comparison	N/n	Outcomes	Result
Derry 2016 (223) Design: MA Search date: (Feb-2016)	Topical diclofenac gel/solution vs topical placebo	N= 4 n= 2342 (Altman 2009, Baer 2005, Baraf 2011, Roth 2004)	Clinical success (for example 50%reduction in pain)	60% vs 50% RR 1.20 (1.12 to 1.29) NNT 9.8 (7.1 to 16) SS in favour of diclofenac
		N= 13 n= 3658 (102-93-1, Altman 2009, Baer 2005, Baraf 2011, Bookman	Local adverse events	14% vs 7.8% RR 1.84 (1.54 to 2.21) NNH 16 (12 to 23) SS: more adverse events with diclofenac

		2004, Bruhlmann 2003, Dreiser 1993, Galeazzi 1993, Grace 1999, Niethard 2005, Roth 1995, Roth 2004, Simon 2009)		
		N= 7 n= 1266 (Bruhlmann 2003, Dreiser 1993, Galeazzi 1993, Grace 1999, Niethard 2005, Roth 2004, Simon 2009)	Systemic adverse events	RR 0.89 (0.59 to 1.34) NS
		N= 10 n= 3240 (Altman 2009, Baraf 2011, Bookman 2004, Bruhlmann 2003, Dreiser 1993, Galeazzi 1993, Grace 1999, Niethard 2005, Roth	Gastrointestinal adverse events	RR 1.10 (0.76 to 1.58) NS

		2004, Simon 2009)		
		N= 12 n= 3552 (108-97, Altman 2009, Baer 2005, Baraf 2011, Bookman 2004, Bruhlmann 2003, Dreiser 1993, Galeazzi 1993, Grace 1999, Niethard 2005, Roth 2004, Simon 2009)	Withdrawals due to adverse events	RR 1.55 (1.14 to 2.11) NNH 51 (30 to 170) SS: more withdrawals due to adverse events with diclofenac
		N= 11 n= 3455 (Altman 2009, Baer 2005, Baraf 2011, Bookman 2004, Bruhlmann 2003, Dreiser 1993, Galeazzi 1993, Grace 1999, Niethard 2005, Roth 2004, Simon 2009)	Withdrawals due to lack of efficacy	RR 0.59 (0.47 to 0.75) NNTp 26 (18 to 47) SS: less withdrawals due to lack of efficacy with diclofenac

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as judged by Cochrane)
102-93-1(224) R, DB, PC, parallel group	122	OA knee (diagnosed by standard radiological criteria and interview) with ≥ moderate pain within previous 2 weeks 2-week washout if confounding medication had been used	6 weeks	(1) Diclofenac solution (with 45.5% DMSO) (2) Control (with 45.5% DMSO) (3) Placebo (with 4.55% DMSO)	- Random sequence generation (selection bias): unclear risk - Allocation concealment (selection bias): unclear risk - Blinding (performance bias and detection bias) - All outcomes: unclear risk - Incomplete outcome data (attrition bias) All outcomes: unclear risk - Study duration: low risk - Size: high risk
108-97(251) R, DB, PC, parallel group	203 (195 for ITT)	OA hand (diagnosed by standard radiological criteria and interview) with ≥ moderate (but not extreme) pain	6 weeks	(1) Diclofenac solution (with 45.5% DMSO) (2) Control (with 45.5% DMSO) (3) Diclofenac solution (with 2.3% DMSO) (4) Placebo (with 2.3% DMSO) Rescue medication: paracetamol (500 mg to maximum 3 g daily) except in 24 h before assessments	- Random sequence generation (selection bias): unclear risk - Allocation concealment (selection bias): unclear risk - Blinding (performance bias and detection bias) - All outcomes: unclear risk - Incomplete outcome data (attrition bias) All outcomes: unclear risk - Study duration: low risk - Size: high risk
Altman 2009(225) R, DB, PC, parallel group	385	Osteoarthritis hand (ACR criteria) for ≥ 12 months, use of NSAID for ≥ 1 episode of pain. Flare required following NSAID washout (≥ 7 days) if applicable M 89, F 296 Mean age 64 years (range 40 to 92) Baseline pain ≥40 mm	8 weeks	Diclofenac sodium gel 1% (Voltaren) with vehicle vs Placebo gel (vehicle carrier) Rescue medication: paracetamol 500 mg (tomaximum 4 g daily) but	- Random sequence generation (selection bias): low risk - Allocation concealment (selection bias): low risk - Blinding (performance bias and detection bias) - All outcomes: low risk - Incomplete outcome data (attrition bias) All outcomes: low risk - Study duration: low risk - Size: unclear risk

				not for 36 h before assessment	
Baer 2005(226) R, DB, PC, parallel groups	216 (212 for efficacy)	Primary OA of at least 1 knee A flare of pain after withdrawal of prior therapy with either NSAID or paracetamol M 94, F 122 Mean age 65 years Mean baseline pain 13/20	6 weeks	Diclofenac sodium 1.5% (with DMSO, Pennsaid®) vs Placebo (vehicle carrier) Rescue medication: paracetamol (maximum 1,5g daily) except during washout and week before final assessment	- Random sequence generation (selection bias): low risk - Allocation concealment (selection bias): low risk - Blinding (performance bias and detection bias) - All outcomes: low risk - Incomplete outcome data (attrition bias) All outcomes: low risk - Study duration: low risk - Size: unclear risk
Baraf 2011(227) 3 separate studies, combined for analysis. R, DB, PC, parallel groups	1426 (ITT = 1424)	OA knee, with radiographic confirmation, according to ACR criteria, and ≥ 6 months after symptom onset. Daily pain requiring treatment for ≥ 2 weeks in previous month Baseline pain on movement ≥ 50/100 mm	12 weeks	Diclofenac sodium gel 1%, Vs Placebo gel (vehicle only) Rescue: paracetamol (maximum 4 g daily) but not within 24 h of assessments	- Random sequence generation (selection bias): low risk - Allocation concealment (selection bias): low risk - Blinding (performance bias and detection bias) - All outcomes: low risk - Incomplete outcome data (attrition bias) All outcomes: unclear risk - Study duration: low risk - Size: unclear risk
Bookman 2004(228) R, DB, PC, parallel groups	248	OA knee (no flare required), radiographically confirmed and with ≥ moderate pain for 2 weeks. Worst affected knee designated as study knee M 91, F 157; Mean age 62 years At least moderate pain, mean baseline pain > 9/20	4 weeks	(1) Diclofenac solution 1.5% in DMSO 45.5% (Pennsaid®), (2) Carrier with DMSO 45.5% (2) Carrier with DMSO 4.55% Rescue: paracetamol (max 3 g daily) except during 24 h before baseline and final assessments	This study did not meet our inclusion criteria (study duration).

Bruhlmann 2003(229) R, DB, PC, parallel groups	103	Symptomatic knee osteoarthritis M 43, F 60 Mean age 64 years Baseline pain ≥ 40 mm	14 days	Diclofenac (DHEP 1.3%) patch vs Placebo patch Rescue: paracetamol 500 mg (maximum 2 g daily)	This study did not meet our inclusion criteria (study duration).
Dreiser 1993(230) R, DB, PC, parallel groups	155	Knee osteoarthritis, diagnosed radiographically, with at least moderate spontaneous pain M 35, F 120 Mean age 67 years Baseline pain ≥ 57/100 Washout: 7 days if NSAIDs had been used	15 days	Diclofenac (DHEP) patch (= 180 mg) Vs Placebo patch Rescue: paracetamol 500 mg after 4 days	This study did not meet our inclusion criteria (study duration).
Galeazzi 1993(231) R, DB, PC, parallel groups	60	Inflammatory peri- and extra-articular rheumatological diseases M 10, F 50 Mean age 57 years Baseline pain on pressure severe Stable (> 2 months) systemic treatment continued unchanged, more recent treatment suspended.	14 days	Diclofenac (DHEP), 2 x plaster (= 180 mg) daily vs Placebo, 2 x plaster daily Rescue: paracetamol when strictly necessary	This study did not meet our inclusion criteria (sample size and study duration).
Grace 1999(232) R, DB, PC, parallel groups	74	Osteoarthritis of the knee (in flare condition at baseline), diagnosed radiographically and by symptoms, of ≥ 3 months' duration, requiring drug therapy	21 days	Diclofenac with lecithin gel, 2%, 3 x 2.5 g daily vs Placebo gel	This study did not meet our inclusion criteria (sample size and study duration).

		M 29, F 45, Mean age 62 years Mean baseline pain ≥ 40 (WOMAC pain subscale)		Rescue: paracetamol. No other concomitant medication for OA allowed.	
Niethard 2005(233) R, DB, PC, parallel groups	238	OA knee, clinically diagnosed, symptomatic, with pain > 50/100 mm and > "moderate" on 4-point scale M 87, F 151; Mean age 66 years Mean baseline pain 67/100 mm	3 weeks	Diclofenac 1.16% gel (Voltaren Emulgel) vs Placebo gel Rescue: paracetamol (maximum 2 g daily)	This study did not meet our inclusion criteria (study duration).
Roth 1995(234) R, DB, PC, parallel group	119	Osteoarthritis requiring NSAID treatment ≥ 1 month M 16, F 103; Mean age 67 years Baseline pain 3.3 (scale 1 to 5) Stable doses of NSAID continued unchanged.	14 days	Diclofenac 3% + hyaluron 2.5% gel vs Placebo + hyaluron 2.5% gel No other analgesics allowed	This study did not meet our inclusion criteria (study duration).
Roth 2004(235) R, DD, PC, and AC, parallel group	397	OA knee with flare, and duration ≥ 6 months M 160, F 237 Mean age 63 years Mean baseline pain > 66/100	6 weeks	Diclofenac 1.5% with DMSO (45.5%; Pennsaid®) Vs Carrier with DMSO (45.5%) Rescue: paracetamol	- Random sequence generation (selection bias): low risk - Allocation concealment (selection bias): low risk - Blinding (performance bias and detection bias) - All outcomes: low risk - Incomplete outcome data (attrition bias) All outcomes: low risk - Study duration: low risk - Size: unclear risk

Simon 2009(42) R, DB (DD), PC, VC, and AC study	755	Primary OA, confirmed radiographically, with pain requiring regular analgesic, and flare following washout M 490, F 292; Mean age 64 years Mean baseline pain 288/500	12 weeks	(1) Diclofenac solution 1.5% (with DMSO 45.5%, Pennsaid®) + oral placebo (2) DMSO (45.5%) vehicle solution + oral placebo (3) Placebo solution (with 2.3% DMSO) + oral placebo (4) Placebo solution (with 2.3% DMSO) + 100 mg slow-release oral diclofenac Rescue medication: paracetamol (maximum 1.3g daily) permitted except during 3 days before each efficacy assessment	- Random sequence generation (selection bias): low risk - Allocation concealment (selection bias): low risk - Blinding (performance bias and detection bias) - All outcomes: low risk - Incomplete outcome data (attrition bias) All outcomes: low risk - Study duration: low risk - Size: unclear risk

Remarks
-In this Cochrane review, studies were divided according to their duration: 6 to 12 weeks and 2 to ≤ 6 weeks for the outcome clinical success. For this outcome, we only report the results of studies with a duration of 6 to 12 weeks in accordance with our inclusion criteria. -For the safety outcomes, the Cochrane review reported their results based on studies of all durations. Some individual studies of the meta-analysis do not meet our inclusion criteria for sample size or study duration. However, we decided not to exclude these studies from our analysis for safety outcomes. -Some studies evaluate concentrations of diclofenac (1.5%) or diclofenac with DMSO which are not available in Belgium. However, we decided not to exclude these studies from our analysis. -The primary outcome 'clinical success' was defined as at least a 50% reduction in pain, or an equivalent measure such as a 'very good' or 'excellent' global assessment of treatment, or 'none' or 'slight' pain on rest or movement, measured on a categorical scale.

Author's conclusions
"Topical diclofenac and topical ketoprofen can provide good levels of pain relief beyond carrier in osteoarthritis for a minority of people, but there is no evidence for other chronic painful conditions. There is emerging evidence that at least some of the substantial placebo effects seen in longer duration studies derive from effects imparted by the NSAID carrier itself, and that NSAIDs add to that." For clinicians: "Topical diclofenac and topical ketoprofen can provide good levels of pain relief in knee osteoarthritis, but only in about 10% more people than with carrier. Adverse events are minimal with topical NSAIDs. For this reason guidelines often suggest the use of topical NSAIDs before oral NSAIDs, particularly in older people. There is little good evidence for topical NSAIDs in other chronic musculoskeletal pain."

16.2 Topical ketoprofen versus topical placebo for chronic musculoskeletal pain

Meta-analysis: Derry 2016(223) Cochrane review. Topical NSAIDs for chronic musculoskeletal pain in adults (review)

Inclusion criteria: Randomised, double-blind, active or inert carrier (placebo) controlled trials in which treatments were administered to adults with chronic musculoskeletal pain of moderate or severe intensity;
Search strategy: The Cochrane Central Register of Controlled Trials (CENTRAL),MEDLINE, EMBASE, and their own in-house database was searched;
the date of the last search was February 2016. The references lists of included studies and reviews were also searched. Unpublished studies were sought by asking personal contacts and searching online clinical trial registers and manufacturers' web sites; studies that stringent quality criteria; at least 10 participants in each treatment arm; with application of treatment at least once daily
Assessment of quality of included trials: yes (GRADE)
ITT analysis: wherever possible
Other methodological remarks:/

Ref	Comparison	N/n	Outcomes	Result

Derry 2016 (223) Design: MA Search date: (Feb-2016)	Topical ketoprofen gel/solution vs topical placebo	N= 4 n= 2573 (Conaghan 2013, Kneer 2013, Rother 2007, Rother 2013)	Clinical success (for example 50%reduction in pain)	63% vs 48% RR 1.1 (1.01 to 1.2) NNT 6.9 (5.4 to 9.3) SS in favour of ketoprofen
		N= 4 n= 2621 (Conaghan 2013, Kneer 2013, Rother 2007, Rother 2013)	Local adverse events	15% vs 13% RR 1.04 (0.85 to 1.27) NS
		N= 4 n= 2621 (Conaghan 2013, Kneer 2013, Rother 2007, Rother 2013)	Gastrointestinal adverse events	RR 0.96 (0.69 to 1.32) NS
		N= 4 n= 2621 (Conaghan 2013, Kneer 2013, Rother 2007, Rother 2013)	Withdrawals due to adverse events	RR 1.28 (0.92 to 1.78) NS
		N= 4 n= 2885 (Conaghan 2013, Kneer 2013, Rother	Withdrawals due to lack of efficacy	RR 1.11 (0.80 to 1.55) NS

		2007, Rother 2013)		

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as judged by Cochrane)
Conaghan 2013(77) R, DB, VC; oral: R, DB, PC	1395	OA knee (function class I-III and ACR criteria) with flare, PI (index knee) on walking ≥ 4/10 Mean age 61 years (range 24 to 90) M 475, F 920 Mean baseline PI 4.8/10 Washout: ≥ 5 days or 5 x half-life of analgesic	12 weeks	(1) Ketoprofen gel 2 x 50 mg daily (2) Ketoprofen gel 2 x 100 mg daily (3) Vehicle 2 x 2.2 g daily (4) Vehicle 2 x 4.4 g daily (5) Oral celecoxib 2 x 100 mg daily (6) Oral placebo Rescue: paracetamol up to 4 x 500 mg daily, but not within 24 h of any study visit. Participants needing ≥ 2 g daily or other analgesic for > 3 successive days were considered treatment failures	- Random sequence generation (selection bias): low risk - Allocation concealment (selection bias): unclear risk - Blinding (performance bias and detection bias) - All outcomes: low risk - Incomplete outcome data (attrition bias) - All outcomes: low risk - Study duration: low risk - Size: low risk
Kneer 2013(236) R, DB, VC, parallel group	866 (ITT 828)	OA knee > 6 months (function class I-III and ACR criteria) with flare Mean age 62 years (range 19 to 78) M 235, F 593 Mean baseline pain 65/100 Washout: 5 x half-life of analgesic + 2 days	12 weeks	(1) Ketoprofen gel 2 x 25 mg daily (2) Ketoprofen gel 2 x 50 mg daily (3) Ketoprofen gel 2 x 100 mg daily (4) Vehicle	- Random sequence generation (selection bias): unclear risk - Allocation concealment (selection bias): unclear risk - Blinding (performance bias and detection bias) - All outcomes: low risk

				Rescue: paracetamol up to 2 g daily up to 5 days in any 7-day period, but not within 48 h of any study visit	- Incomplete outcome data (attrition bias) - All outcomes: unclear risk - Study duration: low risk - Size: unclear risk
Rother 2007(83) R, DB, PC, parallel group	326	Primary OA in at least 1 knee, defined by radiological findings and flare of pain after washout of stable therapy M 105, F 221 Mean age 64 years Mean baseline pain 13/20	12 weeks	(1) Ketoprofen gel 110 mg + placebo tabs (2) Celecoxib tabs 100 mg + placebo gel (3) Placebo gel and tabs Rescue: paracetamol, maximum 3 g daily, not during washout period and 3 days before final assessment at week 12	- Random sequence generation (selection bias): low risk - Allocation concealment (selection bias): low risk - Blinding (performance bias and detection bias) - All outcomes: low risk - Incomplete outcome data (attrition bias) - All outcomes: low risk - Study duration: low risk - Size: unclear risk
Rother 2013(237) R, DB, PC, parallel group	555	OA knee (function class I-III and ACR criteria), PI (index knee) on walking ≥ 4/10. No flare required for inclusion Mean age 62 years (SD 11) M 209, F 346 Mean baseline pain 5.2 (SD 1.0). Washout: ≥ 5 days	12 weeks	Ketoprofen gel 2 x 100 mg daily vs Vehicle 2 x 4.4 g daily Rescue: paracetamol up to 4 x 500 mg daily, but not within 24 h of any study visit. Participants needing ≥ 2 g daily or other analgesic for > 3 successive days were considered treatment failures	- Random sequence generation (selection bias): low risk - Allocation concealment (selection bias): unclear risk - Blinding (performance bias and detection bias) - All outcomes: unclear risk - Incomplete outcome data (attrition bias) - All outcomes: unclear risk - Study duration: low risk - Size: low risk

Remarks
The primary outcome 'clinical success' was defined as at least a 50% reduction in pain, or an equivalent measure such as a 'very good' or 'excellent' global assessment of treatment, or 'none' or 'slight' pain on rest or movement, measured on a categorical scale.

Author's conclusions
"Topical diclofenac and topical ketoprofen can provide good levels of pain relief beyond carrier in osteoarthritis for a minority of people, but there is no evidence for other chronic painful conditions. There is emerging evidence that at least some of the substantial placebo effects seen in longer duration studies derive from effects imparted by the NSAID carrier itself, and that NSAIDs add to that." For clinicians: "Topical diclofenac and topical ketoprofen can provide good levels of pain relief in knee osteoarthritis, but only in about 10% more people than with carrier. Adverse events are minimal with topical NSAIDs. For this reason guidelines often suggest the use of topical NSAIDs before oral NSAIDs, particularly in older people. There is little good evidence for topical NSAIDs in other chronic musculoskeletal pain."

16.3 Other topical NSAID besides diclofenac/ketoprofen versus placebo for chronic musculoskeletal pain

Meta-analysis: Derry 2016(223) Cochrane review. Topical NSAIDs for chronic musculoskeletal pain in adults (review)

Inclusion criteria: Randomised, double-blind, active or inert carrier (placebo) controlled trials in which treatments were administered to adults with chronic musculoskeletal pain of moderate or severe intensity;
Search strategy: The Cochrane Central Register of Controlled Trials (CENTRAL),MEDLINE, EMBASE, and their own in-house database was searched;
the date of the last search was February 2016. The references lists of included studies and reviews were also searched. Unpublished studies were sought by asking personal contacts and searching online clinical trial registers and manufacturers' web sites; studies that stringent quality criteria; at least 10 participants in each treatment arm; with application of treatment at least once daily
Assessment of quality of included trials: yes (GRADE)

ITT analysis: wherever possible
Other methodological remarks: /

Remarks
There were insufficient data for quantitative analysis for ibuprofen, piroxicam and other NSAID not available in Belgium. There were too few studies, participants, and events to draw any conclusions about local adverse events for any of these NSAIDs.

Author's conclusions
"Topical diclofenac and topical ketoprofen can provide good levels of pain relief beyond carrier in osteoarthritis for a minority of people, but there is no evidence for other chronic painful conditions. There is emerging evidence that at least some of the substantial placebo effects seen in longer duration studies derive from effects imparted by the NSAID carrier itself, and that NSAIDs add to that."

