

**INSTITUT NATIONAL D'ASSURANCE
MALADIE-INVALIDITÉ
SERVICE DES SOINS DE SANTÉ**
Comité d'évaluation des pratiques
médicales en matière de médicaments

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

The rational use of opioids for chronic pain

Systematic literature review:
full report

Consensus conference

December 6th 2018

Auditorium Lippens (Royal Library)

Brussels

This literature review was performed by BCFI/CBIP and was supervised by a reading committee.

Researchers

Main researcher:

Griet Goesaert MD, *BCFI/CBIP*

Co-researchers:

Natasja Mortier, MD, *BCFI/CBIP*

Abdelbari Baitar, MSc., PHD, *BCFI/CBIP*

Reading committee

André Crismer, MD (ULg)

Erwin Crombez, MD, (Ugent)

Alain Van Meerhaeghe MD, Prof (UMONS)

Ellen Van Leeuwen, MD, (Ugent)

Administrative and IT support

Stijn Dumon, *BCFI/CBIP*

Translation

Marian & Alain Thysebaert - De Coene

BCFI/CBIP

Inhoudsopgave

INHOUDSOPGAVE	3
1 ABBREVIATIONS.....	1
2 METHODOLOGY	3
2.1 INTRODUCTION	3
2.2 QUESTIONS TO THE JURY	3
2.3 RESEARCH TASK OF THE LITERATURE GROUP	5
2.3.1 <i>Guidelines</i>	6
2.3.2 <i>Study types</i>	7
2.3.3 <i>Specific search criteria</i>	8
2.3.3.1 Populations.....	8
2.3.3.2 Interventions	9
2.3.3.3 Comparisons	9
2.3.3.4 Endpoints.....	10
2.4 SEARCH STRATEGY	11
2.4.1 <i>Principles of systematic search</i>	11
2.4.2 <i>Source documents</i>	11
2.4.3 <i>Search strategy details</i>	13
2.5 SELECTION PROCEDURE.....	13
2.6 ASSESSING THE QUALITY OF AVAILABLE EVIDENCE	14
2.7 SYNOPSIS OF THE STUDY RESULTS	17
3 CRITICAL REFLECTIONS OF THE READING COMMITTEE AND THE LITERATURE GROUP	18
3.1 GUIDELINES	18
3.2 BENEFIT-HARM	18
3.3 EXAMINING THE PLACE OF OPIOIDS WITHIN A BIO-PSYCHO-SOCIAL PAIN TREATMENT FRAMEWORK	18
3.3.1 <i>Opioids versus optimization of non-opioid treatment</i>	19
3.3.2 <i>Opioids versus placebo</i>	19
3.4 STUDY DURATION	20
3.5 POPULATION	20
3.5.1 <i>Types of chronic pain</i>	20
3.5.2 <i>Subgroups</i>	20
3.6 INTERVENTIONS.....	20
3.7 OUTCOMES	21
3.7.1 <i>Pain</i>	21
3.7.2 <i>Function and quality of life</i>	21
3.7.3 <i>Adverse events</i>	21
3.8 DISCONTINUATIONS DURING THE TRIAL	22
3.9 ADDITIONAL REMARKS FROM THE READING COMMITTEE	22
3.10 SOME METHODOLOGICAL ISSUES EXPLAINED	22
3.10.1 <i>Meta-analyses</i>	22
3.10.2 <i>Missing values</i>	22
3.10.3 <i>Enriched enrollment</i>	23
3.10.4 <i>Statistically significant versus clinically relevant</i>	23
4 GENERAL INFORMATION ON SELECTED GUIDELINES.....	25

4.1	SELECTED GUIDELINES.....	25
4.2	GRADES OF RECOMMENDATION.....	26
4.3	AGREE II SCORE.....	31
4.4	INCLUDED POPULATIONS – INTERVENTIONS – MAIN OUTCOMES.....	32
4.5	MEMBERS OF DEVELOPMENT GROUP – TARGET AUDIENCE.....	41
5	INFORMATION/RECOMMENDATIONS FROM GUIDELINES.....	45
5.1	THE BIOPSYCHOSOCIAL APPROACH TO PAIN.....	45
5.1.1	<i>Summary</i>	45
5.1.2	<i>NPC_Canada 2017</i>	45
5.1.3	<i>WOREL 2017</i>	46
5.1.4	<i>CDC 2016</i>	48
5.1.5	<i>NHG 2018</i>	49
5.1.6	<i>NICE 2017</i>	51
5.1.7	<i>ASCO 2016</i>	52
5.1.8	<i>DOH_Ireland 2015</i>	53
5.1.9	<i>KCE 2013</i>	56
5.2	MANAGEMENT OF CHRONIC PAIN WITH OPIOIDS.....	57
5.2.1	<i>Summary</i>	57
5.2.2	<i>NPC_Canada 2017</i>	61
5.2.3	<i>WOREL 2017</i>	63
5.2.4	<i>CDC 2016</i>	68
5.2.5	<i>NHG 2018</i>	72
5.2.6	<i>NICE 2017</i>	76
5.2.7	<i>ASCO 2016</i>	77
5.2.8	<i>DOH_Ireland 2015</i>	82
5.2.9	<i>KCE 2013</i>	97
5.3	OPIOID FORMULATIONS AND ROUTE OF ADMINISTRATION.....	113
5.3.1	<i>Summary</i>	113
5.3.2	<i>NPC_Canada 2017</i>	115
5.3.3	<i>WOREL 2017</i>	115
5.3.4	<i>CDC 2016</i>	116
5.3.5	<i>NHG 2018</i>	116
5.3.6	<i>NICE 2017</i>	116
5.3.7	<i>ASCO 2016</i>	116
5.3.8	<i>DOH_Ireland 2015</i>	116
5.3.9	<i>KCE 2013</i>	120
5.4	OPIOIDS IN ADOLESCENTS, OLDER PATIENTS AND PATIENTS WITH RENAL OR HEPATIC INSUFFICIENCY.....	121
5.4.1	<i>Summary</i>	121
5.4.2	<i>NPC_Canada 2017</i>	122
5.4.3	<i>WOREL 2017</i>	122
5.4.4	<i>CDC 2016</i>	122
5.4.5	<i>NHG 2018</i>	123
5.4.6	<i>NICE 2017</i>	123
5.4.7	<i>ASCO 2016</i>	123
5.4.8	<i>DOH_Ireland 2015</i>	124
5.4.9	<i>KCE 2013</i>	133
5.5	ROTATION OF OPIOIDS.....	136
5.5.1	<i>Summary</i>	136
5.5.2	<i>NPC_Canada 2017</i>	136

5.5.3	WOREL 2017.....	137
5.5.4	CDC 2016.....	138
5.5.5	NHG 2018.....	139
5.5.6	NICE 2017.....	139
5.5.7	ASCO 2016.....	139
5.5.8	DOH_Ireland 2015.....	139
5.5.9	KCE 2013.....	147
5.6	TAPERING/DEPRESCRIBING.....	148
5.6.1	Summary.....	148
5.6.2	NPC_Canada 2017.....	149
5.6.3	WOREL 2017.....	150
5.6.4	CDC 2016.....	150
5.6.5	NHG 2018.....	152
5.6.6	NICE 2017.....	152
5.6.7	ASCO 2016.....	152
5.6.8	DOH_Ireland 2015.....	153
5.6.9	KCE 2013.....	153
5.7	OPIOIDS AND SUBSTANCE USE DISORDER.....	153
5.7.1	Summary.....	153
5.7.2	NPC_Canada 2017.....	154
5.7.3	WOREL 2017.....	155
5.7.4	CDC 2016.....	155
5.7.5	NHG 2018.....	158
5.7.6	NICE 2017.....	159
5.7.7	ASCO 2016.....	159
5.7.8	DOH_Ireland 2015.....	162
5.7.9	KCE 2013.....	166
6	SUMMARY AND CONCLUSIONS FROM THE LITERATURE REVIEW. CHRONIC (NON-CANCER) PAIN, GENERAL.....	167
6.1	LONG TERM OPIOIDS FOR CHRONIC (NON-CANCER) PAIN.....	167
6.2	HIGH DOSE OPIOIDS FOR CHRONIC NON-CANCER PAIN.....	167
7	SUMMARY AND CONCLUSIONS FROM THE LITERATURE REVIEW. OPIOIDS VERSUS OPTIMIZATION OF NON-OPIOID THERAPY FOR CHRONIC (NON-CANCER) PAIN.....	168
7.1	OPIOIDS VERSUS OPTIMIZATION OF NON-OPIOIDS FOR CHRONIC NON-CANCER PAIN.....	168
7.2	OPIOID MEDICATION STRATEGY VERSUS NON-OPIOID MEDICATION STRATEGY FOR CHRONIC BACK PAIN OR CHRONIC PAIN FROM KNEE OR HIP OSTEOARTHRITIS.....	169
8	SUMMARY AND CONCLUSIONS FROM THE LITERATURE REVIEW. OPIOIDS VERSUS PLACEBO FOR CHRONIC (NON-CANCER) PAIN.....	173
8.1	OPIOIDS VERSUS PLACEBO FOR CHRONIC NON-CANCER PAIN IN PATIENTS OPTIMIZED NON-OPIOID TREATMENT BUT PERSISTENT PAIN.....	173
8.2	OPIOIDS VERSUS PLACEBO FOR CHRONIC NON-CANCER PAIN: ADVERSE EVENTS.....	176
8.3	OPIOIDS VERSUS PLACEBO FOR CHRONIC NON-CANCER PAIN: QUALITY OF LIFE.....	178
9	SUMMARY AND CONCLUSIONS FROM THE LITERATURE REVIEW. OPIOIDS VERSUS PLACEBO FOR SPECIFIC MUSCULOSKELETAL PAIN CONDITIONS.....	180
9.1	OPIOIDS VERSUS PLACEBO FOR CHRONIC PAIN IN OSTEOARTHRITIS.....	180
9.2	OPIOIDS VERSUS PLACEBO FOR CHRONIC LOW BACK PAIN.....	182

9.2.1	<i>Opioids versus placebo for chronic low back pain</i>	182
9.2.2	<i>Strong opioids versus placebo for chronic low back pain</i>	183
10	SUMMARY AND CONCLUSIONS FROM THE LITERATURE REVIEW. INDIVIDUAL OPIOIDS VERSUS PLACEBO FOR CHRONIC MUSCULOSKELETAL PAIN	185
10.1	TRAMADOL +/- PARACETAMOL VERSUS PLACEBO FOR CHRONIC PAIN FROM OSTEOARTHRITIS	185
10.2	TRAMADOL +/- PARACETAMOL VERSUS PLACEBO FOR CHRONIC LOW BACK PAIN	189
10.3	TRANSDERMAL BUPRENORPHINE VERSUS PLACEBO FOR CHRONIC PAIN IN KNEE OR HIP OSTEOARTHRITIS	191
10.4	BUPRENORPHINE VERSUS PLACEBO FOR CHRONIC LOW BACK PAIN	193
10.5	METHADONE VERSUS PLACEBO FOR CHRONIC NON-CANCER PAIN	194
10.6	HYDROMORPHONE VERSUS PLACEBO FOR CHRONIC PAIN	195
10.6.1	<i>Hydromorphone versus placebo for chronic pain in osteoarthritis of the hip or knee</i>	196
10.7	OXYCODONE VERSUS PLACEBO FOR CHRONIC PAIN DUE TO OSTEOARTHRITIS	198
10.8	OXYCODONE VERSUS PLACEBO FOR CHRONIC LOW BACK PAIN	200
10.9	TAPENTADOL VERSUS PLACEBO FOR CHRONIC MUSCULOSKELETAL PAIN	203
10.10	CODEINE FOR CHRONIC NON-CANCER PAIN	205
10.11	TILIDINE FOR CHRONIC NON-CANCER PAIN	205
10.12	MORPHINE FOR CHRONIC NON-CANCER PAIN	205
11	SUMMARY AND CONCLUSIONS FROM THE LITERATURE REVIEW. OPIOIDS FOR NEUROPATHIC PAIN .	207
11.1	OPIOIDS IN GENERAL FOR NEUROPATHIC PAIN	207
11.2	CODEINE FOR NEUROPATHIC PAIN	208
11.3	TRAMADOL FOR NEUROPATHIC PAIN	208
11.4	TILIDINE FOR NEUROPATHIC PAIN	208
11.5	BUPRENORPHINE FOR NEUROPATHIC PAIN	209
11.6	FENTANYL FOR NEUROPATHIC PAIN	212
11.7	HYDROMORPHONE FOR NEUROPATHIC PAIN	212
11.8	METHADONE FOR NEUROPATHIC PAIN	212
11.9	MORPHINE FOR NEUROPATHIC PAIN	213
11.10	OXYCODONE FOR NEUROPATHIC PAIN	214
11.11	TAPENTADOL FOR NEUROPATHIC PAIN	216
12	SUMMARY AND CONCLUSIONS FROM THE LITERATURE REVIEW. OPIOIDS FOR CANCER PAIN	219
13	SUMMARY AND CONCLUSIONS FROM THE LITERATURE REVIEW. OPIOID ROTATION	220
14	SUMMARY AND CONCLUSIONS FROM THE LITERATURE REVIEW. TAPERING OF OPIOIDS	220
15	RARE ADVERSE EVENTS. INFORMATION FROM OBSERVATIONAL STUDIES	221
15.1	ENDOCRINOLOGICAL DYSFUNCTION	221
15.1.1	<i>Opioids and hypogonadism</i>	221
15.1.2	<i>Opioids and reproductive dysfunction in women</i>	221
15.1.3	<i>Opioids and erectile dysfunction in men</i>	222
15.1.4	<i>Opioids and testosterone suppression in men</i>	222
15.2	IMMUNOLOGICAL DYSFUNCTION	223
15.2.1	<i>Opioid use and breast cancer recurrence</i>	223
16	ADDITIONAL SAFETY INFORMATION FROM OTHER SOURCES	225
16.1	ADVERSE EFFECTS	225
16.1.1	<i>Opioids in general</i>	225
16.1.2	<i>Additional adverse effects of specific opioids</i>	225
16.2	CONTRAINDICATIONS	226

16.2.1	<i>Opioids in general</i>	226
16.2.2	<i>Additional contraindications for specific opioids</i>	226
16.3	INTERACTIONS.....	226
16.4	USE OF OPIOIDS IN SPECIFIC PATIENT CATEGORIES	228
16.4.1	<i>Hepatic dysfunction</i>	228
16.4.2	<i>Renal dysfunction</i>	228
16.4.3	<i>The elderly</i>	228
16.4.4	<i>Other</i>	228
16.5	PRECAUTIONS AND MONITORING	229
17	APPENDIX. EVIDENCE TABLES. CHRONIC (NON-CANCER) PAIN, GENERAL	231
17.1	LONG TERM OPIOIDS (12 M) FOR CHRONIC PAIN. SYSTEMATIC REVIEW CHOU 2015	231
17.2	LONG TERM OPIOIDS (12 M) FOR CHRONIC PAIN. SYSTEMATIC REVIEW DOWELL 2016.....	233
17.3	LONG TERM OPIOIDS (6M) FOR CHRONIC NON-CANCER PAIN: SYSTEMATIC REVIEW NOBLE 2010.....	235
17.4	HIGH-DOSE OPIOIDS FOR CHRONIC NON-CANCER PAIN. OVERVIEW OF COCHRANE REVIEWS ELS 2017	236
18	APPENDIX. EVIDENCE TABLES. OPIOIDS VERSUS OPTIMIZATION OF NON-OPIOID THERAPY FOR CHRONIC (NON-CANCER) PAIN.....	237
18.1	OPIOIDS VS OPTIMALISATION OF NON-OPIOIDS IN CHRONIC NON-CANCER PAIN. META-ANALYSIS BUSSE 2017	237
18.2	OPIOID MEDICATION STRATEGY VS NON-OPIOID MEDICATION STRATEGY IN CHRONIC LOW BACK PAIN OR CHRONIC PAIN FROM KNEE OR HIP OSTEOARTHRITIS. SPACE TRIAL KREBS 2018	240
19	APPENDIX. EVIDENCE TABLES. OPIOIDS VERSUS PLACEBO FOR CHRONIC (NON-CANCER) PAIN.....	245
19.1	OPIOIDS VS PLACEBO FOR CHRONIC NON-CANCER PAIN IN PATIENTS WITH OPTIMIZED NON-OPIOID TREATMENT BUT PERSISTENT PAIN META-ANALYSIS BUSSE 2017	245
19.2	OPIOIDS VS PLACEBO FOR CHRONIC NON-CANCER PAIN: ADVERSE EVENTS. META-ANALYSIS ELS 2017	276
19.3	OPIOIDS VS PLACEBO FOR CHRONIC NON-CANCER PAIN: QUALITY OF LIFE. META-ANALYSIS THORNTON 2017	282
20	APPENDIX. EVIDENCE TABLES. OPIOIDS VERSUS PLACEBO FOR SPECIFIC MUSCULOSKELETAL PAIN CONDITIONS.....	288
20.1	OPIOIDS VS PLACEBO FOR CHRONIC PAIN IN OSTEOARTHRITIS OF THE KNEE OR HIP. META-ANALYSIS DA COSTA BRUNO 2014	288
20.1.1	<i>Non-tramadol opioids for chronic pain in osteoarthritis of the knee or hip</i>	290
20.1.2	<i>Oxycodone for chronic pain in osteoarthritis of the knee or hip</i>	293
20.1.3	<i>Transdermal buprenorphine for chronic pain in osteoarthritis of the knee or hip</i>	294
20.2	OPIOIDS VS PLACEBO FOR CHRONIC LOW BACK PAIN. SYSTEMATIC REVIEW CHOU 2016 AND 2017	307
20.3	OPIOIDS VS PLACEBO FOR CHRONIC LOW BACK PAIN. META-ANALYSIS ABDEL SHAHEED 2016	308
20.4	OPIOIDS VS PLACEBO FOR CHRONIC LOW BACK PAIN. META-ANALYSIS CHAPARRO 2013.....	317
20.4.1	<i>Strong opioids vs placebo in chronic low back pain</i>	318
20.4.2	<i>Tramadol vs placebo in chronic low back pain</i>	324
21	APPENDIX. EVIDENCE TABLES. INDIVIDUAL OPIOIDS VERSUS PLACEBO FOR CHRONIC NON-CANCER PAIN	328
21.1	TRAMADOL (+/-PARACETAMOL) VS PLACEBO FOR CHRONIC PAIN IN OSTEOARTHRITIS	328
21.2	TRAMADOL VS PLACEBO FOR CHRONIC LOW BACK PAIN.....	334
21.3	BUPRENORPHINE VS PLACEBO FOR CHRONIC NON-CANCER PAIN: SYSTEMATIC REVIEW AYER 2017	335
21.4	BUPRENORPHINE VS PLACEBO FOR CHRONIC PAIN IN OSTEOARTHRITIS	336
21.5	BUPRENORPHINE VS PLACEBO FOR CHRONIC LOW BACK PAIN. RCT STEINER 2011	337
21.6	METHADONE VS PLACEBO FOR CHRONIC NON-CANCER PAIN	341
21.7	HYDROMORPHONE VS PLACEBO FOR CHRONIC NON-CANCER PAIN: SYSTEMATIC REVIEW QUIGLEY 2013	342

21.8	HYDROMORPHONE VS PLACEBO FOR CHRONIC MUSCULOSKELETAL PAIN.....	342
21.9	OXYCODONE VS PLACEBO FOR CHRONIC PAIN IN OSTEOARTHRITIS	343
21.10	OXYCODONE VS PLACEBO FOR CHRONIC LOW BACK PAIN	343
21.11	TAPENTADOL VS PLACEBO FOR CHRONIC MUSCULOSKELETAL PAIN	344
22	APPENDIX. EVIDENCE TABLES. OPIOIDS FOR NEUROPATHIC PAIN	351
22.1	OPIOIDS FOR NEUROPATHIC PAIN. SYSTEMATIC REVIEW McNICOL 2013.....	351
22.2	COMBINATION PHARMACOTHERAPY VERSUS PLACEBO/ACTIVE COMPARATOR FOR NEUROPATHIC PAIN. SYSTEMATIC REVIEW CHAPARRO 2012	352
22.3	CODEINE/DIHYDROCODEINE +PARACETAMOL VS PLACEBO FOR NEUROPATHIC PAIN. SYSTEMATIC REVIEW WIFFEN 2016 353	
22.4	TRAMADOL FOR NEUROPATHIC PAIN. SYSTEMATIC REVIEW DUEHMKE RUDOLF 2017	354
22.5	TRAMADOL FOR DIABETIC NEUROPATHY. SYSTEMATIC REVIEW DY 2017	355
22.6	BUPRENORPHINE FOR NEUROPATHIC PAIN. SYSTEMATIC REVIEW WIFFEN 2015.....	356
22.7	TRANSDERMAL BUPRENORPHINE VERSUS PLACEBO FOR DIABETIC PERIPHERAL NEUROPATHIC PAIN. RCT SIMPSON 2016 357	
22.8	FENTANYL FOR NEUROPATHIC PAIN. SYSTEMATIC REVIEW DERRY 2016.....	360
22.9	HYDROMORPHONE FOR NEUROPATHIC PAIN. SYSTEMATIC REVIEW STANNARD 2016	361
22.10	METHADONE FOR NEUROPATHIC PAIN. SYSTEMATIC REVIEW McNICOL EWAN 2017	362
22.11	MORPHINE FOR NEUROPATHIC PAIN. SYSTEMATIC REVIEW COOPER TESS 2017.....	363
22.12	OXYCODONE +/- NALOXONE FOR NEUROPATHIC PAIN. SYSTEMATIC REVIEW GASKELL 2016	364
22.13	TAPENTADOL FOR DIABETIC PERIPHERAL NEUROPATHY. SYSTEMATIC REVIEW DY 2017	367
23	APPENDIX. EVIDENCE TABLES. OPIOIDS FOR CANCER PAIN	371
23.1	OPIOIDS FOR CANCER PAIN. OVERVIEW OF COCHRANE REVIEWS WIFFEN 2017	371
23.2	MORPHINE, FENTANYL OXYCODONE OR CODEINE FOR CANCER PAIN: ADVERSE EVENTS. OVERVIEW OF COCHRANE REVIEWS WIFFEN PHILIP 2014	372
23.3	TRAMADOL +/- PARACETAMOL FOR CANCER PAIN. COCHRANE SYSTEMATIC REVIEW WIFFEN 2017	373
23.4	CODEINE +/- PARACETAMOL FOR CANCER PAIN. COCHRANE SYSTEMATIC REVIEW STRAUBE 2014	374
23.5	HYDROMORPHONE FOR CANCER PAIN. COCHRANE SYSTEMATIC REVIEW BAO YAN 2016	375
23.6	TRANSDERMAL FENTANYL FOR CANCER PAIN. COCHRANE SYSTEMATIC REVIEW HADLEY 2013.....	376
23.7	METHADONE FOR CANCER PAIN. COCHRANE SYSTEMATIC REVIEW NICHOLSON ALEXANDER 2017	377
23.8	OXYCODONE FOR CANCER PAIN. COCHRANE SYSTEMATIC REVIEW SCHMIDT-HANSEN 2017	378
23.9	BUPRENORPHINE FOR CANCER PAIN. COCHRANE SYSTEMATIC REVIEW SCHMIDT-HANSEN 2014	379
23.10	ORAL TAPENTADOL FOR CANCER PAIN. COCHRANE SYSTEMATIC REVIEW WIFFEN 2015	380
23.11	ORAL MORPHINE FOR CANCER PAIN. COCHRANE SYSTEMATIC REVIEW WIFFEN 2016.....	381
23.12	OPIOIDS IN CANCER SURVIVORS.....	382
24	APPENDIX: OPIOID ROTATION	383
24.1	OPIOID ROTATION VS NO OPIOID ROTATION IN CHRONIC NON-CANCER PAIN. SYSTEMATIC REVIEW BUSSE 2017	383
24.2	OPIOID SWITCHING. COCHRANE SYSTEMATIC REVIEW QUIGLEY 2013	384
24.3	OPIOID ROTATION IN CANCER PAIN. META-ANALYSIS SCHUSTER 2018.....	385
25	APPENDIX: TAPERING	386
25.1	TAPERING FOR OPIOID INDUCED HYPOGONADISM IN CHRONIC NON-CANCER PAIN. SYSTEMATIC REVIEW AMINILARI 2018 386	
25.2	TAPERING VS NO TAPERING IN CHRONIC NON-CANCER PAIN. SYSTEMATIC REVIEW BUSE 2017.....	387
25.3	DOSE REDUCTION OR DISCONTINUATION OF LONG-TERM OPIOID THERAPY FOR CHRONIC PAIN. SYSTEMATIC REVIEW FRANK 2017 388	
26	APPENDIX. AGREE SCORES OF GUIDELINES	391

26.1	AGREE SCORES. SUMMARY	391
26.2	AGREE SCORES. DETAILS	392
27	APPENDIX: SEARCH STRATEGY DETAILS	397
28	APPENDIX. LIST OF EXCLUDED PUBLICATIONS (AFTER EVALUATION OF FULL TEKST)	399
29	REFERENCES.....	405

1 Abbreviations

AE: adverse events
ARR: absolute risk reduction
BOCF: baseline observation carried forward
BPI: Brief pain inventory
BTDS: buprenorphine transdermal system
CI: confidence interval
CO: crossover RCT
DB: double blind
DPNP: diabetic peripheral neuropathic pain
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
MDQ: Roland Morris Disability Questionnaire
MOS SF-36: Medical Outcomes Study 36-item Short Form health survey
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
ODI: owestry disability index
OL: open label
PER: placebo event rate
PG: parallel group
PGIC: Patient Global Impression of Change
PO: primary outcome
RAND –36 Research And Development 36 item survey
RMDQ: Roland Morris Disability Questionnaire
SB: single blind
SD: standard deviation

SF-36: short form health survey (36 items)

SO: secondary outcome

SS: statistically significant

TDS: transdermal system

TER treatment event rate

VAS: Visual Analogue Scale

VR-12: 12-item Health Survey quality-of-life measure

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 opioids for chronic pain**”, which will take place on the 6th of december 2018.

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.
Quelle est la définition d’une douleur chronique ? Quels types de douleurs chroniques faut-il distinguer ?
Wat is de definitie van chronische pijn ? Welke types van chronische pijn moet men onderscheiden?
2.
Quelles sont les différences importantes dans la prise en charge d’une douleur aiguë et d’une douleur chronique, particulièrement dans le domaine du traitement médicamenteux (principes généraux) ?
Welke belangrijke verschillen moet men onderscheiden in de aanpak van acute pijn en chronische pijn, meer specifiek met betrekking tot farmacologische behandelingen (algemene principes)?
3.
Quelle est la place d’un traitement par opioïdes dans une prise en charge bio-psycho-sociale de la douleur chronique ?
Wat is de plaats van een behandeling door middel van opioïden binnen het kader van een bio-psycho-sociale aanpak van chronische pijn?
4.
Quelle est l’efficacité des différents opioïdes et diffère-t-elle selon les types de douleurs chroniques traités ?
Wat is de doeltreffendheid van de verschillende opioïden en verschilt deze doeltreffendheid naargelang het type van chronische pijn die behandeld moet worden?
5.
Quel est le profil des effets indésirables des différents opioïdes en cas de douleur chronique ?
Wat is het profiel van de ongewenste effecten van de verschillende opioïden in omstandigheden van chronische pijn?
6.
Pour les différents opioïdes existe-t-il des contre-indications précises. Quelle est l’importance de la forme galénique ?
Bestaan er specifieke contra-indicaties voor de verschillende opioïden? Wat is het belang van de gebruikte galenische vorm?
7.
Une attention plus particulière doit-elle être apportée à certaines catégories de patients (en insuffisance hépatique, rénale, personnes âgées, adolescents)
Noodzaken sommige patiëntenpopulaties een bijzonder aandacht (patiënten met leverinsufficiëntie,

nierinsufficiëntie, ouderen en adolescenten) ?

8.

Quelles sont les précautions à observer et quel suivi (monitoring de développement de tolérance et d'hyperalgésie aux opioïdes) est nécessaire avec les différents opioïdes? Existe-t-il des différences entre les opioïdes? *Welke voorzorgsmaatregelen moeten worden nageleefd en welke opvolging (monitoring van optreden van tolerantie en hyperalgesie aan opioïden) is noodzakelijk voor de verschillende opioïden? Bestaan er hieromtrent verschillen tussen de verschillende opioïden?*

9.

Dans quelles situations cliniques (syndromes cliniques), une rotation des opioïdes est-elle indiquée ? *In welke klinische omstandigheden (klinische syndromen) bestaat er een indicatie voor uitvoering van een opioïd-rotatie ?*

10. Dans quelles situations/indications une déprescription des opioïdes est-elle indiquée et quelles sont les modalités d'une déprescription ?