16.4 Topical NSAID versus any oral NSAID for chronic musculoskeletal pain

Meta-analysis: Derry 2016(223) Cochrane review. Topical NSAIDs for chronic musculoskeletal pain in adults (review)

Inclusion criteria: Randomised, double-blind, active or inert carrier (placebo) controlled trials in which treatments were administered to adults with chronic musculoskeletal pain of moderate or severe intensity;
Search strategy: The Cochrane Central Register of Controlled Trials (CENTRAL),MEDLINE, EMBASE, and their own in-house database was searched;
the date of the last search was February 2016. The references lists of included studies and reviews were also searched. Unpublished studies were sought by asking personal contacts and searching online clinical trial registers and manufacturers' web sites; studies that stringent quality criteria; at least 10 participants in each treatment arm; with application of treatment at least once daily

Assessment of quality of included trials: yes (GRADE) ITT analysis: wherever possible Other methodological remarks:/

Ref	Comparison	N/n	Outcomes	Result
Derry 2016 (223) Design: MA Search date: (Feb-2016)	Topical NSAID vs oral NSAID	N= 5 n= 1735 (Dickson 1991, Rother 2007, Simon 2009, Tugwell 2004, Zacher 2001)	Clinical success (for example 50%reduction in pain)	55% vs 54% RR 1.03 (0.95 to 1.12) NS
		N= 5 n= 1735 (Dickson 1991, Rother 2007, Sandelin 1997, Simon 2009, Tugwell 2004)	Local adverse events	22% vs 5.8% RR 3.74 (2.76 to 5.06) NNH 6.4 (5.3 to 8.0) SS: more local adverse events with topical NSAID
		N= 6 n= 1961 (Dickson 1991, Rother 2007, Sandelin 1997, Simon 2009, Tugwell 2004, Zacher 2001)	Gastrointestinal adverse events	17% vs 26% RR 0.66 (0.56 to 0.77) NNTp 10 (7.6 to 17) SS: less adverse events with topical NSAID
		N= 6 n= 1961	Withdrawals due to adverse events	RR 0.85 (0.68 to 1.06)

		(Dickson 1991, Rother 2007, Sandelin 1997, Simon 2009, Tugwell 2004, Zacher 2001)		NS
		N= 3 n= 1197 (Rother 2007, Simon 2009, Tugwell 2004)	Withdrawals due to lack of efficacy	7% vs 3% RR 2.47 (1.45 to 4.22) NNTp 23 (14 to 52) SS: more withdrawals due to lack of efficacy with topical NSAID

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as judged by Cochrane)
Dickson 1991(242) R, DD, AC parallel groups	235	Knee osteoarthritis ("well documented, mild") M 80, F 155 Mean age 63 years Baseline pain moderate (median 3-4/9) Washout: 7 days	4 weeks	Piroxicam gel 0.5%, 3 x 1 g (= 5 mg piroxicam) + placebo tablet daily vs Ibuprofen tablet 3 x 400 mg + placebo cream daily Rescue: paracetamol (maximum 4 g daily)	This study did meet our inclusion criteria for study duration.
Rother 2007(83) R, DD, PC, and AC, parallel group	397	OA knee with flare, and duration ≥ 6 months M 160, F 237 Mean age 63 years Mean baseline pain > 66/100	6 weeks	(1) Ketoprofen gel (IDEA-33) 2 x 110 mg daily (2) Celecoxib tabs 2 x 100 mg daily (3) Placebo gel and tabs Rescue: paracetamol	- Random sequence generation (selection bias): low risk - Allocation concealment (selection bias): low risk - Blinding (performance bias and detection bias) - All outcomes: low risk

					- Incomplete outcome data (attrition bias) - All outcomes: low risk - Study duration: low risk - Size: unclear risk
Sandelin 1997(40) R, DD, PC, and AC, parallel group	290	Osteoarthritis of the knee, radiologically confirmed, pain symptoms for most days in last month, requiring treatment. Patients with severe OA or pain excluded M 101, F 189 Mean age 61 years Baseline pain ≥ 48/100 No new physical therapies allowed, but physiotherapy or orthotic devices started ≥ 7 days before study to be continued	4 weeks	1) Eltenac 1% gel + placebo tablets (2) Diclofenac 50 mg tablets + placebo gel (3) Placebo gel and tablets Rescue: not reported.	This study did meet our inclusion criteria for study duration.
Simon 2009(42) R, DB (DD), PC, VC, and AC study	755	Primary OA, confirmed radiographically, with pain requiring regular analgesic, and flare following washout M 490, F 292 Mean age 64 years Mean baseline pain 288/500	12 weeks	(1) Diclofenac solution 1.5% (with DMSO 45.5%, Pennsaid®) + oral placebo (2) DMSO (45.5%) vehicle solution + oral placebo (3) Placebo solution (with 2.3% DMSO) + oral placebo (4) Placebo solution (with 2.3% DMSO) + 100 mg slow-release oral diclofenac	- Random sequence generation (selection bias): low risk - Allocation concealment (selection bias): low risk - Blinding (performance bias and detection bias) - All outcomes: low risk - Incomplete outcome data (attrition bias) - All outcomes: low risk - Study duration: low risk - Size: unclear risk

				Rescue: paracetamol (maximum 1300 mg daily) permitted except during 3 days before each efficacy assessment	
Tugwell 2004(243) R, DD, AC, parallel group	622	OA knee, symptomatic, radiologically confirmed (no flare required) M 266, F 356 Mean age 64 years Mean baseline pain 288/500	12 weeks	Diclofenac solution 1.5% (with DMSO 45.5%, Pennsaid®) + placebo capsule vs Diclofenac capsule + placebo solution	- Random sequence generation (selection bias): low risk - Allocation concealment (selection bias): low risk - Blinding (performance bias and detection bias) - All outcomes: low risk - Incomplete outcome data (attrition bias) - All outcomes: unclear risk - Study duration: low risk - Size: low risk
Zacher 2001(244)	321	Osteoarthritis of the finger joints, "activated" M 38, F 283 Mean age 62 years (35 to 95 years) Baseline pain ≥ 40 mm	21 days	Diclofenac Emulgel + placebo tablets Vs Ibuprofen tablets + placebo gel Rescue: paracetamol	- Random sequence generation (selection bias): unclear risk - Allocation concealment (selection bias): unclear risk - Blinding (performance bias and detection bias) - All outcomes: low risk - Incomplete outcome data (attrition bias) - All outcomes: unclear risk - Study duration: high risk - Size: unclear risk

Remarks
The primary outcome 'clinical success' was defined as at least a 50% reduction in pain, or an equivalent measure such as a 'very good' or 'excellent' global assessment of treatment, or 'none' or 'slight' pain on rest or movement, measured on a categorical scale.

Author's conclusions
"Topical diclofenac and topical ketoprofen can provide good levels of pain relief beyond carrier in osteoarthritis for a minority of people, but there is no evidence for other chronic painful conditions. There is emerging evidence that at least some of the substantial placebo effects seen in longer duration studies derive from effects imparted by the NSAID carrier itself, and that NSAIDs add to that." For clinicians "Topical diclofenac and topical ketoprofen can provide good levels of pain relief in knee osteoarthritis, but only in about 10% more people than with carrier. Adverse events are minimal with topical NSAIDs. For this reason guidelines often suggest the use of topical NSAIDs before oral NSAIDs, particularly in older people. There is little good evidence for topical NSAIDs in other chronic musculoskeletal pain."

16.5 Topical NSAID versus different topical NSAID for chronic musculoskeletal pain

Meta-analysis: Derry 2016(223) Cochrane review. Topical NSAIDs for chronic musculoskeletal pain in adults (review)

Inclusion criteria: Randomised, double-blind, active or inert carrier (placebo) controlled trials in which treatments were administered to adults with chronic musculoskeletal pain of moderate or severe intensity;
Search strategy: The Cochrane Central Register of Controlled Trials (CENTRAL),MEDLINE, EMBASE, and their own in-house database was searched;

the date of the last search was February 2016. The references lists of included studies and reviews were also searched. Unpublished studies were sought by asking personal contacts and searching online clinical trial registers and manufacturers' web sites; studies that stringent quality criteria; at least 10 participants in each treatment arm; with application of treatment at least once daily

Assessment of quality of included trials: yes (GRADE)

Other methodological remarks:/

Remarks
The Cochrane systematic review and meta-analysis by Derry 2016 found one study that compared topical NSAID with other topical NSAID (Burgos 2001). This study compared topical NSAID that are not available in Belgium and did not meet our inclusion criterion for study duration.

16.6 Topical NSAID versus different topical treatment for chronic musculoskeletal pain

Meta-analysis: Derry 2016(223) Cochrane review. Topical NSAIDs for chronic musculoskeletal pain in adults (review)

Inclusion criteria: Randomised, double-blind, active or inert carrier (placebo) controlled trials in which treatments were administered to adults with chronic musculoskeletal pain of moderate or severe intensity;

Search strategy: The Cochrane Central Register of Controlled Trials (CENTRAL),MEDLINE, EMBASE, and their own in-house database was searched;
the date of the last search was February 2016. The references lists of included studies and reviews were also searched. Unpublished studies were sought by asking personal contacts and searching online clinical trial registers and manufacturers' web sites; studies that stringent quality criteria; at least 10 participants in each treatment arm; with application of treatment at least once daily

Assessment of quality of included trials: yes (GRADE)

Other methodological remarks:/

Remarks

The Cochrane systematic review and meta-analysis by Derry 2016 found three studies that compared topical NSAID with different topical treatments (Mcleane 2000(245), van Haselen 2000(240), Widrig 2007(246)). There were insufficient data for meta-analysis for any of these comparisons. None of these studies met our inclusion criterion for study duration.

16.7 DMSO (dimethyl sulfoxide) versus placebo for osteoarthritis

Systematic review:Brien 2008(247) Systematic review of the nutritional supplements dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM) in the treatment of osteoarthritis

Inclusion criteria: RCTs were included if they were in humans; reported comparison of DMSO or MSM to either placebo, or standard treatment in OA; used validated outcome measures for OA; and did not include patients with other joint pathology.
Search strategy: The electronic databases [Cochrane Library, Medline, Embase, Amed, Cinahl and NeLH (1950 to November 2007)] were searched.
Assessment of quality of included trials: yes (JADAD scale)

Remarks
This systematic review included 4 studies with dimethyl sulfoxide (DMSO). None of the studies met our inclusion criteria for study duration (Vuopala 1971, Eberhardt 1995, Bookman 2004, Koenen 1996).

Meta-analysis: Derry 2016(223) Cochrane review. Topical NSAIDs for chronic musculoskeletal pain in adults (review)

Inclusion criteria: Randomised, double-blind, active or inert carrier (placebo) controlled trials in which treatments were administered to adults with chronic musculoskeletal pain of moderate or severe intensity; studies examining participants with neuropathic pain or fibromyalgia were excluded.
Search strategy: The Cochrane Central Register of Controlled Trials (CENTRAL),MEDLINE, EMBASE, and their own in-house database was searched;
the date of the last search was February 2016. The references lists of included studies and reviews were also searched. Unpublished studies were sought by asking personal contacts and searching online clinical trial registers and manufacturers' web sites; studies that stringent quality criteria; at least 10 participants in each treatment arm; with application of treatment at least once daily
Assessment of quality of included trials: yes (GRADE)
Other methodological remarks: /

Remarks

The aim of the Cochrane review of Derry 2016 for chronic musculoskeletal pain was not to compare DMSO with placebo. However, 7 studies were included that compared topical NSAID with DMSO of which four undertook separate analyses of placebo with or without DMSO (102-93-I, 108-97, Bookman 2004, Simon 2009). All four studies were conducted in osteoarthritis. One study did not meet our inclusion criterion for study duration. Two studies (102-93-I, 108-97) were provided to the Cochrane authors only as a synopsis from the manufacturer. Results of the comparison DMSO versus placebo are not reported. It is not clear if such an analysis was included in the original report of the manufacturer.
The study by Simon 2009 compared topical diclofenac solution in a vehicle containing DMSO with topical placebo, DMSO vehicle, and oral diclofenac. The paper does not include statistical tests for efficacy and safety for the comparison DMSO versus placebo. However, in the results section the authors mention no significant efficacy advantage of the DMSO vehicle over placebo for the primary or secondary variables, except for patient overall health assessment.

16.8 Topical capsaicin (8%) versus topical placebo/control in neuropathic pain

Topical capsaicin (8%) versus placebo/control (0.04% capsaicin)

Meta-analysis: Derry 2017(252) Cochrane review. Topical capsaicin (high concentration) for chronic neuropathic pain in adults (Review)

Inclusion criteria: Randomised, double-blind, placebo-controlled studies of at least 6 weeks' duration, using high-concentration (5% or more) topical capsaicin to treat neuropathic pain.
Search strategy: CENTRAL, MEDLINE, Embase, two clinical trials registries, and a pharmaceutical company's website was searched to 10 June 2016.
Assessment of quality of included trials: yes (GRADE)
ITT analysis: modified intention-to-treat basis (all participants who were randomised and received an intervention were included)
Other methodological remarks: see below table

Ref	Comparison	N/n	Outcomes	Result
		Efficacy		
Derry 2017 (252) Design: MA Search date: (Jun-2016)	Topical capsaicin (8%) vs control	N= 3 n=870 (Webster 2010a, Webster 2010b, Irving 2011)	Postherpetic neuralgia ≥ 50% pain intensity reduction over weeks 2 to 8	29% vs 20% RR 1.4 (1.1 to 1.9) NNT 12 (7.2 to 41) SS in favour of capsaicin 8%
		N= 2 n=571 (Webster 2010b, Irving 2011)	Postherpetic neuralgia ≥ 50% pain intensity reduction over weeks 2 to 12	33% vs 24% RR 1.3 (1.0 to 1.7) NNT 11 (6.1 to 62) SS in favour of capsaicin 8%
		N= 4 n=1272 (Backonja 2008, Irving 2011, Webster 2010a,	Postherpetic neuralgia ≥ 30% pain intensity reduction over weeks 2 to 8	43% vs 34% RR 1.3 (1.1 to 1.5) NNT 11 (6.8 to 26) SS in favour of capsaicin 8%

		Webster 2010b)		
		N= 3 n=973 (Backonja 2008, Irving 2011, Webster 2010b)	<u>Postherpetic neuralgia</u> ≥ 30% pain intensity reduction over weeks 2 to 12	46% vs 37% RR 1.3 (1.1 to 1.5) NNT 10 (6.3 to 28) SS in favour of capsaicin 8%
			<u>Postherpetic neuralgia</u> Substantial benefit: Patient Global Impression of Change very much improved at week 8 and week 12	No data
		N= 2 n= 571 (Irving 2011, Webster 2010b)	<u>Postherpetic neuralgia</u> moderate benefit: Patient Global Impression of Change much or very much improved at week 8	36% vs 25% RR 1.4 (1.1 to 1.8) NNT 8.8 (5.3 to 26) SS in favour of capsaicin 8%
		N= 2 n= 571 (Irving 2011, Webster 2010b)	<u>Postherpetic neuralgia</u> moderate benefit: Patient Global Impression of Change much or very much improved at week 12	39% vs 25% RR 1.6 (1.2 to 2.0) NNT 7.0 (4.6 to 15) SS in favour of capsaicin 8%
		N=2 n= 801 (Clifford 2012, Simpson 2008)	<u>HIV neuropathy</u> ≥ 30% pain intensity reduction over weeks 2 to 12	39% vs 30% RR 1.4 (1.1 to 1.7) NNT 11 (6.2 to 47) SS in favour of capsaicin 8%
		N=1 n= 307 (Simpson 2008)	<u>HIV neuropathy</u> Patient Global Impression of Change much or very much improved at week 12	27% vs 10% RR 2.8 (1.4 to 5.6) NNT 5.8 (3.8 to 12) SS in favour of capsaicin 8%
		N= 1	<u>Peripheral diabetic neuropathy</u>	21% vs 18%

		n=369 (STEP 2014)	≥ 50% pain intensity reduction over weeks 2 to 8	RR 1.2 (0.77 to 1.8) NNT not calculated NS
		N= 1 n=369 (STEP 2014)	<u>Peripheral diabetic neuropathy</u> ≥ 50% pain intensity reduction over weeks 2 to 12	22% vs 19% RR 1.2 (0.77 to 1.7) NNT not calculated NS
		N= 1 n=369 (STEP 2014)	<u>Peripheral diabetic neuropathy</u> ≥ 30% pain intensity reduction over weeks 2 to 8	40% vs 33% RR 1.2 (0.92 to 1.6) NNT not calculated NS
		N= 1 n=369 (STEP 2014)	<u>Peripheral diabetic neuropathy</u> ≥ 30% pain intensity reduction over weeks 2 to 12	41% vs 32% RR 1.3 (0.98 to 1.7) NNT not calculated NS
		N= 1 n= 369 (STEP 2014)	<u>Peripheral diabetic neuropathy</u> moderate benefit: Patient Global Impression of Change much or very much improved at week 8	38% vs 28% RR 1.3 (1.0 to 1.8) NNT 10 (5.2 to 520) SS in favour of capsaicin 8%
		N= 1 n= 369 (STEP 2014)	<u>Peripheral diabetic neuropathy</u> moderate benefit: Patient Global Impression of Change much or very much improved at week 12	36% vs 28% RR 1.2 (0.92 to 1.7) NNT not calculated NS
		N= 6 n=2073 (Backonia 2008, Clifford	<u>All conditions combined</u> Withdrawals due to lack of efficacy	1.5% vs 3.1% RR 0.58 (0.32 to 1.04) NNTp 64 (34 to 610)

2012, Irving 2011, Simpson 2008, Webster 2010a, Webster 2010b)		NS
Safety (all conditions combined)		
N= 8 n=2487 (Backonia 2008, Bischoff 2014, Clifford 2012, Irving 2011, Simpson 2008, STEP 2014, Webster 2010a, Webster 2010b)	Withdrawals due to adverse events	1.5% vs 3.1% RR 0.80 (0.36 to 1.8) NNTp not calculated NS
N= 7 n=1993 (Backonia 2008, Bischoff 2014, Irving 2011, Simpson 2008, STEP 2014, Webster 2010a, Webster 2010b)	Serious adverse events	3.5% vs 3.2% RR 1.14 (0.70 to 1.86) NNH not calculated NS
N= 8 n=2487	Death	4 events vs 2 events RR not calculated

		(Backonia 2008, Bischoff 2014, Clifford 2012, Irving 2011, Simpson 2008, STEP 2014, Webster 2010a, Webster 2010b)		
		N=4 n= 1355 (Backonia 2008, Bischoff 2014, Clifford 2012, Irving 2011,)	Local skin reactions: Erythema	Group 1: 75% vs 57% RR 1.4 (1.3 to 1.5) NNH 5.5 (4.3 to 7.7)
		N=1 n= 129 (Webster 2010b)	Local skin reactions: Erythema	Group 2: 5.3% vs 0% RR 6.31 (0.35 to 114.82) NNH not calculated
		N=4 n= 1355 (Backonia 2008, Bischoff 2014, Clifford 2012, Irving 2011,)	Local skin reactions: Pain	Group 1: 69% vs 29% RR 2.3 (2.0 to 2.6) NNH 2.5 (2.2 to 2.8)
		N=4 n= 1005 (Simpson 2008, STEP 2014, Webster	Local skin reactions: Pain	Group 2: 9.9% vs 3.8% RR 2.4 (1.4 to 4.1) NNH 16 (11 to 31)

		2010a, Webster 2010b)		
		N=3 n= 1312 (Backonia 2008, Clifford 2012, Irving 2011)	Local skin reactions: Papules	Group 1: 6.3% vs 2.0% RR 3.6 (1.9 to 6.9) NNH 23 (16 to 46)
		N=3 n= 735 (Simpson 2008, Webster 2010a, Webster 2010b)	Local skin reactions: Papules	Group 2: 3.4% vs 2.4% RR 1.6 (0.59 to 4.2) NNH not calculated
		N=3 n= 1312 (Backonia 2008, Clifford 2012, Irving 2011)	Local skin reactions: Pruritus	Group 1: 3.7% vs 2.0% RR 2.0 (0.98 to 4.0) NNH not calculated
		N=3 n= 735 (Simpson 2008, Webster 2010a, Webster 2010b)	Local skin reactions: Pruritus	Group 2: 14% vs 9.4% RR 1.6 (0.98 to 2.5) NNH not calculated
		N=3 n= 1312 (Backonia 2008, Clifford	Local skin reactions: Oedema	Group 1: 3.9% vs 1.2% RR 3.0 (1.4 to 6.2) NNH 38 (23 to 110)

2012, Irving 2011)		
N=3 n= 735 (Simpson 2008, Webster 2010a, Webster 2010b)	Local skin reactions: Oedema	Group 2: 8.0% vs 6.1% RR 1.3 (0.75 to 2.4) NNH not calculated
N= 6 n=2074 (Backonia 2008, Clifford 2012, Irving 2011, Simpson 2008, Webster 2010a, Webster 2010b)	<u>Patch tolerability</u> <90% application time	1.7% vs 0.3% RR 3.3 (1.2 to 9.2) NNH 77 (45 to 260) SS: less tolerability with capsaicin 8%
N= 3 n=1065 (Clifford 2012, Irving 2011, Webster 2010b)	<u>Patch tolerability</u> Dermal irritation score >2 (range:0-7) at 2 hours	11% vs 0.7% RR 12 (4.0 to 34) NNH 9.6 (7.7 to 13) SS: more dermal irritation with capsaicin 8%
N= 2 n=606 (Simpson 2008, Webster 2010a)	<u>Patch tolerability</u> Dermal irritation score >0 (range:0-7) at 2 hours	40% vs 18% RR 2.3 (1.6 to 3.2) NNH 4.5 (3.3 to 6.7) SS: more dermal irritation with capsaicin 8%
N= 7	<u>Patch tolerability</u>	43% vs 17%

		n=2442 (Backonia 2008, Clifford 2012, Irving 2011, Simpson 2008, STEP 2014, Webster 2010a, Webster 2010b)	Pain medication 0 to 5 days	RR 2.5 (2.2 to 2.9) NNH 3.8 (3.4 to 4.4) SS: more pain medication with capsaicin 8%
			Systemic adverse events including diarrhoea, nausea, vomiting, fatigue, infections, musculoskeletal disorders, hypertension, dizziness, and headache.	Individual events generally occurred in fewer than 5% of participants in each treatment arm, with no obvious differences between different doses and control arms (Appendix 6). Three studies specifically reported on cough, which occurred in 2% to 3% of participants treated with high-concentration capsaicin and 0%to 4%of participants treated with control (Simpson 2008;Webster 2010a;Webster 2010b). No further analysis of systemic adverse events was carried out.