In welke situaties/indicaties is een 'deprescribing' van de opioïden aangewezen en onder welke modaliteiten moet dit worden uitgevoerd?

11.

Comment organiser la prévention, la détection et le traitement des syndromes d'abus des opioïdes?

Hoe worden de preventie, de detectie en de behandeling van opioïd-abusus het best georganiseerd?

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 rare 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.

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

Question 1
<ul style="list-style-type: none">• This question will be answered by an expert-speaker.
Question 2
<ul style="list-style-type: none">• This question will be answered by an expert-speaker.
Question 3
<ul style="list-style-type: none">• The literature group will discuss selected guidelines. This discussion can be found in chapter 5.1 and 5.2.• An expert speaker will provide comments and additional information.
Question 4
<ul style="list-style-type: none">• The literature group will discuss selected guidelines. This discussion can be found in chapter 5.2 and 5.3.• The literature group will perform a literature search of RCTs or systematic reviews/meta-analyses of RCTs. The results of the literature search can be found in chapter 6 to 12 (and the corresponding appendices).• An expert speaker will provide comments and additional information.
Question 5
<ul style="list-style-type: none">• The literature group will discuss selected guidelines. This discussion can be found in chapter 5.2 and 5.3.• The literature group will perform a literature search of RCTs or systematic reviews/meta-analyses of RCTs. The results of the literature search can be found in chapter 6 to 12 (and the corresponding appendices).• The literature group will provide additional information from observational studies for certain rare safety outcomes (see 1.3.3). The results can be found in chapter 15. Additional sources (see 1.3.2) will also be consulted for safety endpoints. The results of additional sources can be found in chapter 16.• An expert speaker will provide comments and additional information.
Question 6
<ul style="list-style-type: none">• The literature group will discuss selected guidelines. This discussion can be found in chapter

<p>5.2 and 5.3.</p> <ul style="list-style-type: none"> • Additional sources (see 1.3.2) will also be consulted. The results of additional sources can be found in chapter 16. • An expert speaker will provide comments and additional information.
Question 7
<ul style="list-style-type: none"> • The literature group will discuss selected guidelines. This discussion can be found in chapter 5.4 • Additional sources (see 1.3.2) will also be consulted. The results of additional sources can be found in chapter 16. • An expert speaker will provide comments and additional information.
Question 8
<ul style="list-style-type: none"> • The literature group will discuss selected guidelines. This discussion can be found in chapter 5.2, 5.3 and 5.7. • Additional sources (see 1.3.2) will also be consulted. The results of additional sources can be found in chapter 16. • An expert speaker will provide comments and additional information.
Question 9
<ul style="list-style-type: none"> • The literature group will discuss selected guidelines. This discussion can be found in chapter 5.5. • The literature group will perform a literature search of RCTs or systematic reviews/meta-analyses of RCTs. The results of the literature search can be found in chapter 13 (and the corresponding appendices). • An expert speaker will provide comments and additional information.
Question 10
<ul style="list-style-type: none"> • The literature group will discuss selected guidelines. This discussion can be found in chapter 5.6. • The literature group will perform a literature search of RCTs or systematic reviews/meta-analyses of RCTs. The results of the literature search can be found in chapter 14 (and the corresponding appendices). • An expert speaker will provide comments and additional information.
Question 11
<ul style="list-style-type: none"> • The literature group will discuss selected guidelines. This discussion can be found in chapter 5.7. • An expert speaker will provide comments and additional information.

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 2013 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 AgreeII 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 opioids 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 treatment: 3 months (12 weeks). For tapering or rotation, shorter durations are acceptable.
- 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

- Prospective or retrospective **cohort** studies
- Minimum number of participants: 1000

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

- Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI) / Centre Belge d'Information Pharmacothérapeutique (CBIP)
 - *Gecommentarieerd geneesmiddelenrepertorium / Répertoire Commenté des Médicaments*
 - *Folia Pharmacotherapeutica*
- Martindale: The complete drug reference, 39th edition

Some publications will be excluded for practical reasons:

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

2.3.3 Specific search criteria

2.3.3.1 Populations

The following populations are to be discussed:

- Adults with chronic pain (somatic, visceral or neuropathic).

Exclusions:

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

The 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
- elderly patients
- adolescents
- patients with substance use disorder (current or previous history)

2.3.3.2 Interventions

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

Opioids and opioid combinations to be studied
Codeine + paracetamol
Codeine + paracetamol + caffeine
Tramadol
Tramadol + paracetamol
Tilidine + naloxone
Buprenorphine
Fentanyl
Hydromorphone
Methadone
Morphine
Oxycodone
Oxycodone + naloxone
Tapentadol

Table: Opioids available in Belgium

Excluded from the literature review are

- Opioids or opioid combinations that are not available on the Belgian market.
(For example: extended-release oxycodone surrounding sequestered naltrexone; extended release morphine surrounding sequestered naltrexone, ...)
- Pharmaceutical formulations that are not available on the Belgian market.
(For example: abuse-deterrent formulation of extended-release oxycodone (oxycodone DETERx® extended release capsules); Fentanyl 1 day patch, buccal buprenorphine film,...)
- Parenteral administration of opioids
- Opioids/opioid combinations that have only an approved indication for substitution treatment in opioid dependence disorder (such as buprenorphine + naloxone, which is sometimes used – off label – in specialist settings for the treatment of pain)

2.3.3.3 Comparisons

The following clinical situations will be studied (information from RCTs or systematic reviews/meta-analyses from RCTs):

- Chronic pain patients that are treated with analgesic drugs (and non-pharmacological treatments), who have inadequate pain relief:
 - ➔ Opioids versus optimisation of non-opioid pain treatment
- Chronic pain patients with optimal non-opioid pain treatment (ideally: an optimal bio-psycho-social pain treatment), who still have inadequate pain relief:
 - ➔ Opioids versus placebo/no opioids

Note: most trials do not meet this 'ideal' situation. We will therefore include studies in which patients have inadequate control with their current (non-opioid) pain treatment and describe the components of this current pain treatment. It is up to the jury to judge whether this population adequately reflects (ideal) clinical practice.

- Chronic pain patients on opioids
 - ➔ Tapering versus no tapering (= continuing current opioid) (any reason)
 - ➔ Rotation versus no rotation (any reason)

2.3.3.4 Endpoints

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

Efficacy
<ul style="list-style-type: none"> • Functioning • Pain • Quality of life <p>for tapering</p> <ul style="list-style-type: none"> • Success of tapering (number of patients successfully tapered) <p>for opioid rotation</p> <ul style="list-style-type: none"> • Success of rotation (number of patients successfully switched)
Safety
<ul style="list-style-type: none"> • Adverse events leading to withdrawal from treatment • Nausea, vomiting, constipation • Sedation, cognitive problems • Addiction, abuse • (Fatal) overdose <p>Rare safety endpoints (information also from observational studies)</p> <ul style="list-style-type: none"> • Sexual or endocrinological dysfunction, hypogonadism • Immunosuppression

2.4 Search strategy

2.4.1 Principles of systematic search

Relevant RCTs, meta-analyses and systematic reviews 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 vzw Farmaka asbl (www.farmaka.be) and 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 National Guideline Clearinghouse and 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:

Source document chronic non-cancer pain

Busse JW, Craigie S, Juurlink DN, Buckley DN, Wang L, Couban RJ, et al. Guideline for opioid therapy and chronic noncancer pain. Canadian Medical Association Journal 2017;189: E659-E66.

Dowell D, Haegerich T, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States. MMWR Recomm Rep 2016;65: 1-49.

Source documents neuropathic pain

References from the systematic search for this guideline

- 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).

The following Cochrane Reviews

- Wiffen Philip J, Knaggs R, Derry S, et al. Paracetamol (acetaminophen) with or without codeine or dihydrocodeine for neuropathic pain in adults. Cochrane Database of Systematic Reviews [Internet]. 2016; (12).
- Duehmke Rudolf M, Derry S, Wiffen Philip J, Bell Rae F, Aldington D, Moore RA. **Tramadol** for neuropathic pain in adults. Cochrane Database of Systematic Reviews [Internet]. 2017; (6)

- Wiffen Philip J, Derry S, Moore RA, Stannard C, Aldington D, Cole P, et al. **Buprenorphine** for neuropathic pain in adults. Cochrane Database of Systematic Reviews [Internet]. 2015; (9).
- Derry S, Stannard C, Cole P, Wiffen Philip J, Knaggs R, Aldington D, et al. **Fentanyl** for neuropathic pain in adults. Cochrane Database of Systematic Reviews [Internet]. 2016; (10).
- Stannard C, Gaskell H, Derry S, Aldington D, Cole P, Cooper Tess E, et al. **Hydromorphone** for neuropathic pain in adults. Cochrane Database of Systematic Reviews [Internet]. 2016; (5).
- McNicol Ewan D, Ferguson McKenzie C, Schumann R. **Methadone** for neuropathic pain in adults. Cochrane Database of Systematic Reviews [Internet]. 2017; (5).
- Cooper Tess E, Chen J, Wiffen Philip J, Derry S, Carr Daniel B, Aldington D, et al. **Morphine** for chronic neuropathic pain in adults. Cochrane Database of Systematic Reviews 2017.
- Gaskell H, Derry S, Stannard C, et al. **Oxycodone** for neuropathic pain in adults. Cochrane Database of Systematic Reviews 2016.

Source documents cancer pain

References from the systematic search for these guidelines

- Department of Health. Pharmacological management of cancer pain in adults: national clinical guideline no 9. 2015. (Ireland)
- Paice JA, Portenoy R, Lacchetti C, Campbell T, Cheville A, Citron M, et al. Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. Journal of Clinical Oncology 2016;34: 3325-45.

The following Cochrane Reviews

- Wiffen Philip J, Wee B, Derry S, et al. Opioids for cancer pain - an overview of Cochrane reviews. Cochrane Database of Systematic Reviews [Internet]. 2017; (7)
- Wiffen Philip J, Derry S, Moore RA. Impact of morphine, fentanyl, oxycodone or codeine on patient consciousness, appetite and thirst when used to treat cancer pain. Cochrane Database of Systematic Reviews [Internet]. 2014; (5)
- Wiffen Philip J, Derry S, Moore RA. Tramadol with or without paracetamol (acetaminophen) for cancer pain. Cochrane Database of Systematic Reviews [Internet]. 2017; (5).
- Straube C, Derry S, Jackson Kenneth C, et al. Codeine, alone and with paracetamol (acetaminophen), for cancer pain. Cochrane Database of Systematic Reviews [Internet]. 2014; (9).
- Bao Yan J, Hou W, Kong Xiang Y, et al. Hydromorphone for cancer pain. Cochrane Database of Systematic Reviews [Internet]. 2016; (10).
- Hadley G, Derry S, Moore RA, et al. Transdermal fentanyl for cancer pain. Cochrane Database of Systematic Reviews [Internet]. 2013; (10).
- Nicholson Alexander B, Watson Graeme R, Derry S, et al. Methadone for cancer pain. Cochrane Database of Systematic Reviews [Internet]. 2017; (2).
- Schmidt-Hansen M, Bennett Michael I, Arnold S, et al. Oxycodone for cancer-related pain. Cochrane Database of Systematic Reviews [Internet]. 2017; (8).
- Schmidt-Hansen M, Bromham N, Taubert M, et al. Buprenorphine for treating cancer pain. Cochrane Database of Systematic Reviews [Internet]. 2015; (3).
- Wiffen Philip J, Derry S, Naessens K, et al. Oral tapentadol for cancer pain. Cochrane Database of Systematic Reviews [Internet]. 2015; (9).
- Wiffen Philip J, Wee B, Moore RA. Oral morphine for cancer pain. Cochrane Database of Systematic Reviews [Internet]. 2016; (4).

Source documents for tapering

References from the systematic search for these guidelines

- Busse JW, Craigie S, Juurlink DN, Buckley DN, Wang L, Couban RJ, et al. Guideline for opioid therapy and chronic noncancer pain. Canadian Medical Association Journal 2017;189: E659-E66.
- Dowell D, Haegerich T, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States. MMWR Recomm Rep 2016;65: 1-49.

Source documents for opioid rotation

References from the systematic search for these guidelines

- Busse JW, Craigie S, Juurlink DN, Buckley DN, Wang L, Couban RJ, et al. Guideline for opioid therapy and chronic noncancer pain. Canadian Medical Association Journal 2017;189: E659-E66.
- Dowell D, Haegerich T, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States. MMWR Recomm Rep 2016;65: 1-49.

The following Cochrane Reviews

- Quigley C. Opioid switching to improve pain relief and drug tolerability. Cochrane Database of Systematic Reviews 2013 (retracted)

Source document for observational studies

- Dowell D, Haegerich T, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States. MMWR Recomm Rep 2016;65: 1-49.

For all these research questions, a search string was developed to search Medline via Pubmed from the research date of the selected source document up until 1st January 2018. If no source document could be found (e.g. for tilidine), a search of Medline without a starting date was performed.

2.4.3 Search strategy details

The full search strategies can be found in appendix 1.

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 Appendix 2.

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

3 Critical reflections of the reading committee and the literature group

3.1 Guidelines

Most guidelines acknowledge the limited benefits of opioids that are found in clinical trials and the important adverse events associated with opioid use. This is reflected by the fact that adding opioids to a pain treatment (that was optimized by non-opioid therapy, both pharmaceutical and non-pharmaceutical) is a weak recommendation.

Guidelines generally advise to weigh the risks and the benefits for the (long term) treatment of chronic pain with opioids, but provide little advice as to how this balance should be established. To assess benefit, the guidelines advise to define clear goals for functional improvement and pain relief before starting opioids, so it can be clearly assessed whether or not these goals are met. For evaluating risks, there is some advice on assessment of risk of abuse and misuse, and the possible adverse events are described.

Not all guidelines discussed the use of tapentadol. This is a relatively new opioid and was probably not on the market at the time some of the guideline were written. Only 1 guidelines published a dose conversion table that includes tapentadol.

3.2 Benefit-harm

The reading committee would like to ask the jury to try to assess in what circumstances the benefits of opioid use in chronic pain may outweigh the risks. Of course there probably is no formal scientific answer to this question, and no general answer for every situation. At best, the available evidence can give, for every situation, an approximation of the possible benefits and harms, but no clear-cut result. Different values and different dimensions of benefits and risks need to be put in the balance. The actual benefits and harms will be also be patient-dependent. A patient may also place a different value on possible benefits and harms than a physician. A patient-centered approach will be very important in this context.

End of life-situations were not a part of this literature review, but it is clear that life expectancy is a major factor influencing these decisions.

Secondly, possible harms of opioids have to be weighted against possible harms of other analgesic drugs or procedures. For example, the use of NSAID will be be restricted or contra-indicated in elderly patients or patients with chronic kidney disease, due to the risk of adverse events, which may leaves us few alternatives in terms of analgesic drugs.

3.3 Examining the place of opioids within a bio-psycho-social pain treatment framework

The organizing committee had 2 major research questions for which a complete search for meta-analyses, systematic reviews and RCTs had to be performed. These research questions were based on a chronic pain treatment plan within a **bio-psycho-social model of pain**, in which **multimodal and**

possible multidisciplinary treatment is envisaged. The organizing committee wishes to adequately assess the place of opioids within this treatment framework.

The first research question examines the initiation of an opioid treatment compared to the optimization of pain treatment using a non-opioid treatment in a patient with chronic pain that is treated with non-opioid analgesics (and non-pharmaceutical treatments).

The second research question aimed to examine patients with chronic pain who have an optimized pain treatment (using non-pharmaceutical and pharmaceutical treatments), but still suffer from pain. The question then was how the initiation of an opioid compared to placebo would influence pain, function and adverse events.

Unfortunately, under these specific research conditions, it would have been impossible to include almost any RCT for the second research question. There are plenty of RCTs starting opioids in patients that have inadequate pain control from their current treatment, but this current treatment is usually only defined by the analgesic drugs that are used. Non-pharmaceutical treatments are either not described, restricted or even prohibited within the study context. There is also a great variability within trials and between trials as to the nature of this 'current' analgesic treatment. On top of that, it is hard to define an 'optimized' treatment.

The inclusion criteria for our Consensus Conference literature review were 'relaxed' to include RCTs that examine the initiation of opioids in patients that have insufficient analgesic relief with their 'current treatment'. A description of this treatment had to be provided, so the reader can judge whether this treatment fulfills the criteria of good clinical practice.

It may be difficult to establish the place of opioids within a bio-psycho-social treatment context based on the available evidence. Opioids have not been examined adequately within this overall setting. The available evidence does give us some idea as to the efficacy and (some aspects of) safety associated with opioid use in general.

3.3.1 Opioids versus optimization of non-opioid treatment

We found hardly any studies for this comparison that had adequate length.

The most interesting study for this comparison is the SPACE trial, in which a 3-step opioid treatment regimen is compared to a 3- step non-opioid treatment regimen. Unfortunately, in the non-opioid treatment arm, step 3 could involve the use of tramadol. Even so, this trial is a great source of information about the possible place of opioids within a chronic pain treatment. This trial is also unique in its use of a patient-centered care framework and its applicability to daily clinical care.

3.3.2 Opioids versus placebo

We found a lot of trials for this comparison (after 'relaxing' the inclusion criteria for this research question). None of these are in a population with an 'optimized bio-psycho-social pain treatment' or if they are, this is not described as such.

These trials aim to prove that opioids provide better pain relief than placebo. To this aim, all other variables that may influence pain relief are often strictly controlled. Some trials organize a wash-out phase in which some or all previous analgesic drugs are discontinued. Other analgesics are usually forbidden within the trial, with the exception of a rescue analgesic.

Current use of drugs that can be used as a co-analgesic is either not reported or is sometimes a criterion for exclusion. The use of physical therapy, biofeedback, TENS and other non-pharmaceutical interventions are often not described or the use of these interventions is sometimes restricted within the trial.

3.4 Study duration

A lot of trials with opioids, even in chronic pain, are of short duration. To assess the possible long-term use of opioids in a chronic pain situation we would need trials with long-term opioid use. The organizing committee chose a minimal treatment duration of 12 weeks as an inclusion criterion for this literature review. One could argue that 12 weeks is still quite short to assess long-term treatment, but we have to draw a line somewhere. Unfortunately, we had to exclude quite a number of trials because they had a shorter duration.

The systematic search that was performed for the CDC guideline on opioid prescribing (1) was more strict in its inclusion criteria and searched only for trials that reported outcomes at 1 year. As a result, no trials met their inclusion criteria.

3.5 Population

3.5.1 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).

There were fewer studies in **neuropathic pain** meeting our inclusion criteria.

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

For opioid rotation and tapering, very few trials exist. None of these met our inclusion criteria for sample size and duration.

3.5.2 Subgroups

There is little specific information on the use of opioids for chronic pain in the **elderly** (> 65 years) and especially the very elderly (> 80 years). Some trials did not define an upper age range in their patient inclusion criteria. Other trials had an upper age limit of 75 years. The mean age in RCTs roughly between 53 years and 63 years for osteoarthritis and between 48 years and 58 years for low back pain.

Most trials include adult patients, defined as ≥ 18 years. We have little information about opioid use for chronic pain in adolescents.

Patients with **substance use disorder** were usually excluded from the RCTs, as were patients with **comorbid psychiatric conditions**.

Patients **with chronic kidney disease or liver disease** were sometimes specifically excluded from the trials, but usually not mentioned outright in the exclusion criteria of the RCTs. Usually a general phrase excluding patients with unstable coexisting disease, (severe) organ dysfunction or conditions that might interfere with dose administration were excluded.

In our 'guidelines' section, we report age-specific guidance statements, as well as recommendations for patients with renal or hepatic insufficiency and patients with (current or previous) substance use disorder.

3.6 Interventions

For codeine, tilidine, morphine and methadone we found no studies that met our inclusion criteria.

For neuropathic pain, we were able to include studies with buprenorphine, oxycodone and tapentadol.

3.7 Outcomes

3.7.1 Pain

There was quite a variability in reporting pain outcomes in the trials. Usually a 0-10 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 (2). 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. Most, but not all trials report pain outcomes in this way.

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

3.7.2 Function and quality of life

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

There are a lot of 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.

3.7.3 Adverse events

Discontinuation due to adverse events was very high in all trials.

Some **common adverse events** like constipation, nausea, vomiting, somnolence were reported frequently in the trials. The frequency of these adverse events is reported in the evidence tables. The GRADE-assessment is usually low: high drop outs, trial design, (the pooling of) different opioid doses and opioids of different strength will influence the reliability of the estimate of actual event rates. Trials were not large enough to reliably detect **rare adverse events**. These are reported in some of the trials, but inconsistently. There is insufficient reporting of possible **abuse, addiction, overdose or other serious adverse events** in the RCTs. Some information about these rarer endpoints exists in observational studies, but these were not part of our literature search task.

The development of **tolerance and hyperalgesia** was not part of our literature search. Rarely, an RCT reported the number of patients experiencing withdrawal effects after stopping treatment.

We searched for observational studies (cohort studies) about **endocrinological dysfunction**. While most authors agree that opioid use may lead to hypogonadism, the literature about actual studies is sparse and consists mostly of cross-sectional studies and very small cohorts. We were able to include 1 cohort study of adequate size about this outcome.

We also searched for observational studies about **immunological dysfunction** with opioid use. There seems to be some uncertainty about the possible immunosuppressant effects of opioids among different authors. Again, there is only sparse data, mostly in peri-operative use of opioids. We were able to include 1 cohort study for this outcome, studying the recurrence of breast cancer.

In the chapter 'Adverse events' we report information from BCFI sources and from Martindale (39th) edition as an addition to the information that was reported in the studies included in our review.

3.8 Discontinuations during the trial

The RCTs comparing opioids to placebo have high drop-out rates. Discontinuations of study medication up to 50% and more are no exception. Adverse events are the number one reason to stop opioids early, whilst lack of efficacy is usually the most cited reason for stopping placebo treatment. The high drop-out rates, the reasons of which are usually unbalanced between groups, will create a high risk of biased study results.

3.9 Additional remarks from the reading committee

The reading committee remarks that there is few information in the guidelines about a **multidisciplinary care**, especially with regards to **primary care**.

Even with little available evidence, the need for **cooperation, coordination and communication** between primary care physician and pharmacist, physiotherapist, nurse, carers, ... would seem evident when considering 'good clinical practice' standards. For example with regards to communication about the correct use of analgesics, monitoring overuse and medical shopping, ...

The need for good communication and cooperation is also very important **between primary and secondary care** for similar reasons. For example, to avoid multiple prescriptions, to avoid interactions or other harms, to discuss situations in which a primary care physician is asked to write repeat prescriptions for opioids started in the second line care...

3.10 Some methodological issues explained

3.10.1 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 insufficient pain relief from paracetamol, NSAID or opioids), different opioid strengths, 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.

A narrow point estimate is no more reliable than a wide point estimate if all the included trials have a high risk of bias from high drop-out rates and the way missing values are handled.

3.10.2 Missing values

The high drop-out rate inevitably causes a lot of missing values in the efficacy and safety data at the end of the trial. Trials use different methods to deal with missing values.

The most common method used in the trials in this literature review was the last observation carried forward (LOCF, the last value that was recorded when the patient was still on study medication is

used as the final value at the end of the trial). This method can overstate drug efficacy (2). Some trials use other imputation methods, such as baseline observation carried forward (BOCF any early drop out is considered a non-responder) or a method combining LOCF and BOCF or a method based on placebo response... Some trials perform sensitivity analysis using different imputation methods. This is very commendable, however, these analyses are rarely reported in detail. No imputation method is perfect. The best way to avoid biased results caused by missing values is to prevent them from occurring.

3.10.3 Enriched enrollment

Study designers have tried to diminish the number of drop outs by creating 'enriched enrollment trials'. Some trials comparing opioids to placebo in this document have this design.

In these trials, all patients that meet the eligibility criteria of the trial are first treated with an opioid in an open label fashion. After a certain time period, the patients that have adequate treatment response and adequate tolerability will be randomized to opioid treatment or to placebo. The authors claim that this design mimics treatment decisions made in clinical practice(3), because only patients who tolerate opioids are likely to use them longer term and that there may be a subgroup of patients who respond well to opioids (4).

In the enriched enrollment trials included in this literature review, 30% to 50% of patients that were started on open label opioids dropped out before the double blind randomization phase.

This design creates a high risk of bias: the difference from placebo-treatment may be artificially inflated in a population that has responded well to treatment and the results cannot be extrapolated to a broader population(5). The comparison between opioid and placebo also may become distorted because of possible carry-over effects or withdrawal symptoms (4).

Some authors have compared the results from enriched enrollment trials and non-enriched enrollment trials and found no apparent bias for efficacy, but a suggestions of an underestimation of safety outcomes (4, 6, 7).

It must be noted again that many non-enriched trials have high drop-out rates (mostly due to adverse events or lack of efficacy), which causes bias and most of these trials use methods of dealing with missing values that may bias towards an overestimation of treatment effect. It may be safer to state that the current enriched enrollment trials do not appear to cause a greater bias in efficacy endpoints than the current non-enriched enrollment trials.

3.10.4 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(8). 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 1 cm on a 10 cm 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.

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
NPC_Canada 2017	Busse JW, Craigie S, Juurlink DN, Buckley DN, Wang L, Couban RJ, et al. Guideline for opioid therapy and chronic noncancer pain. Canadian Medical Association Journal 2017;189: E659-E66. (9)
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. (10) 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. (11)
CDC 2016	Dowell D, Haegerich T, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States. MMWR Recomm Rep 2016;65: 1-49. (1)
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)
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). (13)
ASCO 2016	Guideline on Chronic Pain Management in Adult Cancer Survivors. (14)
DOH_Ireland 2015	Pharmacological management of cancer pain in adults: national clinical guideline no 9. (15)
KCE 2013	Supportive treatment for cancer – Part 3: treatment of cancer pain: most common practices. (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.

NPC_Canada 2017		
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 the Canada 2017 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 changeant 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.

CDC 2016		
Grades of recommendation:	Category A	Category A recommendations apply to all persons in a specified group and indicate that most patients should receive the recommended course of action.
	Category B	Category B recommendations indicate that there should be individual decision making; different choices will be appropriate for different patients, so clinicians must help patients arrive at a decision consistent with patient values and preferences, and specific clinical situations.
Levels of evidence	Type 1	randomized clinical trials or overwhelming evidence from observational studies
	Type 2	randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies
	Type 3	observational studies or randomized clinical trials with notable limitations
	Type 4	Clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations

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

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.

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	

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

KCE 2013		
Grades of recommendation: According to Grade	Strong	The desirable effects of an intervention clearly outweigh the undesirable effects (the intervention is to be put into practice), or the undesirable effects of an intervention clearly outweigh the desirable effects (the intervention is not to be put into practice)
	Weak	The desirable effects of an intervention probably outweigh the undesirable effects (the intervention probably is to be put into practice), or the undesirable effects of an intervention probably outweigh the desirable effects (the intervention probably is not to be put into practice)
	GCP	Some recommendations were not directly based on scientific evidence, but were considered by the expert panel to be good clinical practice. These recommendations are listed separately as GCP (Good Clinical Practice) and a grade of recommendation according to the GRADE system is not assigned.
Levels of evidence	High	According to GRADE (assessment of risk of bias, inconsistency, indirectness, imprecision and reporting bias)
	Moderate	
	Low	
	Very Low	

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
NPC_Canada 2017	7	6	6	6	6	6	5	5	47	84%
WOREL 2017	4	2	3	3	5	5	5	5	32	57 %
CDC 2016	7	7	6	5	6	6	5	4	46	82%
NHG 2018	7	4	5	5	6	7	6	3	43	77%
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%
KCE 2013	7	7	7	5	6	7	7	5	51	91%

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.