* Characteristics of included studies: see below

NNTp: number needed to treat to prevent one withdrawal event

Ref + design	n	Population	Duration	Comparison	Methodology (as judged by Cochrane)
Backonja 2008(253) RCT, DB, multicentre, parallel groups,	402	Postherpetic neuropathy with at least moderate pain, ≥ 6 months since vesicle crusting Exclusion: pain in/around facial area	12 weeks	Capsaicin patch 8% vs Control patch (0.04% capsaicin)	- Random sequence generation (selection bias): unclear risk - Allocation concealment (selection bias): low risk

		M = 190, F = 212 Mean age: 71 years Baseline pain: 30 mm to 90 mm (mean 60 mm)			- Blinding (performance bias and detection bias) - All outcomes: low risk - Incomplete outcome data (attrition bias) - All outcomes: low risk - Size: low risk
Bischoff 2014(260) RCT, DB, PC, parallel group	46	Persistent pain after inguinal herniorrhaphy score ≥ 5/10 for > 6 months M = 42, F = 4 Mean age: 54 years Baseline pain on movement: 5.5/10 (range 3 to 7)	12 weeks	Capsaicin patch 8% vs Placebo patch Stable (≥ 4 weeks) analgesic medication continued without change	This study did not meet our inclusion criteria for sample size
Clifford 2012(257) RCT, DB, parallel groups,	494	HIV-associated distal sensory neuropathy for ≥ 2 months Exclusion: previous use of NGX-4010 (capsaicin) M = 432, F = 62 Mean age: 50 years Baseline pain: 30 mm to 90 mm (mean 60 mm)	12 weeks	(1) Capsaicin patch 8% 30 min (2) Capsaicin patch 8% 60 min (3) control patch (0.04% capsaicin) 30 min (4) control patch (0.04% capsaicin) 60 min	- Random sequence generation (selection bias): unclear risk - Allocation concealment (selection bias): unclear risk - Blinding (performance bias and detection bias) - All outcomes: unclear risk - Incomplete outcome data (attrition bias) - All outcomes: low risk - Size: unclear risk
Irving 2011(254) RCT, DB, multicentre, parallel-group	416	Postherpetic neuropathy with at least moderate pain, ≥ 6 months since vesicle crusting Exclusion: pain above neck area	12 weeks	Capsaicin patch 8% vs Control patch (0.04% capsaicin)	- Random sequence generation (selection bias): unclear risk - Allocation concealment (selection bias): low risk

		M = 190, F = 226 Mean age: 70 years Baseline pain: 30 mm to 90 mm (mean 57 mm)			- Blinding (performance bias and detection bias) - All outcomes: low risk - Incomplete outcome data (attrition bias) - All outcomes: low risk - Size: low risk
Simpson 2008(258) RCT, DB, multicentre, parallel groups,	307	HIV-associated distal sensory polyneuropathy with ≥ 2months' moderate to severe pain in both feet M = 286, F = 21 Mean age: 48 years (range 29 to 74) Baseline pain: 30 mm to 90 mm (mean ~ 60 mm)	12 weeks	Capsaicin patch 8% 30 min (2) Capsaicin patch 8% 60 min (3) Capsaicin patch 8% 90 min (4) Control patch (0.04% capsaicin)	- Random sequence generation (selection bias): unclear risk - Allocation concealment (selection bias): unclear risk - Blinding (performance bias and detection bias) - All outcomes: low risk - Incomplete outcome data (attrition bias) - All outcomes: low risk - Size: unclear risk
STEP 2014(259) RCT, DB, multicentre, parallel groups	369	Painful diabetic neuropathy, distal, symmetrical, > 1 year (score > 3 on Michigan Neuropathy Screening Instrument), glycated haemoglobin ≤ 11% and history indicating control, 24-hour PI ≥ 4/10 in screening period, stable doses of analgesics for ≥ 4 weeks before screening M = 215, F = 154 Mean age: 63 years (range 33 to 89) Mean baseline pain: 6.5/10	12 weeks	Capsaicin patch 8% vs Placebo patch Stable concomitant neuropathic pain medication (antiepileptic or antidepressant drugs) allowed if unchanged	- Random sequence generation (selection bias): unclear risk - Allocation concealment (selection bias): unclear risk - Blinding (performance bias and detection bias) - All outcomes: low risk - Incomplete outcome data (attrition bias) - All outcomes: unclear risk - Size: unclear risk

Webster 2010a(256) RCT, DB, multicentre, parallel-group	299	Postherpetic neuropathy with at least moderate pain, ≥ 6 months since vesicle crusting Exclusion: pain in/around facial area M = 150, F = 149 Mean age: 71 years Baseline pain: 30 mm to 90 mm (mean 55 mm)	12 weeks	(1) Capsaicin patch 8% 30 min (2) Capsaicin patch 8% 60 min (3) Capsaicin patch 8% 90 min (4) Control patch (0.04% capsaicin), 30, 60, 90 min pooled for analysis	- Random sequence generation (selection bias): unclear risk - Allocation concealment (selection bias): unclear risk - Blinding (performance bias and detection bias) - All outcomes: low risk - Incomplete outcome data (attrition bias) - All outcomes: low risk - Size: unclear risk
Webster 2010b(255) RCT, DB, multicentre, parallel-group	155	Postherpetic neuropathy with at least moderate pain, ≥ 6 months since vesicle crusting Exclusion: pain in/around facial area M = 72, F = 83 Mean age: 70 years Baseline pain: 30 mm to 90 mm (mean 53 mm)	12 weeks	Capsaicin patch 8% vs Control patch (0.04% capsaicin)	- Random sequence generation (selection bias): unclear risk - Allocation concealment (selection bias): unclear risk - Blinding (performance bias and detection bias) - All outcomes: low risk - Incomplete outcome data (attrition bias) - All outcomes: low risk - Size: unclear risk

Remarks
-Participants were given a single 30- to 90-minute intervention with topical capsaicin. -Application of capsaicin to the skin, particularly at this high concentration, initially causes erythema (redness) and a burning or stinging sensation in many people. With the exception of 2 studies (Bischoff 2014, STEP 2014), all studies used a low dose (0.04%) of capsaicin in the control patch to produce some degree of skin irritation without effective analgesia, in an attempt to prevent participants from guessing their treatment allocation (double-blinding).

-Because of the localized pain at the application site, no pain measurements were generally made in the first post-treatment week.

-The Cochrane authors retrieved Information of the unpublished STEP 2014 study from the website of the pharmaceutical company. The STEP 2014 study was later published by Simpson 2016. The Cochrane authors checked their data extraction from the STEP 2014 study (ref) with the published paper(ref).

-It was not possible to determine the number of participants with any type of local skin reaction. The Cochrane authors evaluated certain selected individual symptoms: erythema, pain, papules, pruritus, oedema. Because the original studies reported the adverse events differently, 2 analyses were performed: 2 groups. Group 2 reported lower rates of skin adverse events, presumably because events in the first day were not included.

Author's conclusions
"High-concentration topical capsaicin used to treat postherpetic neuralgia, HIV-neuropathy, and painful diabetic neuropathy generated more participants with moderate or substantial levels of pain relief than control treatment using a much lower concentration of capsaicin. These results should be interpreted with caution as the quality of the evidence was moderate or very low. The additional proportion who benefited over control was not large, but for those who did obtain high levels of pain relief, there were usually additional improvements in sleep, fatigue, depression, and quality of life. High-concentration topical capsaicin is similar in its effects to other therapies for chronic pain." "For clinicians. High-concentration topical capsaicin is better than very low-concentration capsaicin in people with postherpetic neuralgia. Good pain relief (moderate or substantial benefit for 2 to 12 weeks) is achieved by about 10% more people with high-concentration capsaicin than control, after a single application. There is limited evidence that a similar proportion of people benefit in painful diabetic neuropathy and HIV-neuropathy. What is less clear is how well repeated applications work, as the therapy needs to be repeated several times a year. High-concentration topical capsaicin is therefore similar to other therapies for chronic pain. The high cost of single and repeated applications suggest that high-concentration topical capsaicin is likely to be used when other available therapies have failed, and that it should probably not be used repeatedly without substantial documented pain relief. Even when efficacy is established, there are unknown risks, especially on epidermal innervation, of repeated application over long periods. Some clinicians would prefer to see more information on safety data relating to quantitative sensory testing or intra-epidermal nerve fibre density."

16.9 Topical lidocaine versus placebo/active control for neuropathic pain

Meta-analysis: Derry 2014(8) Cochrane review. Topical lidocaine for neuropathic pain in adults (Review)

Inclusion criteria: Randomised, double-blind studies were included of at least two weeks' duration comparing any formulation of topical lidocaine with placebo or another active treatment in chronic neuropathic pain. Participants were adults aged 18 and over.
Search strategy: CENTRAL, MEDLINE, and EMBASE were searched from inception to 1 July 2014, together with the reference lists of retrieved papers and other reviews. ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal were also searched to identify additional published or unpublished data.
Assessment of quality of included trials: yes (GRADE)

Remarks
This Cochrane review included 12 studies. None of the studies met our inclusion criteria for sample size and/or study duration.

Author's conclusions
"This review found no evidence from good quality randomised controlled studies to support the use of topical lidocaine to treat neuropathic pain, although individual studies indicated that it was effective for relief of pain. Clinical experience also supports efficacy in some patients. Several large ongoing studies, of adequate duration, with clinically useful outcomes should provide more robust conclusions about both efficacy and harm."

lidocaine plaster versus placebo plaster in localized post-surgical neuropathic pain (PSNP)

Study details	n/Population	Comparison	Outcomes		Methodological
Palladini 2019(261) Design:	n= 363 Mean age: 52 (SD 13.8) years	lidocaine plaster 700mg Vs placebo	Efficacy change from baseline in 24 hour average pain intensity at Week 12 (PO)	lidocaine: LS mean (SE) -1.70 (0.16) 95%CI (-2.11, -1.37) placebo: LS mean (SE) -1.47 (0.16)	RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes

RCT (DB) (PG) Duration of follow-up: 12 weeks	<u>Previous pain intervention</u>: Stable systemic pain medications (such as antidepressants, anti-epileptics or benzodiazepines) used for localized chronic PSNP for > 1 month before enrollment could be continued. <u>Other interventions for pain allowed during study:</u> yes - see "previous pain intervention". -Concomitant use of analgesics: 52.0% (lidocaine) vs 51.1% (placebo). -Rescue medication for PSNP not allowed, but acute pain other than PSNP could be treated with paracetamol. <u>Inclusion</u> -At least 3 months to a maximum of 36 months BSNP with a presumed local pain generator (single		11 point numerical rating scale (NRS)	95%CI (-1.78, -1.03) Difference LS mean (SE) -0.23 (0.23) 95%CI : (-0.69, 0.22) p=0.1533, NS	Remarks on blinding method: identical appearance of lidocaine plasters and placebo FOLLOW-UP: Lost-to follow-up: 1 patient in the placebo arm. Drop-out and Exclusions: • Described: yes • Balanced across groups: yes; 18.3% lidocaine vs 19.7% placebo ITT: Yes. A full analysis set was analyzed, defined as all allocated patients who applied any amount of plaster and had at least one post-baseline 24 hour average pain intensity assessment. SELECTIVE REPORTING: no Other important methodological remarks (schrappen als nvt) (vb. placebo-run-in)
			Responder with ≥30% pain reduction at Week 12	29.1% (lidocaine) vs 23.9% (placebo) No statistical test	
			Responder with ≥50% pain reduction at Week 12	16.2% (lidocaine) vs 16.7% (placebo) No statistical test	
			Patient Global Impression of Change (PGIC) (7-point scale): Very much improved/much improved/minimally improved	61.5% (lidocaine) vs 56.6% (placebo) No statistical test	
			Patient Global Impression of Change (PGIC): Much worse/very much worse/minimally worse	8.9% (lidocaine) vs 8.9% (placebo) No statistical test	
			Quality of life	No statistical tests were done for EQ-5D, sleep problem index (CPSI), and depression/anxiety (HADS)	

	cutaneous area neurologically related to the site of surgery) following surgery. -Baseline 24 hour average pain intensity ≥4/11 (NRS) -Treatment-naïve and previously treated patients with medication for neuropathic pain were eligible -Capsaicin had to be discontinued 6 months before the trial. <u>Exclusion</u> -Any former use of topical lidocaine in the area of localized chronic PSNP was not allowed. - Non-stable pain medication had to be washed out before the treatment period, and any topical products or treatments applied to the affected painful area had to be discontinued.		subgroup analysis for PO: "Add-on" (with concomitant pain treatment)	-1.56 (0.23); 95%CI (-2.02, -1.11) Vs -1.55 (0.22); 95%CI (-1.98, -1.12) Difference: -0.01 (0.32); 95%CI: (-0.64, 0.61)	Sponsor: Grünenthal GmbH, Aachen, Germany
			subgroup analysis for PO: "Plaster-only" (without concomitant pain treatment)	-1.87 (0.23); 95%CI (-2.32, -1.41) Vs -1.36 (0.24); 95%CI (-1.82, -0.89) Difference: -0.51 (0.33); 95%CI: (-1.16, 0.14)	
			subgroup analysis for PO: "≤1 year" after surgery	-1.89 (0.23); 95%CI (-2.35, -1.44) Vs -1.85 (0.23); 95%CI (-2.30, -1.40) Difference: -0.04 (0.33); 95%CI: (-0.68, 0.60)	
			subgroup analysis for PO: ">1 year" after surgery	-1.51 (0.23); 95%CI (-1.95, -1.07) Vs -1.05 (0.23); 95%CI (-1.50, -0.61) Difference: -0.46 (0.32); 95%CI: (-1.09, 0.17)	
			Safety		
			Treatment emergent adverse events	52.0% (lidocaine) vs 45.0% (placebo)	
			Drug-related adverse events	14.0% (lidocaine) vs 8.3% (placebo)	
			Skin-related adverse events	12.8% (lidocaine) vs 10.0% (placebo)	

			Premature discontinuation due to adverse event	3.9% (lidocaine) vs 3.8% (placebo)	

PO: primary outcome; LS mean: least square mean

16.10 Non-opioid topical analgesics vs placebo/topical non-opioid analgesics in chronic cancer pain

Meta-analysis:Huang 2019(222) Comparative Efficacy of Therapeutics for Chronic Cancer Pain: A Bayesian Network Meta-Analysis

Inclusion criteria: RCTs of adult patients with cancer (age 18 years or older) comparing any systemic pharmaceutical intervention and/or combination thereof (including oral, transdermal, intravenous, and subcutaneous routes) for chronic cancer pain.
Search strategy: MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were searched for randomized controlled trials (RCTs) from 1970 to August 2018. Reference lists were searched for additional records.
Assessment of quality of included trials: yes
Other methodological remarks:

Remarks
None of the included studies of this network meta-analysis evaluated topical non-opioid analgesics.

17 Appendix. Evidence tables. Supplements

17.1 Curcuminoids vs placebo for osteoarthritis

Meta-analysis: Bannuru 2018(262) "Efficacy of curcumin and Boswellia for knee osteoarthritis: Systematic review and meta-analysis"

Inclusion criteria: RCTs in human subjects with knee osteoarthritis, treated with orally administered curcuminoid or Boswellia formulations alone or in combination, against placebo or NSAIDs. Exclusion criteria: concomitant treatment with other analgesics (with the exception of rescue medication), nutraceuticals or supplements.
Search strategy: Medline, EMBASE, Google Scholar, Web of Science and the Cochrane Database were searched from inception to February 21, 2018. Reference lists were hand-searched.
Assessment of quality of included trials: yes, using GRADE
ITT analysis: no
Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Bannuru 2018(262) Design: SR + MA Search date: (February 2018)	Curcuminoid Vs placebo	N= 5 n= 331 (Haroyan 2018, Madhu 2013, Moharamzad 2011, Nakagawa 2014, Panahi 2014)	Pain – WOMAC / VAS	**SMD −0.81(−1.25 to −0.37), I^2= 71%** **SS in favour of curcuminoid**
		N= 2 n=165 (Haroyan 2018, Panahi 2014)	Pain – WOMAC only	**SMD −0.47(−0.78 to -0.16), I^2 = 0%** **SS in favour of curuminoid**
		N= 3 n= 232 (Haroyan 2018, Moharamzad	Function	**SMD −0.48(−0.74 to −0.22), I^2= 0%** **SS in favour of curcuminoid**

		2011, Panahi 2014)		
		N= 3 n= 237 (Haroyan 2018, Nakagawa 2014, Panahi 2014)	Serious adverse events	Zero events. Not estimable.
		N= 4 n= 288 (Haroyan 2018, Madhu 2013, Nakagawa 2014, Panahi 2014)	Withdrawals due to adverse events	RR 0.90 (0.21 to 3.79), I^2= 14% NS
		N= 3 n= 247 (Haroyan 2018, Madhu 2013, Panahi 2014)	Gastrointestinal adverse events	RR 2.22 (0.94 to 5.26), I^2= 0% NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Haroyan 2018(263)	134	Degenerative hypertrophic knee osteoarthritis Kellgren-Lawrence grades I-III Mean age 55.4 y	12 weeks	CuraMed capsule (contains 552-578 mg of BCM-95 as a dry extract, and 49-52 mg volatile oil from curcuma longa L. rhizome, 22-23.4 mg turmerone); 3x/day	(as assessed by Bannuru et al.) ALLOCATION CONC: low risk of bias RANDO: low risk of bias BLINDING : low risk of bias INCOMPLETE OUTCOME DATA: low risk of bias

				Vs Placebo capsule 3x/dat	SELECTIVE REPORTING: low risk of bias FUNDING: Industry sponsored, high risk of bias
Madhu 2013(264)	60	Knee osteoarthritis	6 weeks	Curcuma longa extract, 500 mg capsule 2x/day Vs Placebo capsule 2x/day	RCT did not meet our inclusion criteria (sample size)
Moharamzad 2011(265)	67	Knee osteoarthritis	10 weeks	Curcumin capsule, 600 mg/day Vs Placebo capsule	RCT did not meet our inclusion criteria (sample size)
Nakagawa 2014(266)	41	Knee osteoarthritis	8 weeks	Highly-bioavailable curcumin (Theracurmin) 180 mg capsule 6x/day Vs Placebo capsule 6x/day	RCT did not meet our inclusion criteria (sample size)
Panahi 2014(267)	53	Knee osteoarthritis	6 weeks	C3 curcuminoid complex, 500 mg capsule 2x/day Vs Placebo capsule 2x/day	RCT did not meet our inclusion criteria (sample size)

Author's conclusions
"The results of our study suggest that curcuminoid […] formulations could be a valuable addition to the knee OA treatment regimens by relieving symptoms while reducing safety risks. The current body of evidence is not adequate in size or quality to make any meaningful clinical practice recommendations."

Curcuma versus placebo in osteoarthritis of the knee
Excluded from SR Zhu because of concomitant NSAID treatment

Study details	n/Population	Comparison	Outcomes		Methodological
Srivastava 2016(268) Design: RCT (DB, PG) Duration of follow-up: 4 months	n= 160 Mean age: 50 y Previous pain intervention: not described Other interventions for pain allowed during study: not described <u>Inclusion</u>	Curcuma longa extract 500 mg + diclofenac 50 mg/day Vs placebo + diclofenac 50 mg/day	Efficacy		RANDO: Adequate ALLOCATION CONC: unclear BLINDING : Participants: yes Personnel: yes Assessors: unclear Study described as double-blind, not described whether assessors were blinded FOLLOW-UP: Lost-to follow-up: 17 % • Described: yes • Balanced across groups: 15% curcuma, 18% placebo
			Pain (VAS) (PO)	Day 0 Curcuma: 7.94 +- 0.13 placebo: 7.66 +- 0.14 P= 0.15 NS difference between groups at baseline **Day 60** **Curcuma: 4.96 +- 0.07** **placebo: 6.00 +- 0.11** **P= 0.0001** **SS in favour of curcuma** **Day 120** **Curcuma: 4.03 +- 0.08**	

	Primary knee OA (according to guidelines proposed by "The American College of Rheumatology" Altman et al. 1991) Age 40-80y <u>Exclusion</u> Rheumatoid arthritis, diabetes mellitus, renal insufficiency, hepatic disease, cardiovascular disease, gout, pregnant women or any other systematic disease.			**placebo: 5.11 +- 0.14** **P= 0.0001** **SS in favour of curcuma**	ITT: Yes (all randomized participants analyzed according to allocation) SELECTIVE REPORTING: unclear; no statistical analysis of between-group improvement Sponsor: Council of Scientific and industrial research, India Curcuma longa extract was provided by The Himalaya Drug Company, Bangalore
			Pain (WOMAC) (PO)	Day 0 Curcuma: 15.10 +- 0.31 placebo: 15.29 +- 0.26 P= 0.64 NS difference between groups at baseline **Day 60** **Curcuma: 11.19 +- 0.26** **placebo: 12.05 +- 0.21** **P= 0.01** **SS in favour of curcuma** Day 120 Curcuma: 9.48 +- 0.17 placebo: 10.16 +- 0.16 P= 0.06 NS	
			Safety		
			Dyspepsia	Curcuma= 1/78 Placebo= 2/82	

				No statistical analysis	
			Nausea/vomiting	Curcuma= 1/78 Placebo= 1/82 No statistical analysis	
			Constipation	Curcuma= 0/78 Placebo= 1/82 No statistical analysis	
			Total number of patients with AEs	Curcuma= 2/78 Placebo= 4/82 No statistical analysis	

17.2 Curcuminoids vs NSAID for osteoarthritis

Ref	Comparison	N/n	Outcomes	Result (95% CI)
Bannuru 2018(262)	Curcuminoids vs NSAID	N= 2 n= 422 (Kuptniratsaikul 2009,	Pain	SMD −0.05 (−0.41 to 0.31), I^2 = 60% NS

Design: SR + MA Search date: (February 2018)		Kuptniratsaikul 2014)		
		N= 1 n= 100 (Kuptniratsaikul 2009)	Serious adverse events	Zero events. Not estimable.
		N= 2 n= 474 (Kuptniratsaikul 2009, Kuptniratsaikul 2014)	Withdrawals due to adverse events	**RR 0.22 (0.05 to 0.99), I^2 = 0%** **SS fewer withdrawals with curcuminoids**
		N= 2 n= 467 (Kuptniratsaikul 2009, Kuptniratsaikul 2014)	Gastrointestinal adverse events	**RR 0.74 (0.60 to 0.91), I^2 = 0%** **SS fewer GI events with curcuminoids**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Kuptniratsaikul 2009(269)	107	Evidence of radiographic osteophytes at baseline required	6 weeks	Curcuma domestica extract 500 mg capsule 4x/day Vs Ibuprofen 400 mg 2x/day	(as assessed by Bannuru et al.) ALLOCATION CONC: low risk of bias RANDO: low risk of bias BLINDING : open label, high risk of bias INCOMPLETE OUTCOME DATA: low risk of bias

					SELECTIVE REPORTING: unclear risk of bias FUNDING: Not industry sponsored, low risk of bias
Kuptniratsaikul 2014(270)	331	Knee osteoarthritis	4 weeks	Curcuma domestica extract 250 mg capsule 6x/day Vs Ibuprofen 200 mg 6x/day	RCT did not meet our inclusion criteria (duration)
Kizhakkedath 2013(271)	28	Knee osteoarthritis	12 weeks	Curcuma longa extract + Boswellia serrata extract, 500 mg capsule 2x/day Vs Celecoxib 100 mg 2x/day	RCT did not meet our inclusion criteria (sample size)

17.3 Curcuminoids vs placebo for painful diabetic neuropathy

Nano curcumin versus placebo in diabetic sensorimotor polyneuropathy

Study details	n/Population	Comparison	Outcomes	Methodological
Asadi 2019	n= 80		Efficacy	RANDO:

(272) Design: RCT (DB PG) Duration of follow-up: 8 weeks	Mean age: 53.3 (curcumin); 54.6 (placebo) 87.5% female Other interventions for pain allowed during study: participants were excluded for any change in diet or lifestyle, type or dose of hypoglycemic drugs <u>Inclusion</u> Non-insulin-dependent diabetes mellitus Age 30-60 BMI 25-39.9 kg/m^2 Diagnosed with diabetic sensorimotor polyneuropathy <u>Exclusion</u>	Nano curcumin capsule 80 mg 1x/day Vs Placebo capsule 1x/day	Foot pain	Curcumin: Baseline: 30, week 8: 20 Placebo: Baseline: 34, week 8: 33 P for interaction: 0.07 NS	Adequate ALLOCATION CONC: unclear BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 10% Drop-out and Exclusions: 10 % • Described: yes • Balanced across groups: no ITT: Yes (all randomized participants analysed according to allocation) SELECTIVE REPORTING: yes; safety insufficiently reported Other important methodological remarks: multiple (>20) reported outcomes, no primary outcome defined, no correction of multiple comparisons described
			Safety		
				"The reported side effects were two cases with stomach ache in the first few days of study." (not described in which group)	

	Neuropathy not caused by diabetes Patient with particular diet history of gastrointestinal ulcer and bile duct or diagnosed with diseases such as cancer, liver, kidney, autoimmune diseases, and inflammatory, thyroid and nervous and cardiovascular diseases. Intake of analgesic medications such as gabapentin, other painkillers and any dietary supplement. Pregnancy or lactation				Sponsor: Grant from Tehran University of Medical Sciences Curcumin and placebo capsules provided by Exir Nano Sina Company, Iran

17.4 Glucosamine vs placebo for osteoarthritis

Meta-analysis: Zhu 2018(273) "Effectiveness and safety of glucosamine and chondroitin for the treatment of osteoarthritis: a meta-analysis of randomized controlled trials"

Inclusion criteria: RCTs; patients with primary hip and/or knee osteoarthritis; at least two of the following oral treatments: glucosamine, chondroitin, or the two in combination against placebo; EXCLUDED: treatments combined with NSAID; trial arms with sub-therapeutic doses (<1500 mg/day glucosamine and <800 mg/day chondroitin)
Search strategy: PubMed, Embase, Cochrane Library was searched from inception to May 22, 2018.
Assessment of quality of included trials: yes, with Cochrane Risk of Bias Tool

Ref	Comparison	N/n	Outcomes	Result
Zhu 2018(273) Design: SR + MA Search date: May 2018	Glucosamine Vs placebo	N= 14 n= 2845 (Braham 2003, Cibere 2004, Clegg 2006, Fransen 2014, Giordano 2009, Herrero-Beaumont 2007, Houpt 1999, Kwoh 2014, McAlindon 2004, Noack 1994, Pavela 2002, Reginster 2001, Rozendaal 2008, Usha 2004)	Pain	SMD -0.105 (-0.254 to 0.045) p= 0.170 I^2: 72.5% NS
		N= 11 n= not reported (not reported)	Function	SMD -0.126 (-0.264 to 0.012) p= 0.073 I^2: 64.1% NS
		N= 8 n= not reported (Clegg 2006, , Fransen 2014, Herrero-Beaumont 2007, Kwoh 2014, McAlindon 2004, Pavelka 2002, Reginster 2001, Rozendaal 2008)	Adverse events (overall)	RR 0.90 (0.66 to 1.23) I^2= 24.3% NS

* Characteristics of included studies: see below

Ref + design	n (glucosamine/ placebo)	Population	Duration	Comparison	Methodology (risk of bias as assessed by Zhu 2018)
Noack 1994(274)	126/126	Knee osteoarthritis Mean age 55 y	4 weeks	Glucosamine 1500 mg Vs placebo	RCT did not meet our inclusion criteria (duration)
Houpt 1999(275)	58/60	Knee osteoarthritis Mean age 64 y	12 weeks	Glucosamine 1500 mg Vs placebo	RANDOMIZATION: unclear ALLOCATION CONC: unclear BLINDING PARTICIPANTS/ PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER BIAS: low
Reginster 2001(276)	106/106	Knee osteoarthritis Mean age 66 y	144 weeks	Glucosamine 1500 mg Vs placebo	RANDOMIZATION: unclear ALLOCATION CONC: low BLINDING PARTICIPANTS/ PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER BIAS: low
Pavelka 2002(277)	101/101	Knee osteoarthritis Mean age 62 y	144 weeks	Glucosamine 1500 mg Vs placebo	RANDOMIZATION: low ALLOCATION CONC: unclear BLINDING PARTICIPANTS/ PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER BIAS: low
Braham 2003(278)	24/22	Knee osteoarthritis Mean age 43 y	12 weeks	Glucosamine 1500 mg Vs	RCT did not meet our inclusion criteria (sample size)

				placebo	
McAlindon 2004(279)	101/104	Knee osteoarthritis Age >65 y	12 weeks	Glucosamine 1500 mg Vs placebo	RANDOMIZATION: low ALLOCATION CONC: unclear BLINDING PARTICIPANTS/ PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER BIAS: low
Cibere 2004(280)	71/66	Knee osteoarthritis Mean age 64 y	24 weeks	Glucosamine 1500 mg Vs placebo	RANDOMIZATION: low ALLOCATION CONC: low BLINDING PARTICIPANTS/ PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: not assessed OTHER BIAS: not assessed
Usha 2004(281)	30/28	Knee osteoarthritis Mean age 51 y	12 weeks	Glucosamine 1500 mg Vs placebo	RCT did not meet our inclusion criteria (sample size)
Clegg 2006(76)	317/313	Knee osteoarthritis Mean age 58 y	24 weeks	Glucosamine 1500 mg Vs placebo	RANDOMIZATION: unclear ALLOCATION CONC: unclear BLINDING PARTICIPANTS/ PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER BIAS: unclear
Herrero-Beaumont 2007(22)	106/104	Knee osteoarthritis Mean age 64 y	24 weeks	Glucosamine 1500 mg Vs placebo	RANDOMIZATION: low ALLOCATION CONC: unclear BLINDING PARTICIPANTS/ PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low

					INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER BIAS: unclear
Rozendaal 2008(282)	111/111	Hip osteoarthritis Mean age 63 y	96 weeks	Glucosamine 1500 mg Vs placebo	RANDOMIZATION: low ALLOCATION CONC: low BLINDING PARTICIPANTS/ PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: not assessed OTHER BIAS: not assessed
Giordano 2009(283)	30/30	Knee osteoarthritis Mean age 58 y	24 weeks	Glucosamine 1500 mg Vs placebo	RCT did not meet our inclusion criteria (sample size)
Fransen 2014(284)	152/151	Knee osteoarthritis Mean age 61 y	96 weeks	Glucosamine 1500 mg Vs placebo	RANDOMIZATION: low ALLOCATION CONC: unclear BLINDING PARTICIPANTS/ PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER BIAS: low
Kwoh 2014(285)	98/103	Knee osteoarthritis Mean age 52 y	24 weeks	Glucosamine 1500 mg Vs placebo	RANDOMIZATION: low ALLOCATION CONC: low BLINDING PARTICIPANTS/ PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low INCOMPLETE OUTCOME DATA: unclear SELECTIVE REPORTING: low OTHER BIAS: unclear

Author's conclusions
"In conclusion, in accordance with our results, it can be definitively stated that oral chondroitin in recommended dosage is more effective than placebo on relieving pain and improving physical function. Compared with placebo, glucosamine showed significant effect on the outcome of stiffness. In the aspect of safety, both compounds are well tolerated."

Study details	n/Population	Comparison	Outcomes		Methodological
Sawitzke 2010(286) Design: RCT (DB, PG) Duration of follow-up: 24 months	n= 662 Mean age: 57-58y Previous pain intervention: excluded drugs were washed out before baseline Other interventions for pain allowed during study: rescue medication: paracetamol (up to 4	5-arm study: 1) Glucosamine 500 mg 3x/day 2) Chondroitin 400 mg 3x/day 3) Glucosamine + chondroitin ("combination") 4) Celecoxib 200 mg/day Vs 5) placebo	Efficacy		RANDO: Unclear: not all patients randomized to original study GAIT (Clegg 2006) were qualified for the subset study ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Drop-out and Exclusions: 53 % • Described: no • Balanced across groups: yes ITT:
			Pain (PO) 20% WOMAC	Placebo: reference Glucosamine: OR 1.16 (0.65 to 2.04) Chondroitin: OR 0.69 (0.40 to 1.21) Combination: OR 0.83 (0.51 to 1.34) All NS	
			Pain (PO) OMERACT/OARSI	Placebo: reference Glucosamine: OR 1.16 (0.74 to 1.83) Chondroitin: OR 0.89 (0.53 to 1.50) Combination: OR 0.85 (0.55 to 1.31) All NS	
			Pain WOMAC (0-100)	Placebo: reference Glucosamine: Difference -0.97 (-5.66 to 3.72) Chondroitin: Difference 2.30 (-3.08 to 7.68)	

	g/ day); though not within 24h of a follow-up visit ; other analgesics were not permitted <u>Inclusion</u> Knee osteoarthritis Age ≥40 y <u>Exclusion</u>			Combination: Difference 0.21 (-4.29 to 4.70) All NS	"modified intention to treat" not defined SELECTIVE REPORTING: yes; safety data insufficiently reported Other important methodological remarks: This study was a extended study with a subset of the GAIT trial (Clegg 2006) Sponsor: National Institute of Arthritis and Musculoskeletal and Skin Diseases and National Center for Complementary and Alternative Medicine
			Function WOMAC	Placebo: reference Glucosamine: Difference 0.56 (-4.69 to 5.82) Chondroitin: Difference 2.16 (-3.8 to 8.11) Combination: Difference 3.20 (-2.21 to 8.61) All NS	
			Safety		
			Serious adverse events assessed as possibly related to the study drugs	Placebo: 1 coronary angioplasty Combination: 1 myocardial infarction	
			Serious adverse events	Placebo: 1 coronary angioplasty, 1 death, 1 hypertension Glucosamine: 1 myocardial infarction, 1 cerebrovascular accident Chondroitin: Combination: 1 myocardial infarction, 1 hypertension, 1 patient with palpitations, 1 TIA	

17.5 Glucosamine vs NSAID for osteoarthritis

Meta-analysis: Towheed 2005(11)

Inclusion criteria: RCTs evaluating the efficacy and toxicity of glucosamine-only preparations in osteoarthritis; versus placebo or other comparator; EXCLUDING temporomandibular joint disorders
Search strategy: CENTRAL and the Cochrane Database of Systematic Reviews (The Cochrane Library), MEDLINE, PREMEDLINE, EMBASE, AMED, ACP Journal Club, DARE were searched from inception to January 2008; handsearching of reference lists.
Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result
Towheed 2005(11) Design: Search date: (month-year)	Glucosamine vs NSAIDs (piroxicam, ibuprofen, celecoxib)	N= 4 n= 997 (Clegg 2006, Qiu 1998, Rovati 1997, Vaz 1982)	Pain	SMD -0.27 (-0.65 to 0.11) I^2=84% NS
		N= 4 n= 580	Number of patients reporting adverse events	**Glucosamine 25/285** **NSAID 90/295** **I^2=0%**

		(Muller-FassBender 1994, Qiu 1998, Rovati 1997, Vaz 1982)		**RR 0.29 (0.19 to 0.44)** **SS fewer patients reporting adverse events with glucosamine**
		N= 5 n= 1215 (Clegg 2006, Muller-FassBender 1994, Qiu 1998, Rovati 1997, Vaz 1982)	Number of Withdrawals due to Adverse Events	**Glucosamine 10/602** **NSAID 41/613** **I^2=79%** **RR 0.16 (0.02 to 1.46)** **SS fewer withdrawals due to adverse events with glucosamine**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (As assessed by Towheed 2005)
Clegg 2006(76)	1583	Symptomatic osteoarthritis of the knee Mean age : 59 y	24 weeks	Glucosamine 500 mg 3x/day Vs Chondroitin sulfaate 1200 mg/day Vs	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Adequate

				Glucosamine + chondroitin sulfate Vs Celecoxib 200 mg/day Vs placebo	NUMBER AND REASON FOR WITHDRAWALS DESCRIBED IN EACH GROUP: Inadequate
Muller-FassBender 1994(287)	200	Osteoarthritis of the knee Mean age : 54 y	4 weeks	Glucosamine 500 mg 3x/day Vs Ibuprofen 400 mg 3x/day	RCT did not meet our inclusion criteria (duration)
Qiu 1998(288)	178	Osteoarthritis of the knee Mean age : 56 y	4 weeks + 2 weeks followup	Glucosamine 500 mg 3x/day Vs Ibuprofen 400 mg 3x/day	ALLOCATION CONC: Inadequate RANDO: Inadequate BLINDING : Adequate NUMBER AND REASON FOR WITHDRAWALS DESCRIBED IN EACH GROUP: Adequate
Rovati 1997(289)	319	Osteoarthritis of the knee Mean age : 66 y	12 weeks + 8 weeks followup	Glucosamine 1500 mg/day Vs Piroxicam 20 mg/day Vs Glucosamine + piroxicam Vs	ALLOCATION CONC: Adequate RANDO: Adequate BLINDING : Adequate NUMBER AND REASON FOR WITHDRAWALS DESCRIBED IN EACH GROUP: Adequate

				Double placebo	
Vaz 1982(290)	40	Osteoarthritis of the knee Mean age : 58 y	8 weeks	Glucosamine 500 mg 3x/day Vs Ibuprofen 400 mg 3x/day	RCT did not meet our inclusion criteria (sample size)

Study details	n/Population	Comparison	Outcomes		Methodological
Chopra 2013(291) Design: RCT (DB, PG) Equivalence trial	n= 440 Mean age: Previous pain intervention: All patients taking NSAID prior to randomization underwent a washout period of 2-5 days	4-arm trial : Ayurvedic formulation (SGC) vs Ayurvedic formulation (SGCG) vs	Efficacy		RANDO: Adequate ALLOCATION CONC: unclear BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 5% Drop-out and Exclusions: 25%
			Pain VAS (PO)	Glucosamine: -2.45 (-2.88 to -2.03) Celecoxib: -1.82 (-2.20 to -1.44) Difference between mean changes from baseline to completion by treatment groups: 95%CI -1.20 to -0.60 Within a *a priori* selected range of ±1.5cm Equivalence between glucosamine and celecoxib	

Duration of follow-up: 24 weeks	Other interventions for pain allowed during study: rescue with paracetamol 500 mg; regular exercise and/or physiotherapy programme begun prior to current trial was allowed, but starting new activity during trial was discouraged; Physical therapy and local applications of pain relieving ointments/gels not allowed. <u>Inclusion</u> Chronic knee pain Age 40-70 Diagnosis knee OA <u>Exclusion</u>	Glucosamine 2g/day* Vs Celecoxib 200 mg/day* *Comparison reported in this literature review	WOMAC pain (PO)	Glucosamine: -2.72 (-3.34 to -2.10) Celecoxib: -1.90 (-2.48 to -1.31) Difference between mean changes from baseline to completion by treatment groups MD 95%CI -1.52 to 0.20 Within a *a priori* selected range of ±2.5 Equivalence between glucosamine and celecoxib	• Described: yes • Balanced across groups: no ITT: "modified" ITT: patients who did not report for follow-up after randomization were excluded from analysis SELECTIVE REPORTING: unclear Other important methodological remarks: Equivalence ranges for the primary efficacy variables was selected a priori at: • Pain VAS ±1.5cm • WOMAC pain: ±2.5 Last observation carried forward for imputation of missing data Sponsor: NMITLI Cell, Council of Scientific and Industrial Research (CSIR), Government of India
			Safety		
			All adverse events	Glucosamine: 32% Celecoxib: 32% No statistical testing	
			Epigastric discomfort	Glucosamine: 15% Celecoxib: 17% No statistical testing	
			Anorexia	Glucosamine: 4% Celecoxib: 1% No statistical testing	
			Nausea	Glucosamine:3% Celecoxib: 3% No statistical testing	

	Pregnant/ lactating women, or with childbearing potential not following adequate contraception; Non-degenarative joint disorder; Severe disabling arthritis ; History of spine and lower limb surgery; Patients on medication likely to influence efficacy evaluation (except paracetamol rescue); History of peptic ulcer bleed or recent active peptic ulcer; Unstable severe medical disease		Vomiting	Glucosamine: 2% Celecoxib: 0% No statistical testing	
			Diarrhoea	Glucosamine: 3% Celecoxib: 4% No statistical testing	
			Constipation	Glucosamine: 4% Celecoxib: 8% No statistical testing	
			Mucous ulcer	Glucosamine: 2% Celecoxib: 4% No statistical testing	
			Skin rash and/or itching	Glucosamine: 3% Celecoxib: 5% No statistical testing	

17.6 Glucosamine vs placebo for low back pain

Meta-analysis: Sodha 2013(292): "The use of glucosamine for chronic low back pain: a systematic review of randomised control trials"
Inclusion criteria: RCTs that evaluated efficacy and toxicity of glucosamine in adults with at least 12 weeks of back pain in combination with radiographic changes of osteoarthritis in the spine
Search strategy: Medline, AMED, CINHAL, Cochrane and EMBASE were searched up until March 2011. Reference lists were screened. Grey literature was searched via opensigle.
Assessment of quality of included trials: yes

Remarks

Three RCTs were found. Two RCTs did not meet our inclusion criteria (sample size <40 participants per study-arm). Only one RCT (Wilkens 2010(293)) met our inclusion criteria. We will report this RCT below.

Study details	n/Population	Comparison	Outcomes		Methodological
Wilkens 2010(293) Design: RCT (DB, PG)	n= 250 Mean age: 49 y Previous pain intervention: not described	Oral glucosamine 500 mg 3x/day Vs placebo	Efficacy RMDQ (PO) (pain-related disability) Greater levels of disability give higher numbers on 24-point scale	**At 6 months** Glucosamine: mean SD 5.0 (4.2 to 5.8) Placebo: 5.0 (4.2 to 5.8) Relatieve cijfers (CI): 0.0 (-1.1 to 1.2) NS **At 1 year**	RANDO: yes ALLOCATION CONC: yes BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 3% Drop-out and Exclusions: 8% • Described: yes

Duration of follow-up: 1 year (6 months postintervention)	Other interventions for pain allowed during study: yes, both analgesic medication and concomitant therapy was allowed <u>Inclusion</u> Chronic nonspecific low back pain (at least 6 months) Older than 25y At least one of the following MRI criteria: disk signal intensity changes, reduced disk height, facet joint changes, modic changes,or high-intensity zone. <u>Exclusion</u>	(during 6 months)		Glucosamine: mean SD 4.8 (3.9 to 5.6 Placebo: 5.5 (4.7 to 6.4) Relatieve cijfers (CI): -0.8 (-2.0 to 0.4) NS	• Balanced across groups: yes ITT: Yes (all randomized participants were analysed according to allocation) SELECTIVE REPORTING: no Sponsor: grants from the EXTRA funds from the Norwegian Foundation for Health and Rehabilitation through the Norwegian Low Back Association, Norwegian Chiropractic Associations Fund, and Wilhelmsens Research Fund. Study medications produced by and purchased from Pharma Nord.
			Low back pain at rest NRS (pain; 11-point scale 0-10)	**At 6 months** Glucosamine: mean SD 2.5 (2.1 to 2.9) Placebo: 2.4 (2.0 to 2.8) Relatieve cijfers (CI): 0.1 (-0.5 to 0.6) NS **At 1 year** Glucosamine: mean SD 2.5 (2.1 to 2.9) Placebo: 2.8 (2.4 to 3.1) Relatieve cijfers (CI): -0.3 (-0.8 to 0.3) NS	
			Low back pain when active NRS	**At 6 months** Glucosamine: mean SD 3.1 (2.7 to 3.5)	

	Symptomatic intervertebral disk herniation or spinal stenosis; Previous lumbar fracture or surgery; Pregnancy or breastfeeding; Seafood allergy; Ongoing psychiatric or somatic disease potentially influencing a patient's pain; Use of any type of glucosamine 1 year prior to enrollment		(pain; 11-point scale 0-10)	Placebo: 2.9 (2.5 to 3.3) Relatieve cijfers (CI): 0.2 (-0.4 to 0.8) NS **At 1 year** Glucosamine: mean SD 3.0 (2.5 to 3.4) Placebo: 2.9 (2.5 to 3.3) Relatieve cijfers (CI): 0.1 (-0.5 to 0.6) NS	
			Health-related QoL (EQ-5D index) -0359 to 1.0 scale	**At 6 months** Glucosamine: mean SD 0.74 (0.70 to 0.78) Placebo: 0.76 (0.72 to 0.80) Relatieve cijfers (CI): 0.0 (-01 to 0.0) NS **At 1 year** Glucosamine: mean SD 0.74 (0.70 to 0.78) Placebo: 0.70 (0.65 to 0.74)	

				Relatieve cijfers (CI): 0.0 (0.0 to 0.1) NS	
			Health-related QoL (EQ-VAS) 0-100	**At 6 months** Glucosamine: mean SD 7.2 (6.6 to 7.8) Placebo: 7.1 (6.7 to 7.4) Relatieve cijfers (CI): -0.1 (-1.3 to 0.3) NS **At 1 year** Glucosamine: mean SD 7.4 (7.0 to 7.7) Placebo: 6.6 (6.3 to 7.0) Relatieve cijfers (CI): 0.7 (0.2 to 1.2) NS	
			Safety		
			Adverse events resulting in study agent termination	Glucosamine: 3.2% Placebo: 4.8% OR 0.66 (0.48 to 1.36) NS	

			All adverse events	Glucosamine: 32% Placebo: 36.8% OR 0.83 (0.49 to 1.40) NS	

17.7 Chondroitin vs placebo for osteoarthritis

Meta-analysis: Zhu 2018(273) "Effectiveness and safety of glucosamine and chondroitin for the treatment of osteoarthritis: a meta-analysis of randomized controlled trials"

Inclusion criteria: RCTs; patients with primary hip and/or knee osteoarthritis; at least two of the following oral treatments: glucosamine, chondroitin, or the two in combination against placebo; EXCLUDED: treatments combined with NSAID; trial arms with sub-therapeutic doses (<1500 mg/day glucosamine and <800 mg/day chondroitin)
Search strategy: PubMed, Embase, Cochrane Library was searched from inception to May 22, 2018.
Assessment of quality of included trials: yes, with Cochrane Risk of Bias Tool
Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result
Zhu 2018(273) Design: SR + MA	Chondroitin Vs placebo	N= 12 n= 3082 (Bourgeois 1998, Bucsi 1998, Clegg 2006, Fransen 2014, Kahan 2009, Mazieres 2001,	Pain	**SMD -0.216 (-0.360 to -0.071)** **p= 0.003** **I^2: 70.8%**

Search date: May 2018		Mazieres 2006, Michel 2005, Uebelhart 1998, Uebelhart 2004, Wildi 2011, Zegels 2013)		**SS in favour of chondroitin**
		N= 10 n= not reported (not reported)	Function	**SMD -0.220 (-0.358 to -0.081)** **p= 0.002** **I^2: 68.3%** **SS in favour of chondroitin**
		N= 8 n= 2714 (Clegg 2006, Fransen 2014, Kahan 2009, Mazieres 2001, Mazieres 2006, Michel 2005, Wildi 2011, Zegels 2013)	Adverse events (overall)	RR 1.28 (0.96 to 1.70) I^2= 9.4 % NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (risk of bias as assessed by Zhu 2018)
Bucsi 1998(294)	39/46	Knee osteoarthritis Mean age 60 y	24 weeks	Chondroitin 1200 mg Vs placebo	RCT did not meet our inclusion criteria (sample size)
Bourgeois 1998(295)	83/44	Knee osteoarthritis Mean age 63 y	13 weeks	Chondroitin 1200 mg Vs placebo	RANDOMIZATION: low ALLOCATION CONC: low BLINDING PARTICIPANTS/ PERSONNEL: low

					BLINDING OUTCOME ASSESSMENT: unclear INCOMPLETE OUTCOME DATA: unclear SELECTIVE REPORTING: low OTHER BIAS: high
Uebelhart 1998(296)	23/23	Knee osteoarthritis Mean age 59 y	48 weeks	Chondroitin 1200 mg Vs placebo	RCT did not meet our inclusion criteria (sample size)
Mazieres 2001(297)	63/67	Knee osteoarthritis Mean age 67 y	12 weeks	Chondroitin 1200 mg Vs placebo	RANDOMIZATION: low ALLOCATION CONC: unclear BLINDING PARTICIPANTS/ PERSONNEL: low BLINDING OUTCOME ASSESSMENT: unclear INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER BIAS: low
Uebelhart 2004(298)	54/56	Knee osteoarthritis Mean age 63 y	12 weeks	Chondroitin 1200 mg Vs placebo	RANDOMIZATION: low 96ALLOCATION CONC: unclear BLINDING PARTICIPANTS/ PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER BIAS: high
Michel 2005(299)	150/150	Knee osteoarthritis Mean age 63 y	96 weeks	Chondroitin 1200 mg Vs placebo	RANDOMIZATION: low ALLOCATION CONC: unclear BLINDING PARTICIPANTS/ PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low

					INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER BIAS: low
Clegg 2006(76)	318/313	Knee osteoarthritis Mean age 58 y	24 weeks	Chondroitin 1200 mg Vs placebo	RANDOMIZATION: unclear ALLOCATION CONC: unclear BLINDING PARTICIPANTS/ PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER BIAS: unclear
Mazieres 2006(300)	153/154	Knee osteoarthritis Mean age 66 y	24 weeks	Chondroitin 1200 mg Vs placebo	RANDOMIZATION: low ALLOCATION CONC: unclear BLINDING PARTICIPANTS/ PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER BIAS: low
Kahan 2009(301)	309/313	Knee and hip osteoarthritis Mean age 62 y	12 weeks	Chondroitin 1200 mg Vs placebo	RANDOMIZATION: unclear ALLOCATION CONC: unclear BLINDING PARTICIPANTS/ PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: unclear OTHER BIAS: low
Wildi 2011(302)	35/34	Knee osteoarthritis Mean age 62 y	48 weeks	Chondroitin 800 mg Vs placebo	RCT did not meet our inclusion criteria (sample size)

Zegels 2013(303)	236/117	Knee osteoarthritis Mean age 65 y	12 weeks	Chondroitin 1200 mg Vs placebo	RANDOMIZATION: low ALLOCATION CONC: unclear BLINDING PARTICIPANTS/ PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER BIAS: low
Fransen 2014(284)	151/151	Knee osteoarthritis Mean age 60 y	96 weeks	Chondroitin 800 mg Vs placebo	RANDOMIZATION: low ALLOCATION CONC: unclear BLINDING PARTICIPANTS/ PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER BIAS: low

Author's conclusions
"In conclusion, in accordance with our results, it can be definitively stated that oral chondroitin in recommended dosage is more effective than placebo on relieving pain and improving physical function. Compared with placebo, glucosamine showed significant effect on the outcome of stiffness. In the aspect of safety, both compounds are well tolerated."