NPC_Canada 2017	
Population	Adults with chronic (≥ 3 months) non-cancer pain considering first line therapy for pain
Interventions	Opioids vs optimization of NSAIDs Opioids vs optimization of anticonvulsants Opioids vs optimization of tricyclic antidepressants Opioids vs optimization of nabilone Opioids vs optimization of mexiletine
Outcomes	<ul style="list-style-type: none"> - Pain - Physical function - Gastrointestinal side effects - Addiction - Fatal overdose - Non-fatal overdose - Diversion

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

NPC_Canada 2017	
Population	Patients with chronic non-cancer pain, without current or past substance use disorder and without other current serious psychiatric disorders, whose therapy is optimized with non-opioids with persistent problematic pain
Interventions	Opioids vs continue established therapy without opioids
Outcomes	<ul style="list-style-type: none"> - Pain - Physical function - Gastrointestinal side effects - Addiction - Fatal overdose - Non-fatal overdose - Diversion

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

NPC_Canada 2017	
Population	Patients with chronic non-cancer pain with an active substance use disorder whose non-opioid therapy has been optimized
Interventions	Opioids vs continue established therapy without opioids
Outcomes	<ul style="list-style-type: none"> - Pain - Physical function - Gastrointestinal side effects - Addiction - Fatal overdose

	- Non-fatal overdose
--	----------------------

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

Canada 2017	
Population	Patients with chronic noncancer pain with an active psychiatric disorder whose non-opioid therapy has been optimized, and who still experience persistent problematic pain
Interventions	Opioids vs continue established therapy without opioids
Outcomes	<ul style="list-style-type: none"> - Pain - Physical function - Gastrointestinal side effects - Addiction - Fatal overdose - Non-fatal overdose

Canada 2017	
Population	Patients with chronic non-cancer pain with a history of substance use disorder, whose non-opioid therapy has been optimized, who still experience persistent problematic pain
Interventions	Opioids vs continue established therapy without opioids
Outcomes	<ul style="list-style-type: none"> - Pain - Physical function - Gastrointestinal side effects - Addiction - Fatal overdose - Non-fatal overdose

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

Canada 2017	
Population	Patients with chronic noncancer pain beginning opioid therapy
Interventions	Limit opioid dose to a particular maximum dose vs no maximum opioid dose
Outcomes	<ul style="list-style-type: none"> - Pain - Physical function - Gastrointestinal side effects - Addiction - Fatal overdose - Non-fatal overdose - Diversion

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

Canada 2017	
Population	Patients with chronic non-cancer pain with persistent problematic pain and/or problematic side effects

Interventions	Rotation to other opioids vs No change in opioid therapy
Outcomes	- Pain - success of tapering

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

Canada 2017	
Population	Patients with chronic non-cancer pain on opioids with persistent problematic pain
Interventions	Tapering of opioid vs Keeping the dose of opioid the same
Outcomes	- Pain - Physical function - Gastrointestinal side effects - Addiction - Diversion - success of opioid rotation

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

Canada 2017	
Population	Patients who want to taper opioids who are above the threshold dose
Interventions	Multidisciplinary Program vs No Multidisciplinary Program
Outcomes	- Pain - Success of tapering - Physical function

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

Canada 2017	
Population	Patients with chronic non-cancer pain prior to starting long-term opioid therapy
Interventions	Controlled release opioids vs Immediate release opioids
Outcomes	- Gastrointestinal side effects - Pain - Physical function

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

Canada 2017	
Population	Patients with chronic non-cancer pain on long-term opioid therapy with clinical and biochemical evidence of hypogonadism.
Interventions	Hormone replacement therapy while maintaining current opioid dose vs Taper opioids to treat hypogonadism
Outcomes	- Pain reduction - Sexual function - Physical function - Depression

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

Canada 2017

Population	Patients with chronic non-cancer pain prior to starting long term opioid therapy
Interventions	Urine drug screening for baseline substance use vs No urine drug screening for baseline substance use
Outcomes	- opioid overdose

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

Canada 2017	
Population	Patients with chronic non-cancer pain prior to starting long-term opioid therapy
Interventions	Formal structured treatment agreements vs No formal structured treatment agreement
Outcomes	- opioid misuse

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

Canada 2017	
Population	Patients with chronic non-cancer pain prior to starting long-term opioid therapy
Interventions	Provide take-home naloxone along with opioid prescription vs Do not provide take-home naloxone along with opioid prescription
Outcomes	- Fatal overdose - All-cause mortality - Hospitalization

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

WOREL 2017	
Population	<p>Deze richtlijn is van toepassing op patiënten met chronische pijn in de eerste lijn, met uitzondering van kinderen, kankerpatiënten of palliatieve patiënten.</p> <p>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").</p> <p>La population ciblée par ce GPC concerne les patients souffrant de douleur chronique. Sont exclus les patients pédiatriques, cancéreux ou suivis en soins palliatifs.</p> <p>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 »).</p>
Interventions	- Non-pharmaceutical interventions (physiotherapy, exercise, TENS, low level laser therapy (LLLT))

	<ul style="list-style-type: none"> - Psychological interventions (pain education, relaxation, cognitive behavioral therapy, mindfulness) - Alternative treatment (acupuncture, diet therapy) - Pharmaceutical interventions: <ul style="list-style-type: none"> - 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.

CDC 2016	
Population	<p>Adults with chronic pain outside of palliative and end-of-life care.</p> <p>The recommendations also address certain special populations (e.g., older adults and pregnant women) and populations with conditions posing special risks (e.g., a history of substance use disorder).</p>
Interventions	<ul style="list-style-type: none"> - Opioid therapy vs placebo/no opioid therapy - Opioids plus non-opioid interventions (pharmacologic or non-pharmacologic) vs opioids or non-opioid interventions alone - the comparison of different methods of initiating and titrating opioids - immediate-release vs extended release/long-acting (ER/LA) opioids - EX/LA vs EX/LA opioids - immediate-release + EX/LA vs EX/LA opioids - scheduled, continuous vs as-needed dosing of opioids - dose escalation vs dose maintenance or use of dose thresholds - opioid rotation vs maintenance of current opioid therapy - the comparison of different strategies for treating acute exacerbations of chronic pain - decreasing opioid doses or of tapering off opioids vs continuation of opioids - the comparison of different tapering protocols and strategies - the comparison of different risk mitigation strategies - the comparison of different treatment strategies for managing patients with addiction to prescription opioids - effect of opioid therapy vs no opioid therapy for acute pain on long-term opioid use
Outcomes	- Pain

	<ul style="list-style-type: none"> - Function - quality of life - adverse events
--	---

Table: Included population, intervention and main outcomes of the CDC 2016 guideline.

NHG 2018	
Population	<ul style="list-style-type: none"> - Adults and children with acute pain - Adults with chronic pain, neuropathic pain - Adults with pain in the palliative setting
Interventions	<ul style="list-style-type: none"> - 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.

NICE 2017	
Population	<p>Adults with neuropathic pain in non-specialist settings</p> <p>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'.</p>
Interventions	<ul style="list-style-type: none"> - 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	<p>Critical outcomes:</p> <ul style="list-style-type: none"> - 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) <p>Important outcomes:</p> <ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - Nonpharmacological treatment <ul style="list-style-type: none"> - physical medicine and rehabilitation - integrative and neurostimulatory therapies - Psychological approaches - Pharmacological treatment

	<ul style="list-style-type: none"> - Adjuvant analgesics - Cannabinoids - Opioids - Risk assessment, mitigation, and universal precautions
Outcomes	Outcomes for which significant differences were found <ul style="list-style-type: none"> - Pain rating (intensity/relief) - QoL - 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	<ul style="list-style-type: none"> - Buprenorphine vs placebo/alternative analgesia/alternative opioids - Tramadol vs control group/placebo - Codeine vs placebo, other step 2 opioids, other analgesia (paracetamol, NSAIDS) - Tapentadol vs Control groups/placebo/ alternative analgesics. - Morphine vs Control group/placebo - Oxycodone vs no oxycodone - Hydromorphone vs Control group/placebo - Methadone first line or rotated from other strong opioids vs placebo/other strong opioids - topical opioids vs placebo/other topical agents/ other oral analgesia - spinal opioids vs control group/placebo - opioids (TD, SC, IV, PO, PR) vs alternative routes of opioids, intranasal, buccal SL - opioids vs alternative opioids - opioid + opioid antagonist vs placebo/other analgesic medication - a combination of step 3 opioids vs placebo/opioid monotherapy - method of opioid titration vs placebo/control group - Opioid rotation/ switching for the management of opioid toxicity or refractory pain vs control group - management of opioid toxicity/overdose vs control group - opioids + paracetamol vs opioids
Outcomes	Pain scores Safety Patient preference Dependency

DOH_Ireland 2015	
Population	Adult patients with moderate to severe cancer pain directly due to cancer, who need regular stable analgesia 1. never treated with strong opioid 2. treated with opioid
Interventions	- Fentanyl (TD or SC/IV) vs placebo, other opioids, other analgesia (paracetamol, NSAIDS)
Outcomes	Pain scores Safety Patient preference

DOH_Ireland 2015	
Population	Adult patients with cancer related breakthrough pain
Interventions	Opioids for breakthrough pain vs placebo/other opioids
Outcomes	Pain scores

DOH_Ireland 2015	
Population	Adult patients with pain directly due to cancer and with renal or hepatic failure
Interventions	- 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

DOH_Ireland 2015	
Population	Adults patients with opioid dependency who have cancer pain
Interventions	opioids for cancer pain in patients with opioid dependency vs opioids for cancer pain in patients without opioid dependency
Outcomes	Change in pain, opioid requirements and side effects of medication.

KCE 2013	
Population	Adults suffering from pain secondary to cancer (any type) or cancer treatment. Patients in the phase of 'terminal care' are excluded (care

	during the process of dying, i.e. from days to a few weeks before death); all other phases of disease are included.
Interventions	<ul style="list-style-type: none"> - Paracetamol and non-steroidal anti-inflammatory agents (NSAIDs); Opioids; - Corticosteroids; - Antidepressants; - Anticonvulsants, especially gabapentin, pregabalin; - Radiotherapy for painful bone metastases; - Radionuclides for painful bone metastases; - Bisphosphonates for painful bone metastases; - Visceral plexus block of plexus coeliacus. <p>No a-priori criteria for the comparators of the intervention were defined.</p>
Outcomes	<ul style="list-style-type: none"> - Pain intensity, pain reduction, pain relief; - Quality of life, psychological well-being; - Functional impairment due to pain; - Side-effects of the treatment.

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.

NPC_Canada 2017	
Development group	<p>The guideline development process included the following groups:</p> <ul style="list-style-type: none"> - A four-member Steering Committee responsible for planning, oversight and policy decisions. - A 15-member Guideline Panel composed of 13 clinicians, most of whom had extensive methodological training, one of whom was a medical regulator, and two patient representatives. The panel had extensive input into the development and presentation of the recommendations, voted on all recommendations, and is ultimately responsible for the recommendations and their presentation. - A 13-member multi-disciplinary Clinical Expert Committee with expertise in the management of chronic pain and the prescribing of opioids had an advisory role to the panel. - A 16-member Patient Advisory Committee had an advisory role to the panel.
Target audience	<p>The target audience of this guideline are those who prescribe opioids for the management of chronic non-cancer pain or create policy regarding this issue, including but not limited to: primary care physicians, specialists who manage patients with chronic non-cancer pain, nurse practitioners, regulatory agencies and other policy makers. Secondary audiences for this guideline include: patients living with chronic non-cancer pain, pharmacists, other health care professionals who manage patients with chronic non-cancer pain.</p>

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

WOREL 2017	
Development group	<p>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).</p>
Target audience	<p>Care providers in primary care: for example primary care physicians, nurses, physiotherapists, pharmacists, and psychologists.</p>

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

CDC 2016	
Development group	<p>CDC sought the input of experts to assist in reviewing the</p>

	evidence and providing perspective on how CDC used the evidence to develop the draft recommendations. These experts, referred to as the “Core Expert Group” included subject matter experts, representatives of primary care professional societies and state agencies, and an expert in guideline development methodology.
Target audience	Primary care clinicians (e.g., family physicians and internists) who are treating patients with chronic pain (i.e., pain lasting >3 months or past the time of normal tissue healing) in outpatient settings.

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

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.

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.

KCE 2013	
Development group	The composition of the development group, i.e. the panel of consulted experts, consisted of professional experts and representatives of patient associations.
Target audience	This guideline is intended to be used by all care providers involved in the management of patients suffering from any type of cancer, and in the provision of supportive care to these patients, including medical oncologists, surgeons, radiation oncologists, nuclear medicine specialists, anesthesiologists and pain specialists, palliative care specialists, general practitioners and other medical specialties, nurses, pharmacists etc. It could also be of particular interest for patients, for hospital managers and policy makers.

Table: Members of the development group and target audience of the KCE 2013 guideline.

5 Information/Recommendations from guidelines

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

Text taken directly from the guidelines, that is not graded but provides supplemental information or a clarification of the formal recommendations, is written in *italics*.

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 of the NHG 2018 guideline are written in *italics*.

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 written in **bold**.

Comments by the bibliography group are written in plain text.

5.1 The biopsychosocial approach to pain

5.1.1 Summary

Opioids and the biopsychosocial approach of chronic pain

Historically, chronic pain was managed following a predominantly biomedical model of care where all aspects of the pain experience are attributed to the patient's reported pain intensity. Most of the selected guidelines mention briefly or discuss in more detail the importance of the biopsychosocial approach of chronic pain in which pain must be assessed in the context of psychological, social, and spiritual aspects that encompasses pain.

5.1.2 NPC_Canada 2017

The biopsychosocial approach to pain is not addressed as such in this guideline. However, some aspects of this approach are mentioned in the recommendations relating to tapering of opioids.

5.1.3 WOREL 2017

- Een empathische benadering die zich bij de beoordeling en de aanpak van chronische pijn richt op de patiënt, vergroot de kans op een gunstige evolutie. Deze aanpak is zoveel mogelijk het resultaat van een gedeelde besluitvorming ('shared decision') met de patiënt. (GRADE 1C)

- Une approche empathique et centrée sur le patient lors de l'évaluation et de la prise en charge de la douleur chronique est propre à optimiser les chances d'évolution favorable. Cette prise en charge sera autant que possible le fruit d'une décision partagée avec le patient. GRADE 1C

Attitudes for the clinician to facilitate an empathic approach:

1. De patiënt stimuleren tot het uiten van zijn problemen en zorgen door:

- het leggen van oogcontact met de patiënt en interesse te laten blijken;
- de patiënt aan te moedigen om precies te zijn in het beschrijven wanneer de pijn juist optreedt en de belangrijke hiermee gepaard gaande gebeurtenissen;
- aandacht te hebben voor signalen van angst, moeilijkheden en door ze te verhelderen, te verkennen; technieken van actief luisteren aan te wenden, zoals het herhalen, samenvatten of herformuleren van wat de patiënt zegt;
- het verkennen van de aannames van de patiënt over de oorzaken van zijn pijn en van de impact van zijn opvattingen op zijn probleem.

2. De patiënt bevragen over welke informatie hij wenst te krijgen, deze te prioriteren en hem te bezorgen en tegelijk te controleren of hij de informatie heeft begrepen.

3. De behandelingsopties bespreken met de patiënt door hem expliciet te vragen hoe ver hij bij de beslissingen wil betrokken worden.

1. Favoriser l'expression des problèmes et préoccupations du patient en:

- Etablissant un contact visuel avec celui-ci et en lui témoignant de l'intérêt ;
- Encourageant le patient à être précis quant à la séquence d'apparition de la douleur et les événements-clés qui y sont associés ;
- Etant attentif aux indices signalant des peurs, des difficultés et en tentant de les clarifier, de les explorer ;
- Utilisant des techniques d'écoute active comme, par exemple, le fait de reprendre, résumer ou reformuler les dires du patient ;
- Explorant les représentations du patient sur les causes de sa douleur et l'impact de ses croyances sur son problème.

2. Questionner le patient sur les informations qu'il souhaite, les prioriser et les lui fournir en vérifiant que le patient les a bien comprises

3. Discuter les options thérapeutiques en abordant explicitement jusqu'où il

- veut être impliqué dans les décisions.

- Middelen (brochures, website, eenvoudige techniek,...) die de patiënt in staat stelt zijn pijn zelf aan te pakken, zijn aan te bevelen als aanvulling op andere behandelingen van

chronische pijn, met name deze geïdentificeerd en aanbevolen door eventuele lokale multidisciplinaire teams gespecialiseerd in pijnbehandeling ("pijncentra"), en dit in alle fasen van de opvolging. (GRADE 2C)

- Des ressources (dépliants, sites internet, technique simple,...) favorisant la gestion par le patient lui-même de sa douleur devraient être recommandées en complément d'autres thérapies dans le traitement de la douleur chronique, notamment celles identifiées et recommandées par d'éventuelles équipes multidisciplinaires locales de prise en charge de la douleur (« centres de la douleur ») et ce à tous les stades du suivi. GRADE 2C
 - Vroegtijdige identificatie van chronische pijn is belangrijk. Breng de aard (neuropatische, nociceptieve of gemengde vorm), ernst en functionele gevolgen van de pijn in kaart aan de hand van een gestructureerde anamnese, een klinisch onderzoek en een globale beoordeling van de biopsychosociale context van de patiënt. (GPP)
-
- Une mise en évidence précoce de la douleur chronique est probablement importante. L'identification du type de douleur (notamment d'une composante neuropathique), de sa sévérité et de ses répercussions fonctionnelles devrait être réalisée sur la base d'une anamnèse structurée, d'un examen clinique et d'une évaluation plus globale du contexte biopsychosocial du patient. (CBP)
 - De aanpak van chronische pijn moet stoelen op een individueel zorgplan rekening houdend met de noden van de patiënt en de toegankelijkheid van de verschillende diensten die betrokken zijn in de opvolging. Dit zorgplan wordt regelmatig opnieuw geëvalueerd. (GPP)
-
- La prise en charge d'un patient douloureux chronique devrait se baser sur un plan de soins individualisé tenant compte des besoins du patient et de l'accessibilité des différents services pouvant intervenir dans le suivi. Ce plan devrait être régulièrement réévalué. (CBP)

Pijn is een complex fenomeen met fysieke, cognitieve, emotionele, spirituele en relationele componenten. Dit multidimensionele karakter moet een plaats krijgen in de beoordeling van pijn. Chronische pijn vraagt een radicaal andere aanpak dan acute pijn. Bij chronische pijn zijn de farmacologische aspecten ondergeschikt. De voorkeur zou moeten gaan naar een meer dynamische definitie van gezondheid, waarbij de nadruk ligt op het aanpassingsvermogen van het individu in plaats van op 'genezing', zoals die ook wordt toegepast in het chronisch zorgmodel ("Chronic Care Model").

La douleur est un phénomène complexe comportant une composante physique, des aspects cognitifs, émotionnels, spirituels et relationnels. Ce caractère multidimensionnel doit être reconnu lors de l'évaluation. La prise en charge de ces patients est radicalement opposée à celle qui est adoptée

dans la douleur aiguë. Ici, les aspects pharmacologiques passent au deuxième plan. Une définition plus dynamique de la santé, mettant l'accent sur la capacité d'adaptation des individus plutôt que sur la « guérison » 29, gagnerait souvent à être privilégiée, en accord avec le modèle de soins chroniques (« chronic care model »)

In de praktijk stelt de SIGN-richtlijn uit 2013 op basis van expertadvies voor om:

- de op puntstelling en initiële aanpak van chronische pijn te spreiden over verschillende consultaties;*
- een patiëntgerichte benadering toe te passen, met respect voor de cultuur van de patiënt, door de verschillende behandelingsopties toe te lichten en hem zo mogelijk te betrekken bij de besluitvorming;*
- alarmtekens of -symptomen op te sporen, de patiënt te onderzoeken en/of zo nodig te verwijzen, maar bijkomend onderzoek te vermijden als er geen ernstige pathologie wordt vermoed.*
- in alle gevallen het moment te bepalen waarop geen verder onderzoek meer wordt overwogen en dit ook duidelijk uit te leggen aan de patiënt.*
- de aanwezigheid van elementen van neuropathische pijn vast te stellen, waarvan de aanpak specifiek is.*

En pratique SIGN 2013 propose notamment, sur la base d'avis d'experts :

- De répartir la mise au point et la prise en charge initiale sur plusieurs consultations ;*
- D'adopter une approche centrée sur le patient, respectueuse de sa culture, en expliquant les différentes options thérapeutiques et en l'impliquant si possible dans la décision.*
- De rechercher la présence de signes ou de symptômes d'alarme, d'investiguer et/ou de référer le cas échéant, mais d'éviter des investigations complémentaires si aucune pathologie sérieuse n'est suspectée.*
- Dans tous les cas de définir le moment auquel plus aucune investigation n'est envisagée et de l'expliquer clairement au patient.*
- D'identifier la présence d'éléments de douleur neuropathique, dont la prise en charge comporte des spécificités.*

Er dient een zo expliciet mogelijk zorgplan te worden opgesteld, dat toelaat om de zorgverlening te structureren en de verschillende dimensies (somatische, maar ook psychologische, relationele en geestelijke) van de pijnervaring van de patiënt te integreren.

Un plan de soins, permettant de structurer la dispensation des soins, devrait être établi, être aussi explicite que possible, et intégrer les différentes dimensions (somatiques mais aussi psychologiques, relationnelles et spirituelles) du vécu douloureux du patient.

More details and recommendations on non-pharmacological interventions (e.g. psychological) are beyond the scope of this document and can be found in the WOREL guideline.

5.1.4 CDC 2016

Patients can experience persistent pain that is not well controlled. There are clinical, psychological, and social consequences associated with chronic pain including limitations in complex activities, lost work productivity, reduced quality of life, and stigma, emphasizing the importance of appropriate and compassionate patient care.

Multimodal and multidisciplinary therapies (e.g., therapies that combine exercise and related therapies with psychologically based approaches) can help reduce pain and improve function more effectively than single modalities

Integrated pain management requires coordination of medical, psychological, and social aspects of health care and includes primary care, mental health care, and specialist services when needed. Nonpharmacologic physical and psychological treatments such as exercise and CBT are approaches that encourage active patient participation in the care plan, address the effects of pain in the patient's life, and can result in sustained improvements in pain and function without apparent risks. Despite this, these therapies are not always or fully covered by insurance, and access and cost can be barriers for patients. For many patients, aspects of these approaches can be used even when there is limited access to specialty care.

CBT addresses psychosocial contributors to pain and improves function. Primary care clinicians can integrate elements of a cognitive behavioral approach into their practice by encouraging patients to take an active role in the care plan, by supporting patients in engaging in beneficial but potentially anxiety-provoking activities, such as exercise, or by providing education in relaxation techniques and coping strategies. In many locations, there are free or low-cost patient support, self-help, and educational community-based programs that can provide stress reduction and other mental health benefits. Patients with more entrenched anxiety or fear related to pain, or other significant psychological distress, can be referred for formal therapy with a mental health specialist (e.g., psychologist, psychiatrist, clinical social worker). Multimodal therapies should be considered for patients not responding to single-modality therapy, and combinations should be tailored depending on patient needs, cost, and convenience.

5.1.5 NHG 2018

Het ontstaan van chronische pijn staat onder invloed van lichamelijke, psychische en sociale factoren, samen omschreven als biopsychosociale factoren.

Chronische pijn heeft een forse impact op de kwaliteit van leven, het dagelijks functioneren en de stemming. De huisarts vraagt actief naar de werksituatie (soort werk, belasting en verhoudingen in het werk) en werkgerelateerd functioneren. Chronische pijn leidt tot suboptimaal functioneren in het werk en in veel gevallen ook tot langdurig ziekteverzuim. Chronische pijn is geassocieerd met fysieke inactiviteit, verminderde zelfredzaamheid, slaapproblemen en sociale isolatie. Angst, onrust, onzekerheid, eenzaamheid en verveling kunnen de pijnbeleving verergeren; aandacht, geruststelling, duiding/educatie en afleiding kunnen de pijn verminderen. Pijn interfereert vaak met het lichamelijk functioneren. Hierdoor is het gebruik van afleiding als onderdeel van de behandeling van pijnbestrijding soms beperkt mogelijk. Interferentie van pijn met het lichamelijk functioneren neemt toe met de leeftijd (maar hoort niet bij ouder worden) en wordt vaker gezien bij vrouwen dan bij

mannen. Pijn is beter te dragen naarmate de patiënt zelf meer invloed kan uitoefenen op de behandeling. Een goede communicatie met de zorgverlener en een gevoel van veiligheid zijn daarbij van belang. Het gevoel van veiligheid kan worden vergroot door een persoonlijke benadering van de zorgverlener die de patiënt hoort en zijn pijn erkent zonder dat de pijn op de voorgrond blijft staan.

Het risico op het ontstaan van chroniciteit hangt af van verschillende psychosociale factoren, werkgerelateerde factoren, culturele aspecten (soms ook met taalbarrière) en comorbide angst en/of depressie. Angst en depressie kunnen de pijn (beleving) verheviggen. In het bijzonder geldt dit voor kwetsbare ouderen. Centrale sensitisatie is één van de oorzaken van chronische pijn. Psychologische en sociale factoren dragen er toe bij dat de sensitisatie blijft bestaan. Gecombineerde behandeling (psychologische interventie en antidepressiva) van comorbide angst en/of depressie kan bijdragen aan reductie van chronische pijn (zie de NHG-Standaarden Angst en Depressie). Omgekeerd leidt vermindering van pijn tot verbetering van de depressieve symptomen.

Voor het beleid bij patiënten met chronische pijn die onvoldoende somatisch verklaard kan worden en waarbij de relatie met de oorspronkelijke trigger ontbreekt, wordt verwezen naar de NHG-Standaard Somatisch Onvoldoende verklaarde Lichamelijke Klachten (SOLK).

...De huisarts wijst de patiënt met chronische pijn op het bestaan van patiëntenverenigingen en patiëntenorganisaties en bespreekt het belang van lotgenotencontact. Informatie van dergelijke organisaties biedt de patiënt steun in emotionele en praktische zin.

Bij chronische pijn staat educatie centraal. Pijneducatie is gericht op het veranderen van maladaptieve pijn cognities (zoals bijvoorbeeld de gedachte dat pijn altijd een teken is van weefselschade), die kunnen leiden tot catastrofen. Er is bewijs voor de werkzaamheid van pijneducatie op catastrofen. Educatie, zelfinzicht en zelf aan het roer van de behandeling staan spelen een belangrijke rol bij de pijnbeleving en het voorkomen en verminderen van chroniciteit. Hierbij kan gebruikgemaakt worden van informatievoorziening zoals de NHG Publiekswaarschuwingssignaal www.thuisarts.nl en (online) zelfhulpprogramma's. De huisarts stemt het behandelplan met de patiënt af. De huisarts legt uit dat verdwijnen van de pijn vaak niet mogelijk is, maar verbeteren van het functioneren en de kwaliteit van leven wel. Dat betekent niet dat de patiënt geadviseerd moet worden om met de pijn te leren leven: dit wordt regelmatig als kwetsend en niet serieus nemen van klachten ervaren. Uitgangspunt is de pijn zoals die door de patiënt ervaren wordt.

De huisarts legt uit dat:

- lang aanhoudende pijn zonder duidelijke oorzaak in de regel géén waarschuwingssignaal voor weefselschade is en adviseert te stoppen met zoeken naar een lichamelijke oorzaak van de pijn;*
- de pijn (zeer) vervelend, maar niet gevaarlijk is;*
- in beweging blijven in de meeste gevallen goed is tenzij de pijn daardoor substantieel toeneemt;*
- het spreiden van activiteiten nuttig is;*
- afleiding pijn kan verminderen en dat stress, angst en overbelasting pijn juist kunnen verergeren;*
- rond blijven lopen met gevoelens van angst, depressiviteit of frustratie een negatieve*

invloed heeft op de pijn;

- *bij neuropathische pijn de werkzaamheid van sommige medicamenten pas na enige weken intreedt.*

Bovenstaande adviezen zijn niet zonder meer toepasbaar bij pijn bij (terminale) kankerpatiënten.

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.

Het risico op het ontstaan van chronische pijn hangt mede af van diverse psychosociale factoren. Als er sprake is van (dreigende) chronische pijn overweegt de huisarts een systematische klachtexploratie waarbij hij rekening houdt met het patiëntenperspectief en gebruikmaakt van SCEGS. SCEGS bestaat uit vijf dimensies: de Somatische, Cognitieve, Emotionele, Gedragmatige en Sociale dimensie (zie NHG richtlijn voor meer details). De uitgebreidheid van het uitvragen van de vijf dimensies is afhankelijk van de duur van de pijn. Hoe langer de pijn bestaat, hoe groter de noodzaak om alle dimensies uit te vragen.

Het is belangrijk om patiënten met chronische pijn in een vroeg stadium te identificeren volgens het biopsychosociale model waarbij rekening gehouden wordt met lichamelijke, psychische en sociale factoren. Inventarisatie van deze factoren vindt plaats met het SCEGS-acroniem. Stel op basis hiervan, samen met de patiënt, een individueel, multidimensioneel integraal zorgplan op waarbij zelfmanagement een belangrijke plaats inneemt.

Medicamenteuze behandeling wordt ingezet als onderdeel van een multidimensioneel (biopsychosociaal) behandelplan. Dit geldt in het bijzonder voor patiënten met chronische en neuropathische pijn.