Study details	n/Population	Comparison	Outcomes		Methodological
Sawitzke 2010(286)	n= 662 Mean age: 57-58y	5-arm study:	Efficacy		RANDO: Unclear: not all patients randomized to original study
			Pain (PO) 20% WOMAC	Placebo: reference Glucosamine: OR 1.16 (0.65 to 2.04) Chondroitin: OR 0.69 (0.40 to 1.21)	

Design: RCT (DB, PG) Duration of follow-up: 24 months	Previous pain intervention: excluded drugs were washed out before baseline Other interventions for pain allowed during study: rescue medication: paracetamol (up to 4 g/ day); though not within 24h of a follow-up visit ; other analgesics were not permitted <u>Inclusion</u> Knee osteoarthritis Age ≥40 y <u>Exclusion</u>	6) Glucosamine 500 mg 3x/day 7) Chondroitin 400 mg 3x/day 8) Glucosamine + chondroitin ("combination") 9) Celecoxib 200 mg/day Vs 10) placebo		Combination: OR 0.83 (0.51 to 1.34) All NS	GAIT (Clegg 2006) were qualified for the subset study ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Drop-out and Exclusions: 53 % • Described: no • Balanced across groups: yes ITT: "modified intention to treat" not defined SELECTIVE REPORTING: yes; safety data insufficiently reported Other important methodological remarks: This study was a extended study with a subset of the GAIT trial (Clegg 2006) Sponsor:
			Pain (PO) OMERACT/OARSI	Placebo: reference Glucosamine: OR 1.16 (0.74 to 1.83) Chondroitin: OR 0.89 (0.53 to 1.50) Combination: OR 0.85 (0.55 to 1.31) All NS	
			Pain WOMAC (0-100)	Placebo: reference Glucosamine: Difference -0.97 (-5.66 to 3.72) Chondroitin: Difference 2.30 (-3.08 to 7.68) Combination: Difference 0.21 (-4.29 to 4.70) All NS	
			Function WOMAC	Placebo: reference Glucosamine: Difference 0.56 (-4.69 to 5.82) Chondroitin: Difference 2.16 (-3.8 to 8.11) Combination: Difference 3.20 (-2.21 to 8.61) All NS	
			Safety		

			Serious adverse events assessed as possibly related to the study drugs	Placebo: 1 coronary angioplasty Combination: 1 myocardial infarction	National Institute of Arthritis and Musculoskeletal and Skin Diseases and National Center for Complementary and Alternative Medicine
			Serious adverse events	Placebo: 1 coronary angioplasty, 1 death, 1 hypertension Glucosamine: 1 myocardial infarction, 1 cerebrovascular accident Chondroitin: Combination: 1 myocardial infarction, 1 hypertension, 1 patient with palpitations, 1 TIA	

Study details	n/Population	Comparison	Outcomes		Methodological
Reginster 2017(304)	n= 604; 603 analysed Mean age: 65-66y	Chondroitin sulfate 800 mg 1x/day day	Efficacy		RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (method not described)
			Pain (VAS) (PO) Day 182	chondroitin: 28.6 celecoxib : 30.5 placebo: 36.8	

Design: RCT (DB, PG) Duration of follow-up: 6 months	 Previous pain intervention: see exclusion criteria Other interventions for pain allowed during study: rescue analgesia with paracetamol 500 mg (max 3g/day); no other pharmacological or non-pharmacological interventions for osteoarthritis were allowed. <u>Inclusion</u> Outpatient Primary knee OA Age ≥50y	or Celecoxib 200 mg 1x/day Vs placebo (double dummy)		**chondroitin vs placebo p= 0.001** **SS in favour of chondroitin** **Celecoxib vs placebo p= 0.009** **SS in favour of celecoxib** Chondroitin vs celecoxib p=0.446 NS	BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 0 % Drop-out and Exclusions: 16 % • Described: yes • Balanced across groups: unclear (chondroitin 39; celecoxib 27; placebo 33) ITT: Modified intention to treat, defined as all randomized patients who received one dose of the study medication. SELECTIVE REPORTING: no Sponsor: IBSA Institut Biochimique SA, Pambio-Noranco, Switzerland
			VAS- MCII Proportion of patient reaching minimally important improvement (20 mm of VAS reduction)	chondroitin: 68% celecoxib : 69% placebo: 61% chondroitin vs placebo p= 0.122 NS Celecoxib vs placebo p= 0.098 NS Chondroitin vs celecoxib p=0.914 NS	
			Safety		

	Exclusion Use of any intra-articular injection in target knee in last 6 months, NSAID use in last 5 days, Paracetamol use in the 10hrs before enrollment		Treatment-emergent adverse events Serious adverse events Adverse drug reactions Study withdrawals due to adverse events	"no significant difference between chondroitin sulfate, celecoxib or placebo usage in the rate of TEAEs, SAEs, ADRs and withdrawal related to TEAEs." (no numbers or analysis reported)	(pharmaceutical company marketing chondroitin sulfate)

17.8 Chondroitin vs NSAID for osteoarthritis

Meta-analysis: Singh 2015(10) "Chondroitin for osteoarthritis"

Inclusion criteria: All RCTs or quasi-randomized clinical trials; duration >2 weeks; population adults with osteoarthritis (any joint); comparing chondroitin with placebo or an active control (medication or supplements).
Search strategy: the Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, CINAHL, EMBASE, Science Citation Index (Web of Science) and Current Controlled Trials were searched from inception to November 2013. The US Food and Drug Administration (FDA) and European Medicines Agency (EMEA)websites for adverse effects.
Assessment of quality of included trials: yes

Singh 2015(10) found 3 studies, none of which met our inclusion criteria.

Study details	n/Population	Comparison	Outcomes		Methodological
Pelletier 2016(305) Design: RCT (DB, PG) Duration of follow-up: 24 months	n= 138 Mean age: 61 y Other interventions for pain allowed during study: other NSAID not allowed; paracetamol up to 3g/day allowed with the exception of 48hrs before evaluations <u>Inclusion</u> Age ≥40y Primary symptomatic knee OA whose condition justified symptomatic treatment	Chondroitin sulfate 400 mg 3x/day Vs Celecoxib 200 mg/day (+2 placebo capsules)	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 1.5% Drop-out and Exclusions: 35% • Described: yes • Balanced across groups: unclear (chondr 38; celecoxib 30) ITT: "modified intention to treat"; per protocol population plus those with MRI at 12 months but with
			Pain (VAS) at 24 months	Chondroitin: -24.38 Celecoxib: -26.12 p for difference= 0.697 NS	
			Pain (WOMAC) at 24 months	Chondroitin: -8.81 Celecoxib: -11.09 p for difference= 0.225 NS	
			Function (WOMAC) at 24 months	Chondroitin: -26.92 Celecoxib: -33.52 p for difference= 0.286 NS	
			QoL (SF-36) at 24 months	Improvement in both groups without significant differences between groups	

	<u>Exclusion</u> Significant laboratory abnormalities Other exclusion criteria described in supplement document include other bone and articular diseases, increased risk for prostate cancer, history or high risk of cardiovascular events			Data not shown	MRI missing at 24 months. Participants that discontinued treatment or were lost to follow-up were not included in this modified ITT analysis. SELECTIVE REPORTING: yes, not all outcomes reported (such as QoL) Other important methodological remarks: Primary outcome was cartilage volume loss as measured by qMRI Sponsor: Bioibérica SA
			Safety		
			At least one AE	Chondroitin: 78% Celecoxib: 77% p for difference= >0.999 NS	
			Serious adverse events	Chondroitin: 10% Celecoxib: 6% p for difference= 0.435 NS	
			AE related to study treatment	Chondroitin: 27% Celecoxib: 24% p for difference= 0.745 NS	
			AE leading to study withdrawal	Chondroitin: 13% Celecoxib: 11% p for difference= 0.828 NS	

Study details	n/Population	Comparison	Outcomes		Methodological
Reginster 2017(304) Design: RCT (DB, PG)	n= 604; 603 analysed Mean age: 65-66y Previous pain intervention: see exclusion criteria Other interventions for pain allowed during study: rescue	Chondroitin sulfate 800 mg 1x/day day or Celecoxib 200 mg 1x/day Vs placebo	Efficacy Pain (VAS) (PO) Day 182	chondroitin: 28.6 celecoxib : 30.5 placebo: 36.8 **chondroitin vs placebo p= 0.001** **SS in favour of chondroitin** **Celecoxib vs placebo p= 0.009** **SS in favour of celecoxib** Chondroitin vs celecoxib p=0.446 NS	RANDO: Unclear (method not described) ALLOCATION CONC: Unclear (method not described) BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Lost-to follow-up: 0 % Drop-out and Exclusions: 16 % • Described: yes

6 months	analgesia with paracetamol 500 mg (max 3g/day); no other pharmacological or non-pharmacological interventions for osteoarthritis were allowed. <u>Inclusion</u> Outpatient Primary knee OA Age ≥50y <u>Exclusion</u> Use of any intra-articular injection in target knee in last 6 months, NSAID use in last 5 days, Paracetamol use in the 10hrs before enrollment	(double dummy)	VAS- MCII Proportion of patient reaching minimally important improvement (20 mm of VAS reduction)	chondroitin: 68% celecoxib : 69% placebo: 61% chondroitin vs placebo p= 0.122 NS Celecoxib vs placebo p= 0.098 NS Chondroitin vs celecoxib p=0.914 NS	• Balanced across groups: unclear (chondroitin 39; celecoxib 27; placebo 33) ITT: Modified intention to treat, defined as all randomized patients who received one dose of the study medication. SELECTIVE REPORTING: no Sponsor: IBSA Institut Biochimique SA, Pambio-Noranco, Switzerland (pharmaceutical company marketing chondroitin sulfate)
			Safety		
			Treatment-emergent adverse events Serious adverse events Adverse drug reactions Study withdrawals due to adverse events	"no significant difference between chondroitin sulfate, celecoxib or placebo usage in the rate of TEAEs, SAEs, ADRs and withdrawal related to TEAEs." (no numbers or analysis reported)	

17.9 Glucosamine + chondroitin vs placebo for osteoarthritis

Meta-analysis: Zhu 2018(273) "Effectiveness and safety of glucosamine and chondroitin for the treatment of osteoarthritis: a meta-analysis of randomized controlled trials"

Inclusion criteria: RCTs; patients with primary hip and/or knee osteoarthritis; at least two of the following oral treatments: glucosamine, chondroitin, or the two in combination against placebo; EXCLUDED: treatments combined with NSAID; trial arms with sub-therapeutic doses (<1500 mg/day glucosamine and <800 mg/day chondroitin)
Search strategy: PubMed, Embase, Cochrane Library was searched from inception to May 22, 2018.
Assessment of quality of included trials: yes, with Cochrane Risk of Bias Tool
Other methodological remarks:

Ref	Comparison	N/n	Outcomes	Result
Zhu 2018(273) Design: SR + MA Search date: May 2018		N= 4 n= 1200 (Clegg 2006, Fransen 2014, Lugo 2016, Roman-Blas 2017)	Pain	SMD 0.792 (-0.296 to 1.880) p= 0.153 I^2: 98.50% NS
		N= 4 n= 1200 (Clegg 2006, Fransen 2014, Lugo 2016, Roman-Blas 2017)	Function	SMD 0.556 (-0.368 to 1.480) p= 0.238 I^2: 98% NS

		N= 3 n= 1090 (Clegg 2006, Fransen 2014, Roman-Blas 2017)	Adverse events (overall)	RR 1.40 (0.78 to 2.51) I^2= 0% NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (risk of bias as assessed by Zhu 2018)
Clegg 2006(76)	317/313	Knee osteoarthritis Mean age 58 y	24 weeks	Glucosamine 1500 mg + chondroitin 1200 mg Vs placebo	RANDOMIZATION: unclear ALLOCATION CONC: unclear BLINDING PARTICIPANTS/ PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER BIAS: unclear
Fransen 2014(284)	151/151	Knee osteoarthritis Mean age 61 y	96 weeks	Glucosamine 1500 mg + chondroitin 800 mg Vs placebo	RANDOMIZATION: low ALLOCATION CONC: unclear BLINDING PARTICIPANTS/ PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER BIAS: low
Lugo 2016(306)	65/68	Knee osteoarthritis Mean age 53 y	24 weeks	Glucosamine 1500 mg + chondroitin 1200 mg	RANDOMIZATION: low ALLOCATION CONC: unclear

				Vs placebo	BLINDING PARTICIPANTS/ PERSONNEL: low BLINDING OUTCOME ASSESSMENT: unclear INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER BIAS: low
Roman-Blas 2017(307)	80/78	Knee osteoarthritis Mean age 66 y	24 weeks	Glucosamine 1500 mg + chondroitin 1200 mg Vs placebo	RANDOMIZATION: low ALLOCATION CONC: unclear BLINDING PARTICIPANTS/ PERSONNEL: low BLINDING OUTCOME ASSESSMENT: low INCOMPLETE OUTCOME DATA: low SELECTIVE REPORTING: low OTHER BIAS: high

Author's conclusions
"In conclusion, in accordance with our results, it can be definitively stated that oral chondroitin in recommended dosage is more effective than placebo on relieving pain and improving physical function. Compared with placebo, glucosamine showed significant effect on the outcome of stiffness. In the aspect of safety, both compounds are well tolerated."

Study details	n/Population	Comparison	Outcomes		Methodological
Sawitzke 2010(286)	n= 662 Mean age: 57-58y	5-arm study:	Efficacy		RANDO: Unclear: not all patients randomized to original study
			Pain (PO) 20% WOMAC	Placebo: reference Glucosamine: OR 1.16 (0.65 to 2.04) Chondroitin: OR 0.69 (0.40 to 1.21)	

Design: RCT (DB, PG) Duration of follow-up: 24 months	Previous pain intervention: excluded drugs were washed out before baseline Other interventions for pain allowed during study: rescue medication: paracetamol (up to 4 g/ day); though not within 24h of a follow-up visit ; other analgesics were not permitted <u>Inclusion</u> Knee osteoarthritis Age ≥40 y <u>Exclusion</u>	11) Glucosamine 500 mg 3x/day 12) Chondroitin 400 mg 3x/day 13) Glucosamine + chondroitin ("combination") 14) Celecoxib 200 mg/day Vs 15) placebo		Combination: OR 0.83 (0.51 to 1.34) All NS	GAIT (Clegg 2006) were qualified for the subset study ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Drop-out and Exclusions: 53 % • Described: no • Balanced across groups: yes ITT: "modified intention to treat" not defined SELECTIVE REPORTING: yes; safety data insufficiently reported Other important methodological remarks: This study was a extended study with a subset of the GAIT trial (Clegg 2006) Sponsor:
			Pain (PO) OMERACT/OARSI	Placebo: reference Glucosamine: OR 1.16 (0.74 to 1.83) Chondroitin: OR 0.89 (0.53 to 1.50) Combination: OR 0.85 (0.55 to 1.31) All NS	
			Pain WOMAC (0-100)	Placebo: reference Glucosamine: Difference -0.97 (-5.66 to 3.72) Chondroitin: Difference 2.30 (-3.08 to 7.68) Combination: Difference 0.21 (-4.29 to 4.70) All NS	
			Function WOMAC	Placebo: reference Glucosamine: Difference 0.56 (-4.69 to 5.82) Chondroitin: Difference 2.16 (-3.8 to 8.11) Combination: Difference 3.20 (-2.21 to 8.61) All NS	
			Safety		

			Serious adverse events assessed as possibly related to the study drugs	Placebo: 1 coronary angioplasty Combination: 1 myocardial infarction	National Institute of Arthritis and Musculoskeletal and Skin Diseases and National Center for Complementary and Alternative Medicine
			Serious adverse events	Placebo: 1 coronary angioplasty, 1 death, 1 hypertension Glucosamine: 1 myocardial infarction, 1 cerebrovascular accident Chondroitin: Combination: 1 myocardial infarction, 1 hypertension, 1 patient with palpitations, 1 TIA	

17.10 Glucosamine + chondroitin vs NSAID for osteoarthritis

Meta-analysis: Singh 2015(10) “Chondroitin for osteoarthritis”

Inclusion criteria: All RCTs or quasi-randomized clinical trials; duration >2 weeks; population adults with osteoarthritis (any joint); comparing chondroitin with placebo or an active control (medication or supplements).
Search strategy: the Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, CINAHL, EMBASE, Science Citation Index (Web of Science) and Current Controlled Trials were searched from inception to November 2013. The US Food and Drug Administration (FDA) and European Medicines Agency (EMEA)websites for adverse effects.
Assessment of quality of included trials: yes

Singh 2015(10) found 4 studies; 2 of which did not meet our inclusion criteria (sample size). The remaining 2 RCTs did not analyse the comparison of GLU + CHON vs NSAID, but rather compared each arm to placebo. These were previously reported in the chapter “Glucosamine + chondroitin vs placebo”.

Study details	n/Population	Comparison	Outcomes		Methodological
Hochberg 2016(308) Design: RCT (DB, PG) Non-inferiority study	n= 606 (568 included in ITT analysis; 522 in per protocol analysis) Mean age: 62-63y Other interventions for pain allowed during study: rescue medication: paracetamol up to	Chondroitin sulfate 400 mg + Glucosamine 500mg 3x/day Vs Celecoxib 200 mg/day	Efficacy		RANDO: Adequate ALLOCATION CONC: unclear BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Drop-out and Exclusions: 23 % • Described: yes
			WOMAC pain (PO)	Chondroitin+ glucosamine: -185.7 Celecoxib: -186.8 Treatment difference : -1.1 (-22.0 to 19.8) p=0.92 Chondroitin+ glucosamine is non-inferior to celecoxib	
			WOMAC function	Chondroitin+ glucosamine: -504.4 Celecoxib: -525.6 Treatment difference : -21.2 (-87.3 to 45.0) p=0.53	

Duration of follow-up: 6 months	3g/day, except during 48h before clinical evaluation <u>Inclusion</u> Age: ≥40 y Primary knee osteoarthritis Severe pain at inclusion <u>Exclusion</u> Concurrent medical or arthritic conditions that could confound the evaluation of the index joint Coexisting disease that could preclude successful completion of the trial	For 6 months		NS	• Balanced across groups: unclear (CS+G: 64; celecoxib: 74) ITT: Per protocol population and (modified?) intention to treat to test robustness of the results for PO SELECTIVE REPORTING: no Other important methodological remarks: the non-inferiority margin was -40 Sponsor: Bioiberica SA, Barcelona, Spain.
			VAS pain	Chondroitin+ glucosamine: -35.1 Celecoxib: -35.3 Treatment difference : -0.22 (-4.8 to 4.3) P= 0.92 NS	
			EuroQoL-5D VAS	Chondroitin+ glucosamine: 69.1 Celecoxib: 70.2 Treatment difference P=0.54 NS	
			Safety		
			Proportion of subjects having at least one treatment-emergent adverse event	Chondroitin+ glucosamine: 51.0% Celecoxib: 50.5%	

			Serious adverse events	Chondroitin+ glucosamine: 2.3% Celecoxib: 3.3%	

17.11 Hyaluronic acid for chronic pain

We found no systematic reviews or RCTs evaluating oral hyaluronic acid in chronic pain that met our inclusion criteria.

Oe 2016(309) "Oral hyaluronan relieves knee pain: a review" is a narrative review focusing on oral hyaluronic acid for knee pain. The RCTs reported in this review did not meet our inclusion criteria (sample size <40 per study arm).