More details and recommendations on non-pharmacological interventions (e.g. psychological) are beyond the scope of this document and can be found in the NHG 2018 guideline.

5.1.6 NICE 2017

When agreeing a treatment plan with the person, take into account their concerns and expectations, and discuss:

- **the severity of the pain, and its impact on lifestyle, daily activities (including sleep disturbance) and participation**
- **the underlying cause of the pain and whether this condition has deteriorated**
- **why a particular pharmacological treatment is being offered**
- **the benefits and possible adverse effects of pharmacological treatments, taking into account any physical or psychological problems, and concurrent medications**
- **the importance of dosage titration and the titration process, providing the person with individualised information and advice**
- **coping strategies for pain and for possible adverse effects of treatment**

- non-pharmacological treatments, for example, physical and psychological therapies (which may be offered through a rehabilitation service) and surgery (which may be offered through specialist services).

Carry out regular clinical reviews to assess and monitor the effectiveness of the treatment. Each review should include an assessment of:

- pain control
- impact on lifestyle, daily activities (including sleep disturbance) and participation
- physical and psychological wellbeing
- adverse effects
- continued need for treatment.

5.1.7 ASCO 2016

- Clinicians should conduct an initial comprehensive pain assessment. This assessment should include an in-depth interview that explores the multidimensional nature of pain (pain descriptors, associated distress, functional impact, and related physical, psychological, social, and spiritual factors) and captures information about cancer treatment history and comorbid conditions, psychosocial and psychiatric history (including substance use), and prior treatments for the pain. The assessment should characterize the pain, clarify its cause, and make inferences about pathophysiology. A physical examination should accompany the history, and diagnostic testing should be performed when warranted. (Informal consensus; benefits outweigh harms; evidence quality: insufficient strength of recommendation: moderate)
- Clinicians should aim to enhance comfort, improve function, limit adverse events, and ensure safety in the management of pain in cancer survivors. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)
- Clinicians should engage patient and family/caregivers in all aspects of pain assessment and management. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)
- Clinicians should determine the need for other health professionals to provide comprehensive pain management care in patients with complex needs. If deemed necessary, the clinician should define who is responsible for each aspect of care and refer patients accordingly. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)
- Clinicians may prescribe directly or refer patients to other professionals to provide the interventions outlined in Table 4 to mitigate chronic pain or improve pain-related outcomes in cancer survivors. These interventions must take into consideration pre-existing diagnoses and comorbidities. (Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

Table 4. Disciplines and Interventions for Chronic Pain		
Disciplines	Examples of Possible Interventions	Strength of Evidence and Recommendation
Physical medicine and rehabilitation	Physical therapy, occupational therapy, recreational therapy, individualized exercise program, orthotics, ultrasound, heat/cold	Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate
Integrative therapies	Massage, acupuncture, music	Evidence-based; benefits outweigh harms; evidence quality: low; strength of recommendation: weak
Interventional therapies	Nerve blocks, neuraxial infusion (epidural/intrathecal), vertebroplasty/kyphoplasty	Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate
Psychological approaches	Cognitive behavioral therapy, distraction, mindfulness, relaxation, guided imagery	Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate
Neurostimulatory therapies	TENS, spinal cord stimulation, peripheral nerve stimulation, transcranial stimulation	Evidence-based; benefits outweigh harms; evidence quality: low; strength of recommendation: weak

Abbreviation: TENS, transcutaneous electrical nerve stimulation.

Table 4 of the ASCO 2016 guideline

Patient and Clinician Communication

As therapeutic treatment options and outcomes improve, patients with cancer are living longer. Of course, this is good news, but it sometimes comes at a cost. Put simply, chronic pain from treatment-related adverse effects can significantly affect the quality of life of many cancer survivors for years after initial treatment stops. Chronic pain can develop from a variety of sources: peripheral neuropathy, muscle or bone pain, surgery, radiation, and other conditions. Comorbidity with other conditions or syndromes can make assessing chronic pain more difficult. Because post-treatment pain is so complicated, good communication between patients and their medical providers is essential. Cancer survivors are more than their cancer history or their pain; they are individuals with unique needs. They may have varying capacities to deal with a great deal of information that can sometimes be overwhelming. Just as no two cancers are alike, patients experience pain differently. Some patients may even be reluctant to discuss their pain, seeing it as a sign of weakness or fearing a recurrence; some may see it an expected and untreatable complication of their cancer treatment. That is why a pain assessment is recommended at every visit. In teasing out how they are coping, clinicians need to ask patients how chronic pain is affecting them and suggest how they can work together to better manage their symptoms and improve their quality of life. Survivors who understand all aspects of their pain treatment plan (and their role in it) may have a better overall outcome.

5.1.8 DOH_Ireland 2015

Key finding

Cancer pain impacts on a patient's physical, psychosocial and emotional wellbeing.

- **Cancer pain management should address the physical, psychosocial and emotional domains of patient care. Addressing the physical aspects of cancer pain alone is insufficient. (recommendation category A)**

In the uni-dimensional approach to pain, all aspects of the pain experience, including use of analgesics and psychological distress, are attributed to the patient's reported pain intensity. However, it is increasingly recognised that pain encompasses not only physical aspects, but also:

- *Psychological aspects – change in body image and function; fear of pain, or death; feelings of helplessness and dependency; affective components such as mood disturbance and anxiety*
- *Social aspects – loss of role in family, career or society; feelings of abandonment or isolation*
- *Spiritual aspects – search for the meaning of the pain and illness; perception of illness as a punishment.*

Pain must therefore be assessed in the context of these variables.

Pain, especially cancer-related pain, is not a purely nociceptive physical experience, but involves different dimensions such as affect, cognition, behavior and social relations. From a psychosocial perspective, cancer pain is challenging for many reasons. Cancer pain is usually treated medically; because of this, healthcare professionals and patients often underestimate the impact of cancer pain on psychological distress and the potential benefits of including psychological treatments to manage cancer pain. For example, cancer pain may raise concerns about disease progression for patients and their families, causing significant anxiety.

There have been many studies over the past two decades into the association between cancer pain and psychological functioning. ... These studies indicate that the cancer pain experience is associated with higher levels of distress, depression, anxiety, fear and negative mood. Various psychological and cognitive behavioural techniques, along with pharmacological intervention, constitute a comprehensive approach to the management of cancer pain.

Cancer pain management should be undertaken as part of comprehensive palliative care. Relief of other symptoms, and of psychological, social and spiritual problems, is paramount. Attempting to relieve pain without addressing the patient's non-physical concerns is likely to lead to frustration and failure.

Key finding

Involving and educating patients about their pain management improves patient understanding and can decrease pain intensity.

- **Patients should be given appropriate information about their pain, and pain management, and be encouraged to participate in their treatment plan. (recommendation category B)**

The active involvement of patients through the provision of information, instruction and education regarding pain, and pain treatments, is an integral component of pain management strategies.

Key finding

The cornerstone of comprehensive pain assessment is the taking of a detailed patient history and the performance of a thorough physical examination. The psychological and spiritual impact of a patient's pain should also be considered.

Pain is a subjective experience.

- **Systematic assessment of cancer pain including physical, psychological, and spiritual domains is essential.**
The patient should be the prime assessor of his or her pain. (recommendation category C)

Key finding

A number of assessment tools exist in relation to the physical, psychosocial and spiritual domains of cancer pain.

- **The use of pain and other symptom assessment tools should be considered as part of the comprehensive ongoing evaluation of cancer patients. (recommendation category D)**
- **Pain assessment in the cognitively impaired should involve self-reported pain scales where appropriate. Observational pain rating scales and behavioural assessment tools should be considered for those who cannot complete a self-assessment scale. (recommendation category D)**

However, selfreporting of pain and other symptoms may not be feasible in patients who are unable to verbalise, for example those who are critically ill, unconscious, dying or who have cognitive impairment.

...These guidelines relied on a systematic approach to patients in these situations as follows:

1. Use the hierarchy of pain assessment tools

-Self-report: attempts should be made to obtain self-report from all patients

-Search for potential causes of pain, such as pathologic conditions or procedures known to cause pain (e.g. surgery, wound care, positioning).

2. Observe patient behaviours: Non-verbal cues as to patient discomfort may be

-Facial expression: grimacing, rapid blinking, frowning

-Negative vocalisation: groaning, aggressive behavior, sighing

-Body language: tense posture, guarding, fidgeting

-Changes in activity patterns of routines: sleep patterns, appetite changes, wandering or pacing

-Changes in interpersonal interactions: withdrawn, combative, refusing care

-Mental status changes: increased confusion, irritability, agitation.

3. Surrogate reporting: by family members, parents, caregivers. Discrepancies exist between self-report of pain and external observer judgments of pain severity; these occur across varied raters (e.g. physician, nurse, family, aides) and settings (e.g. inpatient, outpatient, acute care, long-term care). Thus, judgments by caregivers and clinicians may not be accurate reflections of the severity of pain experienced by non-verbal persons and should be combined with other evidence when possible. A multifaceted approach is recommended, that combines direct observation, family/caregiver input and evaluation of response to treatment.

5.1.9 KCE 2013

- Prior to treatment, an accurate assessment should be performed to determine the cause, type and severity of pain, and its functional and psychosocial impact on the patient. Validated assessment questionnaires should be used as well as clinical evaluation and, if necessary, medical investigations. The assessment should be repeated if treatment does not alleviate the pain even after careful adjustment. (good clinical practice)
- The patient is the most reliable assessor of pain and should, whenever possible, be the prime assessor of his or her pain. (good clinical practice)
- Patients with cancer pain should have their pain monitored regularly using unidimensional pain instruments such as visual analogue scales (VAS), numerical rating scales (NRS) or verbal rating scales (VRS). Multidimensional pain instruments should be used for complex pain syndromes. Examples are the McGill Pain questionnaire and the Brief Pain Inventory, which incorporate NRS and VRS. Observational pain rating scales should be preferred in patients who cannot complete a self assessment scale. (good clinical practice)
- The minimal objective of pain treatment should be a clinically relevant decrease of the pain (on a 0-10 scale, a decrease by 2 points, and/or a decrease of 30%, and preferentially a pain intensity <5). (good clinical practice)
- Patients should be given information about pain and instruction about pain management; they should be encouraged to take an active role in their pain management. (good clinical practice)

Pain is a highly complex and subjective phenomenon, including physical, functional, psychological, social and spiritual aspects.

An important condition for adequate pain treatment is a systematic and comprehensive assessment of pain, encompassing these multidimensional components. Pain assessment is a responsibility of all health care providers (physicians, nurses, pharmacists, etc), and team work or an interdisciplinary approach to cancer pain is essential (SIGN 2008, Dutch Guideline on cancer pain 2008, Guideline of the MoH Malaysia 2008, Portenoy 2011).

Pain assessment should be performed prior to treatment in order to plan for appropriate interventions, and after treatment initiation to assess its effectiveness. It should aim to determine:

- *the pathophysiology of pain,*
- *pain intensity as well as other aspects of pain, such as the type of pain, its location, duration etc*
- *the impact of pain on a person's functions, psychosocial and spiritual well-being, and quality of life,*
- *the response to pain interventions.*

Similar to other clinical assessment, a complete pain assessment requires a detailed history and physical examination, as well as standardized assessment tools. This should be completed by laboratory tests, medical imaging or other diagnostic tests if these are necessary to determine appropriate clinical management. The assessment should be repeated if treatment does not alleviate the pain even after careful adjustment (SIGN 2008, Dutch Guideline on cancer pain 2008, Guideline of the MoH Malaysia 2008).

Multidisciplinary approach of pain treatment

In this report we focused on the effectiveness of specific (medical) interventions, without taking into account the organization of health services. In clinical practice, a multidisciplinary approach by different health care professionals should be encouraged. This approach should not only cover the medical needs of the patient but should also consider the psychosocial needs related to cancer pain.

Patient-centered care

The choice of a treatment should not only consider medical aspects related to cancer pain, but should also take into account patient preferences. Patients should be well and timely informed about all treatment options and the advantages and disadvantages related to these treatments. Indeed, patients and patient representatives involved in the development of this report emphasized the need for patient information. This information should ideally be clear and repeated over time. Also more emphasis should be put on potential adverse events related to each treatment. In the Dutch guideline on cancer pain treatment (2008)⁸ an overview is given of different topics which should be discussed with the patient. In addition to aspects related to pharmacological and non-pharmacological treatments, also self-management should be promoted. In this report no studies are included on the effectiveness of patient-oriented interventions.

5.2 Management of chronic pain with opioids

5.2.1 Summary

Overview of the selected guidelines

The 8 guidelines that were selected for this evidence report have a different focus. Three guidelines focus on chronic non-cancer pain (NPC_Canada 2017, WOREL 2017, CDC 2016). One guideline (NHG 2018) focuses on chronic pain in general not excluding cancer pain. One guideline focuses specifically on neuropathic pain (NICE 2017), but two guidelines from the aforementioned guidelines that focus on chronic non-cancer pain also pay attention to neuropathic pain (NHG 2018, WOREL 2017). Three guidelines focus on patients with cancer. One guideline focuses on chronic pain in patients with cancer irrespective of cause (ASCO 2016) and two guidelines (DOH_Ireland 2015, KCE 2013) focus on cancer-related pain.

Prescribing opioids for chronic pain

All guidelines stress the importance of improvement in function besides pain relief.

The guidelines all have a strong preference or recommend **optimization of non-opioid pharmacotherapy and non-pharmacological therapy** for patients with chronic pain, rather than a trial of opioids.

Furthermore, **a trial of opioids is suggested (= weak recommendation) in patients who have persistent problematic pain despite optimized non-opioid therapy.** (NPC_Canada 2017, CDC 2016,

NHG 2018, ASCO 2016; KCE 2013). Other recommendations and suggestions are given for patients with current or past substance use disorder or other active psychiatric disorders: see section “opioids and substance use disorder”.

The guidelines underline that the potential **risks and benefits** should be assessed when initiating treatment that will incorporate long-term use of opioids. See also section “opioids and substance use disorder”. For the assessment of benefit, the clear improvement of pain and function must be established. If this benefit is not established, the trial of opioids should not be continued (NPC_Canada 2017, Worel 2017, CDC 2016).

Informing the patient of the risks is recommended by most guidelines (Worel 2017, CDC 2016, NHG 2018).

Four guidelines (Worel 2017, NHG 2018, DOH_Ireland 2015, KCE 2013) refer to the WHO ladder for the management of pain. The guidelines that do not specifically focus on patients with cancer note that this stepwise approach was developed for cancer pain and its value for non-cancer patients is unclear.