17.12 Traumeel for chronic pain

Meta-analysis: Bao 2014(310) "Complementary and alternative medicine for cancer pain: an overview of systematic reviews" Inclusion criteria: systematic review or meta-analyses of complementary and alternative medicine (with or without conventional cancer treatments) on adult cancer pain. Search strategy: Cochrane Library, PubMed, Embase, and ISIWeb of Knowledge were searched up until February 2014.

Assessment of quality of included trials: assessment of included reviews (AMSTAR)

Remarks
Systematic review Bao 2014 found an SR including two RCTs evaluating Traumeel for cancer pain. They did not meet our inclusion criteria (sample size <40 per study arm).

18 Appendix. Evidence tables. Safety

18.1 Paracetamol and respiratory adverse events

Children

SR Cheelo 2015(311) searched for cohort studies and controlled trials of incident asthma that exmined exposure to paracetamol during pregnancy and/or during the first 2 years of life, and included asthma outcomes after the age of 5.

EMBASE and PUBMED was searched up until August 2013.

Ten cohort studies were found.

*details of included cohort studies below

SR Cheelo 2015(311) (10 studies) Search up until august 2013	country population follow-up	n	comparison	Main results **Outcome: Asthma**
Källen 2013(335) Retrospective cohort	Sweden Paracetamol use during pregnancy 2-10 years	685015	Paracetamol use vs no paracetamol use	**Adj. OR 1.50 (1.37 to 1.63)** **SS** **More risk with paracetamol** Confounders adjusted for: Year of birth, parity, BMI, maternal age, smoking
Andersen 2012(336) Retrospective cohort	Denmark Paracetamol use during pregnancy 2-13 years	197060	Paracetamol use vs no paracetamol use	**Adj RR 1.35 (1.17 to 1.57)** **SS** **More risk with paracetamol** Confounders adjusted for: Gender, birth order, maternal smoking, maternal asthma, maternal age at delivery, maternal use of antibiotics, BMI, delivery mode, year of birth, country of residence, gestational age
Kreiner-Møller 2012(337) Prospective cohort	Denmark Paracetamol use up until 12 months of age 7 years	411	Paracetamol use vs no paracetamol use	Cohort study did not meet our inclusion criteria (sample size) Adj OR 0.98 (0.75 to 1.29) NS Confounders adjusted for: **Concurrent lower respiratory tract infections**

Bakkeheim 2011(338) Prospective cohort	Norway Paracetamol use during pregnancy and up to 6 months of age 10 years	1016	Paracetamol use vs no paracetamol use	Adj OR 1.43 (0.80 to 2.56) NS Confounders adjusted for: Gender, **respiratory tract infections**
Lowe 2010 (339)Prospective cohort	Australia Paracetamol use up to 2 years of age 7 years	620	Association between total days of paracetamol use and risk of asthma	Cohort study did not meet our inclusion criteria (sample size) Adj OR 1.08 (0.91 to 1.29) NS Confounders adjusted for: Gender, older siblings, parental history of asthma or eczema, **respiratory tract infection**
Schnabel 2010(340)Prospective cohort	Germany Paracetamol use from 6 to 24 months of age 6 years	2296	Paracetamol use for non-respiratory tract infection in children with asthma vs not in asthma	P 0.89 NS Confounders adjusted for: **Respiratory tract infections**, sex, parental education, study region
Wickens 2010 (341)Prospective cohort	New Zealand Paracetamol use from birth to 15 months of age 5-6 years	914	Paracetamol use vs no paracetamol use	Adj OR 1.78 (0.75 to 4.21) NS Confounders adjusted for: Gender, antibiotic use, maternal age, parental history of asthma, eczema or hay fever, socioeconomic status, **respiratory tract infections,** parity, siblings

Shaheen 2010(342) & Shaheen 2005(343) Prospective cohort	UK Paracetamol use during pregnancy and up to 6 months of age 7 years	11438 And 8511	Paracetamol use vs no paracetamol use	Adj OR 1.29 (0.74 to 2.27) NS **Prenatal use 1.39 (1.21 to 1.61)** **SS** **More risk with paracetamol** Confounders adjusted for: Partner's paracetamol use, postnatal paracetamol use, Gender, maternal asthma, maternal age, multiple pregnancy, maternal smoking, parity, mother's education level, mother's ethnicity, and 24 other factors, not including respiratory tract infections
Kang 2009 (344)Prospective cohort	USA Paracetamol use during pregnancy 6 years	1505	Paracetamol use vs no paracetamol use	Adj OR 0.76 (0.53 to 1) NS Confounders adjusted for: Maternal ethnicity and allergy, **childhood respiratory tract infections**, exposure to tobacco antibiotic use and 8 other factors
Rebordosa 2008(345) Prospective cohort	Denmark Paracetamol use during pregnancy 7 years	12733	Paracetamol use vs no paracetamol use	**Adj RR 1.15 (1.02 to 1.29)** **SS** **More risk with paracetamol** Confounders adjusted for: Gender, antibiotic use during pregnancy, exposure to tobacco smoke, social class

Our literature search yielded an additional 5 cohort study and one RCT

Study	country population follow-up	n	comparison	Main results **Outcome: Asthma**
Wang 2013(346) Prospective cohort	Taiwan Paracetamol use up until 1 year of age 6 years	263620	Paracetamol use vs no paracetamol use	Birth cohort 1998 **Adj HR 1.66 (1.58 to 1.74)** **SS** **More risk with paracetamol** Birth cohort 2003 HR 1.04 (0.90 to 1.21) NS Confounders adjusted for: gender, socio-economic status at birth, geographical area at birth and healthcare utilization (including numbers of ambulatory visits, inpatient visits, otitis media diagnoses and **bronchitis diagnoses**)
Liu 2016(347) Prospective cohort	Denmark Paracetamol use during pregnancy 3 years or longer	63652	Paracetamol use vs no paracetamol use	**Adj HR 1.16 (1.11 to 1.22)** **SS** **More risk with paracetamol** Adjusted for maternal age at delivery, maternal parity, maternal pre-pregnancy body mass index, socioeconomic status, maternal smoking during pregnancy, maternal history of asthma, maternal fever during pregnancy, maternal inflammation or infection during pregnancy, maternal antibiotic use for respiratory tract infections, maternal muscle or joint disease during pregnancy, maternal nausea during pregnancy, and sex of the child.
Magnus 2016(348)	Norway	45607	Paracetamol use vs no paracetamol use	**Prenatal exposure only** **Adj RR 1.17 (1.04 to 1.31)**

Prospective cohort	Paracetamol use during pregnancy up until 6 months of age 7 years			**SS more risk with paracetamol** **Infant exposure only** **Adj RR 1.27 (1.11 to 1.46)** **SS more risk with paracetamol** **Both** **Adj RR 1.26 (1.10 to 1.43)** **SS more risk with paracetamol** Confounders adjusted for: Associations adjusted for maternal age, parity, education, pre-pregnancy body-mass index, smoking during pregnancy, asthma, respiratory tract infections/influenza during pregnancy, fever during pregnancy, pain during pregnancy and antibiotic use during pregnancy, in addition to the child's gender, birth weight, breastfeeding the first 6 months of life, **respiratory tract infections by 6 months**, body mass index at 6 months and use of antibiotics by 6 months.
Piler 2018(349) Prospective cohort	Czech republic Paracetamol use during pregnancy up until 6 months of age 11 years	3329	Paracetamol use vs no paracetamol use	Prenatal exposure only Adj OR 1.12 (0.25 to 4.98) NS **Infant exposure only** **Adj OR 1.56 (1.06 to 2.30)** **SS more risk with paracetamol** Both Adj OR 1.83 (0.91 to 3.71) NS

				Adjusted for mother's age, mother's education, marital status, parity, father's age, mother's asthma history, father's asthma history, pre-pregnancy body mass index, cold/influenza during pregnancy, child gender, birth weight, breastfeeding period, type of house, pet at house, visits kindergarten at the age of 3, mother smoking during pregnancy, passive smoking at age of 3 and mother's alcohol consumption during first trimester
Sordillo 2015(350) Prospective cohort	USA Paracetamol use during pregnancy and first year of life 10 years	1490	Paracetamol use vs no paracetamol use	Early life intake: Early childhood outcomes (3-5 years) Adj OR 0.94 (0.78 to 1.14) NS Midchildhood outcomes (7-10 y) Adj OR 1.19 (0.94 to 1.50) NS Adjusted for: **respiratory tract and ear infections,** covariates for child's sex and multivitamin intake, mother's age at enrollment, race/ethnicity, prepregnancy BMI, household income, number of children less than 12 years of age in the home, breast-feeding duration, passive smoking exposure, smoking during pregnancy, child care attendance, and maternal and paternal history of asthma. Prenatal intake:

				Early childhood outcomes (3-5 years) **Adj OR 1.26 (1.02 to 1.58)** **SS** **More risk with prenatal paracetamol intake** Midchildhood outcomes (7-10 y) Adj OR 1.25 (0.94 to 1.65) NS Adjusted for: child's sex and multivitamin intake, mother's age at enrollment, race/ethnicity, prepregnancy BMI, household income, number of children less than 12 years of age in the home, breast-feeding duration, passive smoking exposure, smoking during pregnancy, child care attendance, and maternal and paternal history of asthma Cumulative exposure: Early childhood outcomes (3-5 years) **Adj OR 1.27 (1.08 to 1.49)** **SS** **More risk with paracetamol intake** Midchildhood outcomes (7-10 y) **Adj OR 1.34 (1.11 to 1.62)** **SS** **More risk with paracetamol intake** Adjusted for: **respiratory tract and ear infections** in the first year of life.

Study	country population follow-up	n	comparison	Main results **Outcome: Number of asthma exacerbations**
Sheehan 2016(312) RCT	USA Children (12 to 59 months) with mild persistent asthma 46 weeks	300	Paracetamol vs ibuprofen (when needed for the alleviation of fever or pain over the course of 48 weeks)	Paracetamol 0.81 per participant Ibuprofen 0.87 per participant Paracetamol vs ibuprofen Relative rate 0.94 (0.69 to 1.28) NS

Adults

Study	country population follow-up	n	comparison	Main results
Barr 2004(313) Prospective cohort	USA Nurses' Health study (married female registered nurses age 30-55y) 8 years	121700	>14 days/month paracetamol use Vs nonuse	**Outcome:new diagnosis of asthma** **Adj . RR 1.63 (1.11 to 2.39)** **SS** **More risk with paracetamol** Adjusted for: age, time period of diagnosis, frequency of aspirin use, frequency of other NSAID use, race/ethnicity, husband's educational attainment, region, smoking

				status, secondhand smoke exposure, body mass index, postmenopausal hormone use, and type of menopause.
Amberbir 2011(314) Retrospective cohort	Ethiopia Women 3 years after giving birth 1 year	1065	Paracetamol use vs no paracetamol use in past month	**Outcome: Asthma** 1-3 tablets Adj. OR 1.76 (0.36,8.62 NS 4 or more tablets: Adj. OR 1.64 (0.52,5.14) NS Adjusted for age, area of residence and education level
Study	country population follow-up	n	comparison	Main results
Ioannides 2014(315) RCT	New Zealand Adults with asthma 12 weeks	94	Paracetamol 1 g 2x/day Vs placebo	**Bronchial hyper-responsiveness** (measured as the provocation concentration of methacholine causing a 20% reduction in FEV1 at week 12) MD -0.48 (-1.28 to 0.32) NS

18.2 Paracetamol and hepatic adverse events

Dart 2007(316) sought articles involving repeated dosing of a therapeutic dose (4 g/day or less) of paracetamol of at least 24 hours.
MEDLINE and EMBASE were searched up until 2003.

Results:

791 articles were found, including RCTs, observational studies, case studies and chart reviews. The RCTs and observational studies ("prospective studies") were analyzed separately from the case studies and chart reviews ("retrospective studies") It was not reported how many RCTs and how many and what kind of observational studies were found.

30865 patients were enrolled in the RCTs and observational studies. The median duration of treatment with paracetamol was 6 days.

No reports of liver failure, transplantation, or death were made.

An increase in the serum aminotransferase level that exceeded the upper limit of normal was reported in 129 patients (0.4%)

A comparison group was not reported or evaluated.

18.3 NSAIDs and gastrointestinal adverse events

SR Castellsague 2012(317) sought observational studies (case-control or cohort studies) comparing the risk of upper gastrointestinal complications (peptic ulcer perforations, obstructions and bleeding) of individual NSAIDs with non-use of NSAIDs.

MEDLINE was searched up until May 2011.

Results:
Ibuprofen: RR 1.94 (1.62 to 2.32); SS more UGIC with ibuprofen
Naproxen: RR 3.67 (2.84 to 4.75); SS more UGIC with naproxen
Diclofenac: RR 3.33 (2.51 to 4.41); SS more UGIC with diclofenac

* included cohort study details reported below

Study	country population follow-up	n	comparison	Main results **UGIC**
Garcia-Rodriguez 1998(351)	Study did not meet our inclusion criteria (case-control)			
Garcia-Rodriguez 2001(352)	Study did not meet our inclusion criteria (case-control)			
Garcia-Rodriguez 2007(353)	Study did not meet our inclusion criteria (case-control)			
Griffin 1991(354)	Study did not meet our inclusion criteria (case-control)			
Helin-Salmivaara 2007(355)	Study did not meet our inclusion criteria (case-control)			
Hippisley-Cox 2005(356)	Study did not meet our inclusion criteria (case-control)			
Castellsague 2009(357)	Study did not meet our inclusion criteria (case-control)			
McMahon 1997(358)	Scotland	156398	NSAID prescription vs no NSAID prescription	Ibuprofen RR 0.24 (0.05 to 1.19) NS **Naproxen RR 4.49 (2.50 to 8.06) SS** **Diclofenac RR 5.48 (3.20 to 9.39) SS**
Menniti-Ippolito 1998(359)	Italy	201357	NSAID prescription vs no NSAID prescription	Naproxen RR 1.70 (0.52 to 5.51) NS **Diclofenac RR 3.20 (1.90 to 5.39) SS**
Perez-Gutthann 1997(360)	Study did not meet our inclusion criteria (case-control)			

SR Arias 2019(318) sought observational studies (case-control, case-crossover or cohort studies) comparing the risk of any gastrointestinal event of COX-2-selective NSAID with non-use of NSAID.

MEDLINE and EMBASE was searched up until September 2017.

Results:
Celecoxib: RR 1.53 (1.19 to 1.97); SS more gastrointestinal adverse outcomes with celecoxib

* included cohort study details reported below

Study	country population follow-up	n	comparison	Main results **UGIC**
Battistella 2005(361)	Study did not meet our inclusion criteria (case-control or case-crossover)			
Castellsague 2013(362)	Study did not meet our inclusion criteria (case-control or case-crossover)			
Chang 2011a(363)	Study did not meet our inclusion criteria (case-control or case-crossover)			
Chang 2011b(364)	Study did not meet our inclusion criteria (case-control or case-crossover)			
Helin Salmivaara 2007(355)	Study did not meet our inclusion criteria (case-control or case-crossover)			
Hippisley-Cox 2005(356)	Study did not meet our inclusion criteria (case-control or case-crossover)			
Lanas 2006(365)	Study did not meet our inclusion criteria (case-control or case-crossover)			
Laporte 2004(366)	Study did not meet our inclusion criteria (case-control or case-crossover)			
Mamdani 2002(367)	Canada	143969	Coxib use vs no coxib use	Celecoxib RR 1.00 (0.70 to 1.43); NS
Nagata 2014a(368)	Study did not meet our inclusion criteria (case-control or case-crossover)			
Nagata 2014b(369)	Study did not meet our inclusion criteria (case-control or case-crossover)			
Nørgård 2004(370)	Study did not meet our inclusion criteria (case-control or case-crossover)			

18.4 NSAIDs and renal adverse events

NSAID use and acute kidney injury

SR Zhang(319) searched for cross-sectional, cohort and case-control studies evaluating the association between NSAID use and acute kidney injury.

MEDLINE and EMBASE were searched up until June 2016.

Results:
10 case-control studies were found. We do not report details of these studies as they did not meet our inclusion criteria.

A higher pooled odds ratio of acute kidney injury was found for current NSAID exposure compared to no exposure: OR 1.73 (1.44 to 2.07).

A risk of OR 2.51 (1.52 to 2.68) was observed in older people.

SR Ungprasert 2015(320) sought observational studies (case-control or cohort studies) comparing the risk of acute kidney injury in NSAID users versus non-users.

MEDLINE, EMBASE and Cochrane databases were searched up until September 2014.

Results:
One retrospective cohort study* and four case-control studies were found. Results were pooled according to NSAID.

Ibuprofen v no ibuprofen: **RR 1.99 (1.55 to 2.56); SS more AKI with ibuprofen**
Naproxen vs no naproxen : **RR 1.69 (1.23 to 2.32); SS more AKI with naproxen**
Diclofenac vs no diclofenac: RR 1.77 (0.92 to 3.44); NS

* included cohort study details reported below

Study	country population follow-up	n	comparison	Main results **AKI**
Guess 1985(371)	Canada Subjects who filled a prescription for NSAIDs in 1983. Controls were subjects without NSAID prescription from same database. 1 year	950384	NSAID prescription vs no NSAID prescription	Ibuprofen RR 0.94 (0.13 to 6.85); NS Naproxen RR 2.26 (0.54 to 9.43); NS Diclofenac RR 4.64 (0.63 to 33.94); NS

NSAID use and progression of chronic kidney disease

SR Nderitu 2013(321) searched observational studies with durations evaluating the association between NSAID use and chronic kidney disease progression.

MEDLINE, EMBASE, Cochrane, AMED, BNI and CINAHL databases were searched up until September 2011.

Results:
Five cohort studies, one case-control and one cross-sectional study were found.
The results of three cohort studies were pooled.

Risk of accelerated CKD progression:

NSAID use vs no NSAID use:
OR =1.04 (0.90 to 1.20)
NS

High-dose NSAID vs no NSAID use
OR= 1.26 (1.06 to 1.50)
SS more accelerated CKD progression with high-dose NSAID use

* included cohort study details reported below

Study	country population follow-up	n	comparison	Main results **Accelerated eGFR decline**
Gooch 2007(372)	Canada CKD	10184	NSAID use vs no NSAID use NSAID high dose use (>90th percentile) vs no NSAID use	Any NSAID use OR 0.82 (0.59 to 1.15) NS **High dose** **OR 1.26 (1.04 to 1.53)** **SS more accelerated eGFR decline with high dose NSAID**
Hemmelgarn 2007(373)	Canada CKD	10184	NSAID use vs no NSAID use	OR 1.00 (0.90 to 1.20) NS

Yarger 2011(374)	USA CKD	34295	No NSAID use vs medium use vs high use (criteria not defined)	Low-medium dose OR 0.94 (0.78 to 1.12) NS High dose OR 1.28 (0.84 to 1.93) NS

NSAID use and analgesic nephropathy

SR Yaxley 2016)(322) searched for observational studies and RCTs evaluating the association between long-term heavy NSAID use and renal insufficiency.

PubMed and Griffith University Library electronic databases were searched up until March 2016.

Results:
5 cohort studies and four case-control studies were found.

No meta-analysis of the results was made.

None of the cohort studies identified a relationship between long-term heavy NSAID use and the development of chronic renal impairment.

Study	country population follow-up	n	comparison	Main results **Renal impairment**

Agodoa 2008(375)	Random civilians reporting daily ibuprofen ingestion for at least 1 month at any time previously	305 study patients, 1691 controls	Vs max consecutive daily ibuprofen consumption of less than 1 month	OR 1.21 (0.7-2.1); NS
Curhan 2004(376)	Female registered nurses reporting lifetime consumption of 100-499 g NSAIDs, 500-2999 g NSAIDs, or ≥3000 g NSAIDs	840 study patients, 790 controls	vs < 100 g lifetime consumption of NSAID	100-499 g NSAIDs OR 1.33 (0.79 to 2.24); NS 500-2999 g NSAIDs OR 1.10 (0.70 to 1.92); NS ≥3000 g NSAIDs OR 1.08 (0.67 to 1.76); NS
Kohlhagen 2002(377)	Study did not meet our inclusion criteria (sample size)			
Moller 2015(378)	Health registry patients with rheumatoid arthritis and at least one filled prescription for NSAIDs over study duration 3.2 years	2739 study patients, 1362 controls	RA patients, no filled prescription for NSAID over study duration	GFR decline P=0.63 NS
Rexrode 2001(379)	Male physicians reporting lifetime consumption of 12-1499 NSAID tablets, 1500-2499 tablets, or ≥2500 tablets	4686 study patients, 5700 controls	vs lifetime consumption of < 12 tablets of NSAID	12-1499 NSAID tablets RR 1.01 (0.84 to 1.23); NS 1500-2499 tablets RR 1.06 (0.66 to 1.72); NS ≥2500 tablets RR 1.01 (0.73 to 1.14); NS

18.5 NSAIDs and cardiovascular adverse events

SR Gunter 2016(323) sought RCTs and prospective cohort studies that evaluated cardiovascular risks of 8 NSAIDs (**ibuprofen**, **diclofenac**, **naproxen**, meloxicam, **etoricoxib**, **celecoxib**, lumiracoxib, rofecoxib) against other NSAID or against placebo.

MEDLINE, EMBASE and Cochrane databases were searched up until August 2014.

Results:

NSAID vs placebo

Outcome: Myocardial infarction (MI)
Celecoxib OR 0.917 (0.978 to 2.224); NS
Naproxen OR 1.516 (0.699 to 3.288); NS

Outcome: Stroke
Celecoxib OR 1.520 (0.559 to 4.135); NS
Diclofenac OR 2.618 (0.106 to 64.861); NS
Naproxen OR 2.168 (0.821 to 5.722); NS

Outcome: CV death
Celecoxib OR 1.553 (0.844 to 2.858); NS
Naproxen OR 1.508 (0.597 to 2.601) NS

Outcome: Composite CV (= Any MI, any stroke, CV death)
Celecoxib OR 1.351 (0.862 to 2.116); NS
Diclofenac OR 2.618 (0.106 to 64.861); NS
Naproxen OR 1.711 (0.971 to 3.015); NS

Celecoxib vs nonselective NSAID (ibuprofen, naproxen, diclofenac)

Outcome: Myocardial infarction (MI)
OR 1.089 (0.683 to 1.735); NS

Outcome: Stroke
OR 0.517 (0.287 to 0.929)
SS fewer strokes with celecoxib

Outcome: CV death
OR 1.249 (0.629 to 2.477); NS

Outcome: Composite CV (= Any MI, any stroke, CV death)
OR 0.897 (0.650 to 1.237); NS

* included cohort study details reported below

Study	country population follow-up	n	comparison
ADAPT Research group 2006(380) RCT	Alzheimer's disease 36 months	2528	Celecoxib vs naproxen vs placebo
Laharie 2010(381) Cohort	France 2.5 months	46454	Celecoxib vs nonselective NSAID
Silverstein 2000(382) RCT	Rheumatoid arthritis and osteoarthritis 12 months	7968	Celecoxib vs ibuprofen vs diclofenac
Papadimitrakopoulou 2008(383) RCT	Premalignant oral lesions 7 months	RCT did not meet our inclusion criteria (sample size)	Celecoxib vs placebo
Arber 2006(384) RCT	Colorectal adenomatous polyps 36 months	1738	Celecoxib vs placebo
Cryer 2013(385) RCT	Osteoarthritis 6 months	8067	Celecoxib vs placebo

Singh 2006(386) RCT	Osteoarthritis 3 months	13274	Celecoxib vs naproxen vs diclofenac
Farkouh 2004(387) RCT	Osteoarthritis 14 months	18325	Ibuprofen vs naproxen
Ghosh 2007(388) RCT	Osteoarthritis 1 month	427	Diclofenac vs placebo

18.6 Topical NSAIDs versus oral NSAIDs

We did not find any additional systematic reviews of observational studies that searched for and reported safety outcomes of topical NSAIDs versus oral NSAIDs.

19 Appendix. Search strategy

19.1 Paracetamol

("Chronic Pain"[Mesh] OR "Pain Management"[Mesh] OR ((chronic[tiab] OR intractable[tiab] OR refractory[tiab] OR persistent[tiab] OR long-term[tiab] OR long dur*[tiab]) AND (pain[tiab] OR "Pain"[Mesh])) OR Neuralg*[tiab] OR *neuropath*[tiab] OR "Peripheral Nervous System Diseases"[Mesh] OR "cranial Nerve Diseases"[Mesh] OR "Somatosensory Disorders"[Mesh] OR "Cancer Pain"[Mesh] OR cancer pain[tiab] OR oncologic pain[tiab] OR cancer-related pain[tiab] OR "Osteoarthritis"[Mesh])
AND
("Acetaminophen"[Mesh] OR acetaminophen[tiab] OR paracetamol[tiab])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])
AND
("2015/07/01"[Date - Publication] : "2019/05/01"[Date - Publication])

19.2 NSAID

("Chronic Pain"[Mesh] OR "Pain Management"[Mesh] OR ((chronic[tiab] OR intractable[tiab] OR refractory[tiab] OR persistent[tiab] OR long-term[tiab] OR long dur*[tiab]) AND (pain[tiab] OR "Pain"[Mesh])) OR Neuralg*[tiab] OR *neuropath*[tiab] OR "Peripheral Nervous System Diseases"[Mesh] OR "cranial Nerve Diseases"[Mesh] OR "Somatosensory Disorders"[Mesh] OR "Cancer Pain"[Mesh] OR cancer pain[tiab] OR oncologic pain[tiab] OR cancer-related pain[tiab] OR "Osteoarthritis"[Mesh])
AND
("Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR "Diclofenac"[Mesh] OR "Ketorolac"[Mesh] OR "Ibuprofen"[Mesh] OR "Ketoprofen"[Mesh] OR "Naproxen"[Mesh] OR "Oxaprozin"[Mesh] OR "Indomethacin"[Mesh] OR "Meloxicam"[Mesh] OR "Piroxicam"[Mesh] OR "Celecoxib"[Mesh] OR "Etoricoxib"[Mesh] OR "Nabumetone"[Mesh] OR "Cyclooxygenase 2 Inhibitors"[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 Aceclofenac[tiab] OR Diclofenac[tiab] OR Ketorolac[tiab] OR Dexketoprofen[tiab] OR Ibuprofen[tiab] OR Ketoprofen[tiab] OR Naproxen[tiab] OR Oxaprozin*[tiab] OR Indometacin*[tiab] OR Proglumetacin*[tiab] OR Meloxicam[tiab] OR Piroxicam[tiab] OR Tenoxicam[tiab] OR Celecoxib[tiab] OR Etoricoxib[tiab] OR Parecoxib[tiab] OR Nabumeton*[tiab] OR "Aspirin"[Mesh] OR aspirin[tiab] OR acetylsalicyl*[tiab])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])
AND
("2015/04/01"[Date - Publication] : "2019/05/01"[Date - Publication])

19.3 Additional search: nabumetone

("Chronic Pain"[Mesh] OR "Pain Management"[Mesh] OR ((chronic[tiab] OR intractable[tiab] OR refractory[tiab] OR persistent[tiab] OR long-term[tiab] OR long dur*[tiab]) AND (pain[tiab] OR "Pain"[Mesh])) OR Neuralg*[tiab] OR *neuropath*[tiab] OR "Peripheral Nervous System Diseases"[Mesh] OR "cranial Nerve Diseases"[Mesh] OR "Somatosensory Disorders"[Mesh] OR "Cancer Pain"[Mesh] OR cancer pain[tiab] OR oncologic pain[tiab] OR cancer-related pain[tiab] OR "Osteoarthritis"[Mesh])
AND
("Nabumetone"[Mesh] OR Nabumeton*[tiab])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

19.4 Additional search: dexketoprofen

("Chronic Pain"[Mesh] OR "Pain Management"[Mesh] OR ((chronic[tiab] OR intractable[tiab] OR refractory[tiab] OR persistent[tiab] OR long-term[tiab] OR long dur*[tiab]) AND (pain[tiab] OR "Pain"[Mesh])) OR Neuralg*[tiab] OR *neuropath*[tiab] OR "Peripheral Nervous System Diseases"[Mesh] OR "cranial Nerve Diseases"[Mesh] OR "Somatosensory Disorders"[Mesh] OR "Cancer Pain"[Mesh] OR cancer pain[tiab] OR oncologic pain[tiab] OR cancer-related pain[tiab] OR "Osteoarthritis"[Mesh])
AND
(Dexketoprofen[tiab])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

19.5 Adjuvant analgesics

("Chronic Pain"[Mesh] OR "Pain Management"[Mesh] OR ((chronic[tiab] OR intractable[tiab] OR refractory[tiab] OR persistent[tiab] OR long-term[tiab] OR long dur*[tiab]) AND (pain[tiab] OR "Pain"[Mesh])) OR Neuralg*[tiab] OR *neuropath*[tiab] OR "Peripheral Nervous System Diseases"[Mesh] OR "cranial Nerve Diseases"[Mesh] OR "Somatosensory Disorders"[Mesh] OR "Cancer Pain"[Mesh] OR cancer pain[tiab] OR oncologic pain[tiab] OR cancer-related pain[tiab] OR "Osteoarthritis"[Mesh])
AND
(Antidepress*[tiab] OR SSRI*[tiab] OR SNRI*[tiab] OR (Serotonin[tiab] AND Reuptake[tiab]) OR TCA*[tiab] OR (tricyclic[tiab] AND antidepress*[tiab]) OR Amitriptylin*[tiab] OR Nortriptylin*[tiab] OR Duloxetin*[tiab] OR Venlafaxin*[tiab] OR "Antidepressive Agents"[Mesh] OR "Serotonin Uptake

Inhibitors"[Mesh] OR "Serotonin and Noradrenaline Reuptake Inhibitors"[Mesh] OR "Antidepressive Agents, Tricyclic"[Mesh] OR "Amitriptyline"[Mesh] OR "Nortriptyline"[Mesh] OR "Duloxetine Hydrochloride"[Mesh] OR "Venlafaxine Hydrochloride"[Mesh] OR "Anticonvulsants"[Mesh] OR "Carbamazepine"[Mesh] OR "Gabapentin"[Mesh] OR "Pregabalin"[Mesh] OR Antiepileptic*[tiab] OR Anticonvuls*[tiab] OR Carbamazepin*[tiab] OR Gabapentin*[tiab] OR Pregabalin*[tiab])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])
AND
("2013/04/01"[Date - Publication] : "2019/05/01"[Date - Publication])

19.6 Topical analgesics

19.6.1 Capsaicin

("Chronic Pain"[Mesh] OR "Pain Management"[Mesh] OR ((chronic[tiab] OR intractable[tiab] OR refractory[tiab] OR persistent[tiab] OR long-term[tiab] OR long dur*[tiab]) AND (pain[tiab] OR "Pain"[Mesh])) OR Neuralg*[tiab] OR *neuropath*[tiab] OR "Peripheral Nervous System Diseases"[Mesh] OR "cranial Nerve Diseases"[Mesh] OR "Somatosensory Disorders"[Mesh] OR "Cancer Pain"[Mesh] OR cancer pain[tiab] OR oncologic pain[tiab] OR cancer-related pain[tiab] OR "Osteoarthritis"[Mesh])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])
AND
("Capsaicin"[Mesh] OR capsaicin[tiab])
AND
("2012/06/01"[Date - Publication] : "2019/05/01"[Date - Publication])

19.6.2 Lidocaine

("Chronic Pain"[Mesh] OR "Pain Management"[Mesh] OR ((chronic[tiab] OR intractable[tiab] OR refractory[tiab] OR persistent[tiab] OR long-term[tiab] OR long dur*[tiab]) AND (pain[tiab] OR "Pain"[Mesh])) OR Neuralg*[tiab] OR *neuropath*[tiab] OR "Peripheral Nervous System Diseases"[Mesh] OR "cranial Nerve Diseases"[Mesh] OR "Somatosensory Disorders"[Mesh] OR "Cancer Pain"[Mesh] OR cancer pain[tiab] OR oncologic pain[tiab] OR cancer-related pain[tiab] OR "Osteoarthritis"[Mesh])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])
AND
(“Lidocaine"[Mesh]) OR "Prilocaine"[Mesh] OR "Tetracaine"[Mesh] OR lidocain*[tiab] OR prilocain*[tiab] OR tetracain*[tiab])
AND
("2014/06/01"[Date - Publication] : "2019/05/01"[Date - Publication])

19.6.3 DMSO

("Chronic Pain"[Mesh] OR "Pain Management"[Mesh] OR ((chronic[tiab] OR intractable[tiab] OR refractory[tiab] OR persistent[tiab] OR long-term[tiab] OR long dur*[tiab]) AND (pain[tiab] OR "Pain"[Mesh])) OR Neuralg*[tiab] OR *neuropath*[tiab] OR "Peripheral Nervous System Diseases"[Mesh] OR "cranial Nerve Diseases"[Mesh] OR "Somatosensory Disorders"[Mesh] OR "Cancer Pain"[Mesh] OR cancer pain[tiab] OR oncologic pain[tiab] OR cancer-related pain[tiab] OR "Osteoarthritis"[Mesh])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])
AND
("Dimethyl Sulfoxide"[Mesh] OR (dimethyl[tiab] AND sulfoxide[tiab]) OR dmso[tiab])

19.6.4 NSAID

("Chronic Pain"[Mesh] OR "Pain Management"[Mesh] OR ((chronic[tiab] OR intractable[tiab] OR refractory[tiab] OR persistent[tiab] OR long-term[tiab] OR long dur*[tiab]) AND (pain[tiab] OR "Pain"[Mesh])) OR Neuralg*[tiab] OR *neuropath*[tiab] OR "Peripheral Nervous System Diseases"[Mesh] OR "cranial Nerve Diseases"[Mesh] OR "Somatosensory Disorders"[Mesh] OR "Cancer Pain"[Mesh] OR cancer pain[tiab] OR oncologic pain[tiab] OR cancer-related pain[tiab] OR "Osteoarthritis"[Mesh])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])
AND
((Topical[tiab] AND analgesic[tiab]) OR "Administration, Topical"[Mesh]) AND ("Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR ((Non-steroidal[tiab] OR nonsteroidal[tiab]) AND (anti-inflammatory[tiab])) OR NSAID*[tiab] OR Diclofenac[tiab] OR Ibuprofen[tiab] OR Ketoprofen[tiab] OR Indometacin*[tiab] OR Piroxicam[tiab] OR Etofenamate[tiab] OR niflumin*[tiab] OR "Diclofenac"[Mesh] OR "Ibuprofen"[Mesh] OR "Ketoprofen"[Mesh] OR "Indomethacin"[Mesh] OR "Piroxicam"[Mesh] OR "Niflumic Acid"[Mesh]))

19.7 Supplements

19.7.1 Curcumin

("Chronic Pain"[Mesh] OR "Pain Management"[Mesh] OR ((chronic[tiab] OR intractable[tiab] OR refractory[tiab] OR persistent[tiab] OR long-term[tiab] OR long dur*[tiab]) AND (pain[tiab] OR "Pain"[Mesh])) OR Neuralg*[tiab] OR *neuropath*[tiab] OR "Peripheral Nervous System Diseases"[Mesh] OR "cranial Nerve Diseases"[Mesh] OR "Somatosensory Disorders"[Mesh] OR "Cancer Pain"[Mesh] OR cancer pain[tiab] OR oncologic pain[tiab] OR cancer-related pain[tiab] OR "Osteoarthritis"[Mesh])

AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])
AND
("Curcumin"[Mesh] OR "Curcuma"[Mesh] OR curcum*[tiab] OR turmeric[tiab])
AND
("2015/09/01"[Date - Publication] : "2019/05/01"[Date - Publication])

19.7.2 Traumeel

("Chronic Pain"[Mesh] OR "Pain Management"[Mesh] OR ((chronic[tiab] OR intractable[tiab] OR refractory[tiab] OR persistent[tiab] OR long-term[tiab] OR long dur*[tiab]) AND (pain[tiab] OR "Pain"[Mesh])) OR Neuralg*[tiab] OR *neuropath*[tiab] OR "Peripheral Nervous System Diseases"[Mesh] OR "cranial Nerve Diseases"[Mesh] OR "Somatosensory Disorders"[Mesh] OR "Cancer Pain"[Mesh] OR cancer pain[tiab] OR oncologic pain[tiab] OR cancer-related pain[tiab] OR "Osteoarthritis"[Mesh])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])
AND
(Traumeel[tiab])

19.7.3 Chondroitin

("Chronic Pain"[Mesh] OR "Pain Management"[Mesh] OR ((chronic[tiab] OR intractable[tiab] OR refractory[tiab] OR persistent[tiab] OR long-term[tiab] OR long dur*[tiab]) AND (pain[tiab] OR "Pain"[Mesh])) OR Neuralg*[tiab] OR *neuropath*[tiab] OR "Peripheral Nervous System Diseases"[Mesh] OR "cranial Nerve Diseases"[Mesh] OR "Somatosensory Disorders"[Mesh] OR "Cancer Pain"[Mesh] OR cancer pain[tiab] OR oncologic pain[tiab] OR cancer-related pain[tiab] OR "Osteoarthritis"[Mesh])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])
AND
("Chondroitin"[Mesh] OR chondroitin*[tiab])
AND
("2013/10/01"[Date - Publication] : "2019/05/01"[Date - Publication])

19.7.4 Glucosamine

("Chronic Pain"[Mesh] OR "Pain Management"[Mesh] OR ((chronic[tiab] OR intractable[tiab] OR refractory[tiab] OR persistent[tiab] OR long-term[tiab] OR long dur*[tiab]) AND (pain[tiab] OR "Pain"[Mesh])) OR Neuralg*[tiab] OR *neuropath*[tiab] OR "Peripheral Nervous System

Diseases"[Mesh] OR "cranial Nerve Diseases"[Mesh] OR "Somatosensory Disorders"[Mesh] OR "Cancer Pain"[Mesh] OR cancer pain[tiab] OR oncologic pain[tiab] OR cancer-related pain[tiab] OR "Osteoarthritis"[Mesh])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])
AND
("Glucosamine"[Mesh] OR glucosamine*[tiab])
AND
("2007/12/01"[Date - Publication] : "2019/05/01"[Date - Publication])

19.7.5 Hyaluronic acid

("Chronic Pain"[Mesh] OR "Pain Management"[Mesh] OR ((chronic[tiab] OR intractable[tiab] OR refractory[tiab] OR persistent[tiab] OR long-term[tiab] OR long dur*[tiab]) AND (pain[tiab] OR "Pain"[Mesh])) OR Neuralg*[tiab] OR *neuropath*[tiab] OR "Peripheral Nervous System Diseases"[Mesh] OR "cranial Nerve Diseases"[Mesh] OR "Somatosensory Disorders"[Mesh] OR "Cancer Pain"[Mesh] OR cancer pain[tiab] OR oncologic pain[tiab] OR cancer-related pain[tiab] OR "Osteoarthritis"[Mesh])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])
AND
("Hyaluronic Acid"[Mesh] OR hyaluron*[tiab])

19.8 AE Paracetamol asthma

(“Acetaminophen/adverse effects"[Mesh] OR ((acetaminophen[tiab] OR paracetamol[tiab]) AND (adverse[tiab] OR side[tiab]))
AND
("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] OR randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])
AND
("Respiratory Tract Infections"[Mesh] OR "Respiratory Tract Diseases"[Mesh] OR asthma*[tiab] OR respiratory[tiab] OR pneumo*[tiab] OR pulmo*[tiab] OR lung[tiab])

19.9 AE paracetamol liver

(“Acetaminophen/adverse effects"[Mesh] OR ((acetaminophen[tiab] OR paracetamol[tiab]) AND (adverse[tiab] OR side[tiab]))
AND
("Liver/adverse effects"[Mesh] OR liver[tiab] OR hepatic[tiab])

Filter: systematic reviews

19.10 AE NSAID

("Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR "Diclofenac"[Mesh] OR "Ketorolac"[Mesh] OR "Ibuprofen"[Mesh] OR "Ketoprofen"[Mesh] OR "Naproxen"[Mesh] OR "Oxaprozin"[Mesh] OR "Indomethacin"[Mesh] OR "Meloxicam"[Mesh] OR "Piroxicam"[Mesh] OR "Celecoxib"[Mesh] OR "Etoricoxib"[Mesh] OR "Nabumetone"[Mesh] OR "Cyclooxygenase 2 Inhibitors"[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 Aceclofenac[tiab] OR Diclofenac[tiab] OR Ketorolac[tiab] OR Dexketoprofen[tiab] OR Ibuprofen[tiab] OR Ketoprofen[tiab] OR Naproxen[tiab] OR Oxaprozin*[tiab] OR Indometacin*[tiab] OR Proglumetacin*[tiab] OR Meloxicam[tiab] OR Piroxicam[tiab] OR Tenoxicam[tiab] OR Celecoxib[tiab] OR Etoricoxib[tiab] OR Parecoxib[tiab] OR Nabumeton*[tiab] OR "Aspirin"[Mesh] OR aspirin[tiab] OR acetylsalicyl*[tiab])
AND

(kidney[tiab] OR renal[tiab] OR "Kidney/adverse effects"[Mesh] OR "Renal Insufficiency"[Mesh] OR "Cardiovascular Diseases/adverse effects"[Mesh] or cardio*[tiab] OR "Gastrointestinal Agents/adverse effects"[Mesh] OR gastrointestin*[tiab])

Filter: systematic reviews

19.11 AE NSAID topical

(((Topical[tiab] AND analgesic[tiab]) OR "Administration, Topical"[Mesh]) AND ("Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR ((Non-steroidal[tiab] OR nonsteroidal[tiab]) AND (anti-inflammatory[tiab])) OR NSAID*[tiab] OR Diclofenac[tiab] OR Ibuprofen[tiab] OR Ketoprofen[tiab] OR Indometacin*[tiab] OR Piroxicam[tiab] OR Etofenamate[tiab] OR niflumin*[tiab] OR "Diclofenac"[Mesh] OR "Ibuprofen"[Mesh] OR "Ketoprofen"[Mesh] OR "Indomethacin"[Mesh] OR "Piroxicam"[Mesh] OR "Niflumic Acid"[Mesh]))
AND ("Drug-Related Side Effects and Adverse Reactions"[Mesh] OR side effect*[tiab] OR adverse[tiab]))

Filter: systematic reviews

20 Appendix. Excluded articles

20.1 Paracetamol

1. Aminoshariae A, Kulild JC, Donaldson M, et al. Evidence-based recommendations for analgesic efficacy to treat pain of endodontic origin: A systematic review of randomized controlled trials. J Am Dent Assoc 2016;147:826-39.**n; no mention of chronicity**
2. Axon DR, Patel MJ, Martin JR, et al. Use of multidomain management strategies by community dwelling adults with chronic pain: evidence from a systematic review. Scand J Pain 2019;19:9-23.**n; intervention**
3. Bartolo M, Chio A, Ferrari S, et al. Assessing and treating pain in movement disorders, amyotrophic lateral sclerosis, severe acquired brain injury, disorders of consciousness, dementia, oncology and neuroinfectivology. Evidence and recommendations from the Italian Consensus Conference on Pain in Neurorehabilitation. Eur J Phys Rehabil Med 2016;52:841-54.**n; publication type**
4. Bedaiwi MK, Sari I, Wallis D, et al. Clinical Efficacy of Celecoxib Compared to Acetaminophen in Chronic Nonspecific Low Back Pain: Results of a Randomized Controlled Trial. Arthritis Care Res (Hoboken) 2016;68:845-52.**n; sample size**
5. Benitez-Camps M, Morros Padros R, Pera-Pujadas H, et al. Effect of effervescent paracetamol on blood pressure: a crossover randomized clinical trial. J Hypertens 2018;36:1656-62.**n; outcome**
6. Chou R, Deyo R, Friedly J, et al. Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. Ann Intern Med 2017;166:480-92.**n; summary of Chou 2016**
7. de Heer EW, Dekker J, Beekman ATF, et al. Comparative Effect of Collaborative Care, Pain Medication, and Duloxetine in the Treatment of Major Depressive Disorder and Comorbid (Sub)Chronic Pain: Results of an Exploratory Randomized, Placebo-Controlled, Multicenter Trial (CC:PAINDIP). Front Psychiatry 2018;9:118.**n; sample size**
8. Ennis ZN, Dideriksen D, Vaegter HB, et al. Acetaminophen for Chronic Pain: A Systematic Review on Efficacy. Basic Clin Pharmacol Toxicol 2016;118:184-9.**n; SR limited search strategy**
9. Ioannides SJ, Siebers R, Perrin K, et al. The effect of 1g of acetaminophen twice daily for 12 weeks on alanine transaminase levels--A randomized placebo-controlled trial. Clin Biochem 2015;48:713-5.**n; population no chronic pain**

10. Jevsevar DS, Shores PB, Mullen K, et al. Mixed Treatment Comparisons for Nonsurgical Treatment of Knee Osteoarthritis: A Network Meta-analysis. J Am Acad Orthop Surg 2018;26:325-36.**n; more comprehensive SR selected**
11. Jung SY, Jang EJ, Nam SW, et al. Comparative effectiveness of oral pharmacologic interventions for knee osteoarthritis: A network meta-analysis. Mod Rheumatol 2018;28:1021-8.**n; other SR selected**
12. Koes BW, Backes D, Bindels PJE. Pharmacotherapy for chronic non-specific low back pain: current and future options. Expert Opin Pharmacother 2018;19:537-45.**n; evaluates cochrane reviews**
13. Lundberg TR, Howatson G. Analgesic and anti-inflammatory drugs in sports: Implications for exercise performance and training adaptations. Scand J Med Sci Sports 2018;28:2252-62.**n; population no chronic pain**
14. Moore RA, Derry S, Wiffen PJ, et al. Overview review: Comparative efficacy of oral ibuprofen and paracetamol (acetaminophen) across acute and chronic pain conditions. Eur J Pain 2015;19:1213-23.**n; overview of SRs**
15. Paterson KL, Gates L. Clinical Assessment and Management of Foot and Ankle Osteoarthritis: A Review of Current Evidence and Focus on Pharmacological Treatment. Drugs Aging 2019;36:203-11.**n; study type**
16. Pinto RZ, Verwoerd AJH, Koes BW. Which pain medications are effective for sciatica (radicular leg pain)? Bmj 2017;359:j4248.**n; review unclear search strategy**
17. Skou ST, Roos EM, Simonsen O, et al. The efficacy of non-surgical treatment on pain and sensitization in patients with knee osteoarthritis: a pre-defined ancillary analysis from a randomized controlled trial. Osteoarthritis Cartilage 2016;24:108-16.**n; comparison**
18. van Dam PH, Achterberg WP, Gussekloo J, et al. Quality of life and paracetamol in advanced dementia (Q-PID): protocol of a randomised double-blind placebo-controlled crossover trial. BMC Geriatr 2018;18:279.**n; protocol**
19. Verkleij SP, Luijsterburg PA, Willemsen SP, et al. Effectiveness of diclofenac versus paracetamol in knee osteoarthritis: a randomised controlled trial in primary care. Br J Gen Pract 2015;65:e530-7.**n; comparison**
20. Wertli MM, Steurer J. [Pain medications for acute and chronic low back pain]. Internist (Berl) 2018;59:1214-23.**n; not SR**
21. Wiffen PJ. Systematic Reviews Published in the July 2016 Issue of the Cochrane Library. J Pain Palliat Care Pharmacother 2016;30:324-5.**n; publication type**
22. Wiffen PJ. Systematic Reviews Published in the April 2016 Issue of the Cochrane Library. J Pain Palliat Care Pharmacother 2016;30:231-2.**n; publication type**
23. Wiffen PJ. Systematic Reviews Published in the Cochrane Library January-March 2017. J Pain Palliat Care Pharmacother 2017;31:167-9.**n; publication type**
24. Wong JJ, Cote P, Ameis A, et al. Are non-steroidal anti-inflammatory drugs effective for the management of neck pain and associated disorders, whiplash-associated disorders, or non-specific low back pain? A systematic review of systematic reviews by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. Eur Spine J 2016;25:34-61.**n; review limited search strategy**
25. Wong JJ, Cote P, Sutton DA, et al. Clinical practice guidelines for the noninvasive management of low back pain: A systematic review by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. Eur J Pain 2017;21:201-16.**n; publication type**
26. Wordliczek J, Kotlinska-Lemieszek A, Leppert W, et al. Pharmacotherapy of pain in cancer patients - recommendations of the Polish Association for the Study of Pain, Polish Society of Palliative Medicine, Polish Society of Oncology, Polish Society of Family Medicine, Polish Society of Anaesthesiology and Intensive Therapy and Association of Polish Surgeons. Pol Przegl Chir 2018;90:55-84.**n; publication type**

20.2 NSAID

1. Aitken P, Stanescu I, Playne R, et al. An integrated safety analysis of combined acetaminophen and ibuprofen (Maxigesic ((R)) /Combogesic((R))) in adults. J Pain Res 2019;12:621-34.**n; intervention**
2. Altman R, Hochberg M, Gibofsky A, et al. Efficacy and safety of low-dose SoluMatrix meloxicam in the treatment of osteoarthritis pain: a 12-week, phase 3 study. Curr Med Res Opin 2015;31:2331-43.**n; not in Be**
3. Altman RD, Strand V, Hochberg MC, et al. Low-dose SoluMatrix diclofenac in the treatment of osteoarthritis: A 1-year, open-label, Phase III safety study. Postgrad Med 2015;127:517-28.**n; intervention**

4. Anonymous. Low-dose meloxicam (Vivlodex) for osteoarthritis pain. Med Lett Drugs Ther 2016;58:35-6.**n; comparison**
5. Axon DR, Patel MJ, Martin JR, et al. Use of multidomain management strategies by community dwelling adults with chronic pain: evidence from a systematic review. Scand J Pain 2019;19:9-23.**n; not a research question**
6. Babatunde OO, Legha A, Littlewood C, et al. Comparative effectiveness of treatment options for plantar heel pain: a systematic review with network meta-analysis. Br J Sports Med 2019;53:182-94.**n; comparison**
7. Bartolo M, Chio A, Ferrari S, et al. Assessing and treating pain in movement disorders, amyotrophic lateral sclerosis, severe acquired brain injury, disorders of consciousness, dementia, oncology and neuroinfectivology. Evidence and recommendations from the Italian Consensus Conference on Pain in Neurorehabilitation. Eur J Phys Rehabil Med 2016;52:841-54.**n; population**
8. Bowen DK, Dielubanza E, Schaeffer AJ. Chronic bacterial prostatitis and chronic pelvic pain syndrome. BMJ Clin Evid 2015;2015.**n; population**
9. Chang KL, Fillingim R, Hurley RW, et al. Chronic pain management: pharmacotherapy for chronic pain. FP Essent 2015;432:27-38.**n; publication type**
10. Chou R, Deyo R, Friedly J, et al. AHRQ Comparative Effectiveness Reviews. Noninvasive Treatments for Low Back Pain 2016.**n; other review selected**
11. Chou R, Deyo R, Friedly J, et al. Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. Ann Intern Med 2017;166:480-92.**n; summary of AHRQ Chou 2016**
12. Curatolo M. Pharmacological and Interventional Management of Pain After Whiplash Injury. J Orthop Sports Phys Ther 2016;46:845-50.**n; population**
13. Derry S, Conaghan P, Da Silva JA, et al. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev 2016;4:Cd007400.**n; topical**
14. Devin CJ, McGirt MJ. Best evidence in multimodal pain management in spine surgery and means of assessing postoperative pain and functional outcomes. J Clin Neurosci 2015;22:930-8.**n; population**
15. Enthoven WTM, Roelofs PD, Koes BW. NSAIDs for Chronic Low Back Pain. Jama 2017;317:2327-8.**n; summary of Cochrane Enthoven 2016**
16. FitzGerald GA. Imprecision: Limitations to Interpretation of a Large Randomized Clinical Trial. Circulation 2017;135:113-5.**n; subject**
17. Foletti A, Egan CG, Baron P. Effect of biophysical therapy on articular pain in a primary care setting compared to ibuprofen and placebo: a randomized controlled trial. J Biol Regul Homeost Agents 2018;32:407-13.**n; comparison**
18. Forder S, Voelker M, Lanas A. Gastrointestinal Safety of Aspirin for a High-Dose, Multiple-Day Treatment Regimen: A Meta-Analysis of Three Randomized Controlled Trials. Drugs R D 2016;16:263-9.**n; population**
19. Gaertner J, Stamer UM, Remi C, et al. Metamizole/dipyrone for the relief of cancer pain: A systematic review and evidence-based recommendations for clinical practice. Palliat Med 2017;31:26-34.**n; intervention**
20. Garg Y, Singh J, Sohal HS, et al. Comparison of Clinical Effectiveness and Safety of Newer Nonsteroidal Anti-inflammatory Drugs in Patients of Osteoarthritis of Knee Joint: A Randomized, Prospective, Open-label Parallel-group Study. Indian J Pharmacol 2017;49:383-9.**n; sample size, open label**
21. Gibofsky A, Altman R, Daniels S, et al. Low-dose SoluMatrix diclofenac : a review of safety across two Phase III studies in patients with acute and osteoarthritis pain. Expert Opin Drug Saf 2015;14:1327-39.**n; intervention**
22. Gregori D, Giacovelli G, Minto C, et al. Association of Pharmacological Treatments With Long-term Pain Control in Patients With Knee Osteoarthritis: A Systematic Review and Meta-analysis. Jama 2018;320:2564-79.**n; included NSAID too limited**
23. Grosser T, Woolf CJ, FitzGerald GA. Time for nonaddictive relief of pain. Science 2017;355:1026-7.**n; publication type**
24. Guyot P, Pandhi S, Nixon RM, et al. Efficacy and safety of diclofenac in osteoarthritis: Results of a network meta-analysis of unpublished legacy studies. Scand J Pain 2017;16:74-88.**n; not an SR**
25. Haggman-Henrikson B, Alstergren P, Davidson T, et al. Pharmacological treatment of oro-facial pain - health technology assessment including a systematic review with network meta-analysis. J Oral Rehabil 2017;44:800-26.**n; none of the included rcts meet inclusion criteria**
26. Harle CA, Danielson EC, Derman W, et al. Analgesic Management of Pain in Elite Athletes: A Systematic Review. Clin J Sport Med 2018;28:417-26.**n; population**

27. Hauser W, Schuler M. [Errors and Solutions During Medical Therapy for Chronic Pain]. Dtsch Med Wochenschr 2018;143:1381-8.**n; subject**
28. Hermann W, Lambova S, Muller-Ladner U. Current Treatment Options for Osteoarthritis. Curr Rheumatol Rev 2018;14:108-16.**n; not an SR**
29. Ho KY, Gwee KA, Cheng YK, et al. Nonsteroidal anti-inflammatory drugs in chronic pain: implications of new data for clinical practice. J Pain Res 2018;11:1937-48.**n; publication type**
30. Holsgaard-Larsen A, Christensen R, Clausen B, et al. One year effectiveness of neuromuscular exercise compared with instruction in analgesic use on knee function in patients with early knee osteoarthritis: the EXERPHARMA randomized trial. Osteoarthritis Cartilage 2018;26:28-33.**n; comparison**
31. Huang KC, Huang TW, Yang TY, et al. Chronic NSAIDs Use Increases the Risk of a Second Hip Fracture in Patients After Hip Fracture Surgery: Evidence From a STROBE-Compliant Population-Based Study. Medicine (Baltimore) 2015;94:e1566.**n; study type**
32. Huang R, Jiang L, Cao Y, et al. Comparative Efficacy of Therapeutics for Chronic Cancer Pain: A Bayesian Network Meta-Analysis. J Clin Oncol 2019:Jco1801567.**n; different review selected**
33. Jung SY, Jang EJ, Nam SW, et al. Comparative effectiveness of oral pharmacologic interventions for knee osteoarthritis: A network meta-analysis. Mod Rheumatol 2018;28:1021-8.**n; network MA no direct comparisons reported**
34. Kim SH, Yun JM, Chang CB, et al. Prevalence of upper gastrointestinal bleeding risk factors among the general population and osteoarthritis patients. World J Gastroenterol 2016;22:10643-52.**n; study type**
35. Koes BW, Backes D, Bindels PJE. Pharmacotherapy for chronic non-specific low back pain: current and future options. Expert Opin Pharmacother 2018;19:537-45.**n; overview of cochrane reviews**
36. Kotter T, da Costa BR, Fassler M, et al. Metamizole-associated adverse events: a systematic review and meta-analysis. PLoS One 2015;10:e0122918.**n; intervention**
37. Kroenke K, Cheville A. Management of Chronic Pain in the Aftermath of the Opioid Backlash. Jama 2017;317:2365-6.**n; publication type**
38. Lundberg TR, Howatson G. Analgesic and anti-inflammatory drugs in sports: Implications for exercise performance and training adaptations. Scand J Med Sci Sports 2018;28:2252-62.**n; subject**
39. MacDonald TM, Hawkey CJ, Ford I, et al. Randomized trial of switching from prescribed non-selective non-steroidal anti-inflammatory drugs to prescribed celecoxib: the Standard care vs. Celecoxib Outcome Trial (SCOT). Eur Heart J 2017;38:1843-50.**n; mixed population osteoarthritis and rheumatoid arthritis, no subgroep analyses**
40. Machado GC, Maher CG, Ferreira PH, et al. Non-steroidal anti-inflammatory drugs for spinal pain: a systematic review and meta-analysis. Ann Rheum Dis 2017;76:1269-78.**n; different review selected**
41. Manoukian MAC, Migdal CW, Tembhekar AR, et al. Topical Administration of Ibuprofen for Injured Athletes: Considerations, Formulations, and Comparison to Oral Delivery. Sports Med Open 2017;3:36.**n; population**
42. Moore RA, Derry S, Wiffen PJ, et al. Overview review: Comparative efficacy of oral ibuprofen and paracetamol (acetaminophen) across acute and chronic pain conditions. Eur J Pain 2015;19:1213-23.**n; paracetamol**
43. Na HS, Oh AY, Koo BW, et al. Preventive Analgesic Efficacy of Nefopam in Acute and Chronic Pain After Breast Cancer Surgery: A Prospective, Double-Blind, and Randomized Trial. Medicine (Baltimore) 2016;95:e3705.**n; prevention not treatment of chronic pain**
44. Patel DP, Schenk JM, Darke A, et al. Non-steroidal anti-inflammatory drug (NSAID) use is not associated with erectile dysfunction risk: results from the Prostate Cancer Prevention Trial. BJU Int 2016;117:500-6.**n; publication type**
45. Paterson KL, Gates L. Clinical Assessment and Management of Foot and Ankle Osteoarthritis: A Review of Current Evidence and Focus on Pharmacological Treatment. Drugs Aging 2019;36:203-11.**n; study type**
46. Pelletier JP, Martel-Pelletier J, Rannou F, et al. Efficacy and safety of oral NSAIDs and analgesics in the management of osteoarthritis: Evidence from real-life setting trials and surveys. Semin Arthritis Rheum 2016;45:S22-7.**n; not an SR**
47. Pelletier JP, Raynauld JP, Beaulieu AD, et al. Chondroitin sulfate efficacy versus celecoxib on knee osteoarthritis structural changes using magnetic resonance imaging: a 2-year multicentre exploratory study. Arthritis Res Ther 2016;18:256.**n; included in chondroitin search**
48. Pergolizzi JV, Jr., Raffa RB, Nalamachu S, et al. Evolution to low-dose NSAID therapy. Pain Manag 2016;6:175-89.**n; publication type**
49. Pinto RZ, Verwoerd AJH, Koes BW. Which pain medications are effective for sciatica (radicular leg pain)? Bmj 2017;359:j4248.**n; other review selected**

50. Qaseem A, Wilt TJ, McLean RM, et al. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med 2017;166:514-30.**n; publication type**
51. Raschle J. Praxis (Bern 1994) 2017;106:433-4.**n; publication type**
52. Rasmussen-Barr E, Held U, Grooten WJ, et al. Nonsteroidal Anti-inflammatory Drugs for Sciatica: An Updated Cochrane Review. Spine (Phila Pa 1976) 2017;42:586-94.**n; summary of cochrane**
53. Reginster JL, Group CI. CONCEPT provides robust evidence that chondroitin sulfate is superior to placebo and similar to celecoxib in the symptomatic management of osteoarthritis. Ann Rheum Dis 2018;77:e11.**n; comparison**
54. Reginster JY, Reiter-Niesert S, Bruyere O, et al. Recommendations for an update of the 2010 European regulatory guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis and reflections about related clinically relevant outcomes: expert consensus statement. Osteoarthritis Cartilage 2015;23:2086-93.**n; publication type**
55. Ribaldone DG, Fagoonee S, Astegiano M, et al. Coxib's Safety in Patients with Inflammatory Bowel Diseases: A Meta-analysis. Pain Physician 2015;18:599-607.**n; population**
56. Roberto G, Simonetti M, Piccinni C, et al. Risk of Acute Cerebrovascular and Cardiovascular Events Among Users of Acetaminophen or an Acetaminophen-Codeine Combination in a Cohort of Patients with Osteoarthritis: A Nested Case-Control Study. Pharmacotherapy 2015;35:899-909.**n; intervention**
57. Ruschitzka F, Borer JS, Krum H, et al. Differential blood pressure effects of ibuprofen, naproxen, and celecoxib in patients with arthritis: the PRECISION-ABPM (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen Ambulatory Blood Pressure Measurement) Trial. Eur Heart J 2017;38:3282-92.**n; mixed population OA and RA no subgroep analyses**
58. Sivordova LE, Zavodovsky BV, Polyakova JV, et al. [Evidence of feasibility etoricoxib therapy in osteoarthritis in elderly patients]. Adv Gerontol 2016;29:286-90.**n; language**
59. Skou ST, Roos EM, Simonsen O, et al. The efficacy of non-surgical treatment on pain and sensitization in patients with knee osteoarthritis: a pre-defined ancillary analysis from a randomized controlled trial. Osteoarthritis Cartilage 2016;24:108-16.**n; intervention**
60. Smith SR, Deshpande BR, Collins JE, et al. Comparative pain reduction of oral non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: systematic analytic review. Osteoarthritis Cartilage 2016;24:962-72.**n; more comprehensive SR selected**
61. Solomon DH, Husni ME, Libby PA, et al. The Risk of Major NSAID Toxicity with Celecoxib, Ibuprofen, or Naproxen: A Secondary Analysis of the PRECISION Trial. Am J Med 2017;130:1415-22 e4.**n; study type**
62. Song GG, Seo YH, Kim JH, et al. Relative efficacy and tolerability of etoricoxib, celecoxib, and naproxen in the treatment of osteoarthritis : A Bayesian network meta-analysis of randomized controlled trials based on patient withdrawal. Z Rheumatol 2016;75:508-16.**n; more comprehensive SR selected**
63. Sostres C, Carrera-Lasfuentes P, Lanas A. Non-steroidal anti-inflammatory drug related upper gastrointestinal bleeding: types of drug use and patient profiles in real clinical practice. Curr Med Res Opin 2017;33:1815-20.**n; publication type**
64. Spies CK, Langer M, Hahn P, et al. The Treatment of Primary Arthritis of the Finger and Thumb Joint. Dtsch Arztebl Int 2018;115:269-75.**n; intervention**
65. Stahl I, Ginesin E, Hous N, et al. [Non-Arthroplasty Treatment for Knee Osteoarthritis]. Harefuah 2017;156:455-9.**n; language**
66. Stephenson A, Kelsberg G, Neher JO, et al. FPIN's Clinical Inquiries. Treatments for sciatica. Am Fam Physician 2015;91:612-3, 5a, 5b.**n; publication type**
67. Strand V, Bergman M, Singh JA, et al. Low-dose SoluMatrix diclofenac in patients with osteoarthritis pain: impact on quality of life in a controlled trial. Clin Rheumatol 2017;36:1357-67.**n; comparison**
68. Terracina S, Robba C, Prete A, et al. Prevention and Treatment of Postoperative Pain after Lumbar Spine Procedures: A Systematic Review. Pain Pract 2018;18:925-45.**n; population**
69. Toroski M, Nikfar S, Mojahedian MM, et al. Comparison of the Cost-utility Analysis of Electroacupuncture and Nonsteroidal Antiinflammatory Drugs in the Treatment of Chronic Low Back Pain. J Acupunct Meridian Stud 2018;11:62-6.**n; outcome**
70. Wertli MM, Steurer J. [Pain medications for acute and chronic low back pain]. Internist (Berl) 2018;59:1214-23.**n; not an sr**
71. Wong JJ, Cote P, Ameis A, et al. Are non-steroidal anti-inflammatory drugs effective for the management of neck pain and associated disorders, whiplash-associated disorders, or non-specific low back pain? A systematic review of systematic reviews by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. Eur Spine J 2016;25:34-61.**n; not full SR**

72. Wong JJ, Cote P, Sutton DA, et al. Clinical practice guidelines for the noninvasive management of low back pain: A systematic review by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. Eur J Pain 2017;21:201-16.**n; review of guidelines**
73. Wordliczek J, Kotlinska-Lemieszek A, Leppert W, et al. Pharmacotherapy of pain in cancer patients - recommendations of the Polish Association for the Study of Pain, Polish Society of Palliative Medicine, Polish Society of Oncology, Polish Society of Family Medicine, Polish Society of Anaesthesiology and Intensive Therapy and Association of Polish Surgeons. Pol Przegl Chir 2018;90:55-84.**n; publication type**
74. Xu C, Gu K, Yasen Y, et al. Efficacy and Safety of Celecoxib Therapy in Osteoarthritis: A Meta-Analysis of Randomized Controlled Trials. Medicine (Baltimore) 2016;95:e3585.**n; cochrane review selected**
75. Yang JH, Suk KS, Lee BH, et al. Efficacy and Safety of Different Aceclofenac Treatments for Chronic Lower Back Pain: Prospective, Randomized, Single Center, Open-Label Clinical Trials. Yonsei Med J 2017;58:637-43.**n; duration**
76. Zeng C, Wei J, Li H, et al. Effectiveness and safety of Glucosamine, chondroitin, the two in combination, or celecoxib in the treatment of osteoarthritis of the knee. Sci Rep 2015;5:16827.**n; supplements**
77. Zou K, Wong J, Abdullah N, et al. Examination of overall treatment effect and the proportion attributable to contextual effect in osteoarthritis: meta-analysis of randomised controlled trials. Ann Rheum Dis 2016;75:1964-70.**n; subject**

20.3 Adjuvant analgesics

1. Gabapentin for Adults with Neuropathic Pain: A Review of the Clinical Evidence and Guidelines. CADTH Rapid Response Reports 2014.**n; other SR selected**
2. Aiyer R, Barkin RL, Bhatia A. Treatment of Neuropathic Pain with Venlafaxine: A Systematic Review. Pain Med 2017;18:1999-2012.**n; different SR selected**
3. Al-Atiyyat N, Obaid A. Management of peripheral neuropathy induced by chemotherapy in adults with cancer: a review. Int J Palliat Nurs 2017;23:13-7.**n; other SR selected**
4. Alev L, Fujikoshi S, Yoshikawa A, et al. Duloxetine 60 mg for chronic low back pain: post hoc responder analysis of double-blind, placebo-controlled trials. J Pain Res 2017;10:1723-31.**n; not a research question**
5. Alviar MJ, Hale T, Dungca M. Pharmacologic interventions for treating phantom limb pain. Cochrane Database Syst Rev 2016;10:CD006380.**n; othere SR selected**
6. Ammendolia C, Stuber KJ, Rok E, et al. Nonoperative treatment for lumbar spinal stenosis with neurogenic claudication. Cochrane Database Syst Rev 2013:Cd010712.**n; SR too old**
7. Ananias J, Irarrazaval S. Is duloxetine an alternative in the treatment of osteoarthritis? Medwave 2017;17:e7063.**n; more recent SR selected**
8. Arnold LM, McCarberg BH, Clair AG, et al. Dose-response of pregabalin for diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia. Postgrad Med 2017;129:921-33.**n; outcome**
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