In the step in which weak opioids are added to non-opioids, the NHG 2018 guideline does not recommend codeine (including paracetamol-codeine combinations) but only tramadol. The guideline does not recommend the combination tramadol/paracetamol. However, the DOH_Ireland 2015 guideline prefers the use of codeine and paracetamol-codeine combinations over tramadol or tapentadol for mild to moderate cancer pain. The other guidelines do not make a selection. Furthermore, as mentioned in three guidelines (NHG 2018, DOH_Ireland 2015, KCE 2013), the clinical usefulness of this step before starting strong opioids has been questioned for patients with cancer.

The NHG 2018 guideline does not recommend buprenorphine in primary care. The CDC 2016 guideline mentions that only clinicians who are familiar with the dosing and absorption properties of transdermal fentanyl should consider prescribing it. The DOH_Ireland 2015 guideline also refers to the challenges presented by the pharmacokinetic and dynamic characteristics of transdermal opioids such as fentanyl and buprenorphine.

Multiple guidelines recommend the use of methadone only under specialist supervision or by physicians with the required expertise.

The KCE 2013 guideline states that the combination of 2 strong opioids might be an option in some cancer patients with inadequate pain relief (background pain) and/or intolerable opioid-related adverse effects while using a single strong opioid. This might also be considered to prevent opioid-related hyperalgesia. The second strong opioid should be selected carefully. The initiation of such treatment should be restricted to medical experts in pain treatment or palliative care (KCE 2013).

Strong opioids do not have a place in the management of neuropathic pain (WOREL 2017). Tramadol (a weak opioid) might be used in neuropathic pain after seeking advice from a specialist (NHG 2018, DOH_Ireland 2015). The NICE 2017 guideline states that tramadol should only be considered as rescue medication and not for long-term use. If monotherapy with the recommended drugs for neuropathic pain (i.e. antidepressants and anticonvulsants) is insufficient, combination therapy of drugs with a different mechanism of action is recommended. In combination therapy, opioids might

be an option when advised by a specialist (NHG 2018, NICE 2017). However, current evidence is insufficient to provide any recommendations on combination therapies (NICE 2017).

Given its pharmacological properties (i.e. blocking the NMDA receptor), methadone might theoretically be useful in the treatment of neuropathic pain. The KCE 2013 guideline refers to this possibility but states that, based on the available evidence, it is not possible to conclude on the superiority of methadone to morphine in patients with neuropathic cancer pain.

There seems to be no difference between the available oral opioid preparations in terms of analgesic efficacy (KCE 2013, DOH_Ireland 2015). The guidelines do not describe a different efficacy between strong opioids with a different mechanism of action (i.e. action through mu, delta, or kappa receptors or non-opioid mechanisms), nor do they describe specific indications according to the mechanism of action. However, genetic polymorphisms may lead to inter-individual variation in response to opioids.

Dosing of opioids and duration

There is no standardized dosage of opioids for the treatment of pain. A individual dose titration is required. The dose should be titrated until the lowest effective dose (WOREL 2017, CDC 2016, KCE 2013).

It is suggested to restrict the prescribed dose to < 50 mg morphine equivalents daily (NPC_Canada 2017, WOREL 2017, CDC 2016) and avoid increasing dosage to ≥ 90 mg morphine equivalents (WOREL 2017, CDC 2016).

The analgesic effect of weak opioids (codeine, dihydrocodeine, tramadol) is characterized by a ceiling effect (KCE 213, DOH_Ireland 2015). In contrast, the analgesic effect of strong opioids (morphine, hydromorphone, oxycodone, fentanyl and methadone) with increasing the dosage is only limited (besides adverse effects) by the appearance of hyperalgesia (KCE 213). Buprenorphine (a partial agonist) may demonstrate a ceiling effect in that above a certain dose their effects do not increase proportionally with dose (KCE 2013).

There is limited evidence to recommend specific intervals for dosage titration (CDC 2016). However, most guidelines provide instructions regarding different aspects of dose titrations.

Maintenance opioid therapy should be taken 'by the clock', i.e. at pre-defined regular time intervals.

If opioids are used, opioid therapy should only be continued if there is clinically meaningful improvement in pain and function that outweigh risks to patient safety.

See also the section "Opioids in older patients and patients with renal or hepatic insufficiency".

Breakthrough pain

Three guidelines provide instructions for the management of breakthrough pain (NHG 2018, DOH_ireland 2015, KCE 2013).

For breakthrough pain, the dosage of rescue medication is calculated based on the 24h dosage for background pain (DOH_Ireland 2015, NHG 2018, KCE 2013). However, the dose of fast acting fentanyl preparations should be titrated according to manufacturer's guidance since the rescue dose of these preparations is independent of the background pain (DOH_Ireland 2015). See also the NHG 2018 guideline for specific instructions for breakthrough pain while on fentanyl. (Dosing for breakthrough pain was beyond the scope of the KCE 2013 review)

Safety profile of opioids

Only the ASCO 2016 guideline refers to possible dysimmune effects and tumor proliferative effects from opioid drugs. This guideline concludes that there is insufficient evidence to determine whether there are clinically important risks but that this concern needs to be addressed when discussing the benefit risk ratio of long-term use of opioids in cancer survivors.

Chronic opioid therapy might cause hypogonadism. There is currently no evidence for this relationship with buprenorphine (NHG 2018).

Tramadol has been associated with hypoglycemia; caution is warranted in diabetic patients taking hypoglycemic drugs (WOREL 2017, NHG 2018).

Patients should avoid driving a motor vehicle during dosage titration until a stable dosage is established and it is certain the opioid does not cause sedation, especially when taking opioids with alcohol, benzodiazepines, or other sedating drugs. (CDC 2016, NPC_Canada 2017)

For other and more common side-effects and interactions related to opioids, we refer to each guideline in this document. For a general overview of long-term side-effect see for example table 7 of the ASCO 2016 guideline. See also below "specific contra-indications for the different opioids".

Specific warnings and contra-indications for the different opioids

There is an increased risks for respiratory depression when opioids are taken with benzodiazepines, alcohol, or other sedative drugs or agents.

In combination with other drugs with a serotonergic effect (SSRI, SNRI, TCA), tramadol might increase the risk of a serotonin syndrome (WOREL 2017, NHG 2018).

Tramadol might increase the risk of convulsions, especially in combination with other drugs known for this risk (e.g. TCA, SSRI, antipsychotics, central nervous stimulants, quinolone antibiotics, theophylline) (WOREL 2017).

An increased skin blood flow (due to transpiration, fever, or a hot shower) can lead to an increased risk for side effects related to transdermal opioids (NHG 2018, KCE 2013).

Transdermal opioids might not be effective in cachectic patients due to impaired absorption (DOH_Ireland 2015, KCE 2013). (see “Opioids formulations and route of administration”)

Methadone might cause QT prolongation, as pointed out by most guidelines, especially at high doses. ASCO 2016 is the only guideline that also refers to this increased risk with buprenorphine.

See also “opioids in older patients and patients with renal or hepatic insufficiency” and “opioids and substance use disorder”.

5.2.2 NPC_Canada 2017

- **The guideline recommends optimization of non-opioid pharmacotherapy and non-pharmacological therapy, rather than a trial of opioids, for patients with chronic non-cancer pain. (Strong recommendation)**

Rationale. When added to nonopioids, opioids may achieve, on average, modest improvements in pain and function relative to other pain treatments at the cost of a small but important risk of nonfatal and fatal unintentional overdose, very frequent physical dependence and frequent addiction. As first-line treatment for patients with chronic noncancer pain, several nonopioid therapies may achieve a similar degree of improvement in pain and function (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], graduated exercise, cognitive behavioural therapy).

- **The guideline suggests adding a trial of opioids rather than continued therapy without opioids for patients with chronic noncancer pain, without current or past substance use disorder and without other active psychiatric disorders, who have persistent problematic pain despite optimized nonopioid therapy. (Weak recommendation)**

By a trial of opioids, we mean initiation, titration and monitoring of response, with discontinuation of opioids if important improvement in pain or function is not achieved.

Rationale. When added to nonopioids, opioids achieve, on average, modest improvements in pain and function. Adverse effects include relatively frequent constipation, nausea and vomiting, sedation and addiction, and a small but important risk of unintentional overdose which can be fatal. The risk of unintentional overdose increases progressively with the daily dose prescribed.

Table 3 lists the possible options for initiating opioid therapy. Table 4 indicates opioids that should not be used for first prescription.

Table 3: Opioid options for initiating a trial of therapy for patients with chronic non-cancer pain

Opioid	Comments
Morphine	Avoid in renal insufficiency
Oxycodone	~1.5x as potent as morphine. Available in a tamper-resistant formulation
Hydromorphone	~5x as powerful as morphine. Available in a tamper-resistant formulation
Oxycodone/Naloxone	Naloxone combination may minimize constipation and possibly act as an abuse deterrent
Buprenorphine	Oral formulations preferred over transdermal for initial trial
Codeine	
Tapentadol	Available in a tamper-resistant formulation. Combined noradrenaline reuptake inhibitor and weak opioid
Tramadol	A prodrug (serotonin-norepinephrine reuptake inhibitor) that is converted to an opioid in a highly variable fashion.

Table 4: Opioids that are not recommended for initiating a trial of therapy for patients with chronic non-cancer pain

Opioid	Comments
Methadone	Requires a specific Health Canada exemption to provide
Fentanyl (transdermal)	Not in opioid-naïve patients
Meperidine	Limited effectiveness; toxic metabolite accumulates in high doses or in renal insufficiency
Pentazocine	Limited effectiveness. High incidence of dysphoria

Some Guiding Principles for Initiation of Opioids

- *Despite the availability of various screening instruments, none have been shown to predict patients unsuitable for opioid therapy*
- *Start at the lowest available dose of the opioid*
- *Prescriptions should be provided by the primary treating physician only, for no more than 28 days at a time. Intervals may be shorter when initiating therapy, in cases of suspected diversion or during dose escalation*
- *In patients with continuous pain including pain at rest, clinicians can prescribe controlled release opioids for both for comfort and simplicity of treatment during the day. Activity related pain might not require sustained release treatment and opioid therapy may be initiated with immediate release alone.*
- *During dosage titration, advise patients to avoid driving a motor vehicle until a stable dosage is established and it is certain the opioid does not cause sedation. This is especially true when taking opioids with alcohol, benzodiazepines, or other sedating drugs*
- *A reasonable trial of therapy should be accomplished within 3-6 months; opioids provide less pain relief after 3-months and some patients may continue use to address inter-dose withdrawal symptoms*
- *Patients will develop tolerance and a withdrawal syndrome within as little as two to four weeks. This will significantly hamper any effort to taper opioids if the trial fails.*
- *Other potential adverse effects of opioids that warrant consideration include falls, fractures, sleep-disordered breathing (including sleep apnea, depression and a worsening of pain itself (opioid-induced hyperalgesia)*

- **The guideline recommends restricting to less than 90 mg morphine equivalents daily (MED) (strong recommendation)**

Some patients may gain important benefit at a dose of more than 90 mg morphine equivalents daily. Referral to a colleague for a second opinion regarding the possibility of increasing the dose to more than 90 mg morphine equivalents daily may therefore be warranted in some individuals.

- **The guideline suggests restricting the prescribed dose to less than 50mg morphine equivalents daily for patients with chronic noncancer pain who are beginning opioid therapy. (Weak recommendation)**

The weak recommendation to restrict the prescribed dose to less than 50 mg morphine equivalents daily acknowledges that there are likely to be some patients who would be ready to accept the increased risks associated with a dose higher than 50 mg in order to potentially achieve improved pain control.

Rationale. Observational studies provide moderate-quality evidence of a progressive increase in the likelihood of unintentional nonfatal overdose or death as the prescribed dose of opioids increases. These serious outcomes are very uncommon in patients prescribed less than 50 mg MED, but increase in those prescribed doses of 50 mg to 90 mg, and although still uncommon, are further increased in those prescribed doses of more than 90 mg MED.

Risk mitigation

The systematic reviews found only low or very low quality evidence regarding strategies intended to reduce the adverse impact of opioid prescribing. In each case the evidence did not support the intervention, nor did it provide compelling evidence that the intervention was useless. This was the case for the use of urine drug screening, treatment agreements, naloxone co-prescription in the case of opioid use for chronic pain alone, rather than in the case of addiction, tamper-resistant formulations, patch exchange programs and choosing between immediate release vs. controlled release opioids.

The Clinical Expert Committee felt, in general, that prescribers of opioids for chronic non-cancer pain may wish to consider implementation of risk mitigation strategies with the aim of reducing harm. However, there is also concern that prescribers adopting potentially ineffective risk mitigation strategies may become less vigilant about possible opioid-related harms, and more willing to prescribe opioids for chronic non-cancer pain.

5.2.3 WOREL 2017

Voor deze aanbeveling is het belangrijk om de bijdrage van geneesmiddelen in het juiste daglicht te plaatsen. De paradox bij chronische pijn is dat de medicamenteuze behandelingen in de literatuur een hoog niveau van bewijskracht kunnen hebben, terwijl hun belang in de praktijk altijd moet worden gerelativeerd. De behandeling van acute pijn is meestal etiologisch en bestaat uit goede 'pijnstilling'. Bij het chronischepijnsyndroom daarentegen kan de zinvolheid van een medicamenteuze aanpak van pijn in vraag worden gesteld.

De klassieke 3 WHO-treden van de pijnbehandeling stoelen op geen enkele wetenschappelijke basis; ze berusten op een brede consensus en zijn goed verankerd in de praktijk. Deze aanbevelingen werden in 1986 ontwikkeld door een comité van internationale experts en waren oorspronkelijk bedoeld voor de behandeling van kankerpijn. De bedoeling was om een eenvoudige methode te implementeren die in verschillende landen toepasbaar was, zowel in ziekenhuizen als in de eerste lijn. Volgens deze benadering gebeurt de pijnstilling stapsgewijs, in functie van de pijnintensiteit. Wordt de pijn onvoldoende gestild met een pijnstiller van stap 1, dan schakelt men over op een pijnstiller van

stap 2. Combinaties van een niet-opioïd (stap 1) met een zwak of sterk opioïd (stap 2 of 3) zou het pijnstillende effect kunnen versterken.

Dertig jaar later is het zaak om de relevantie van deze aanbevelingen te herzien, vooral in de context van chronische pijn...

Pour cette recommandation, il importe de remettre l'apport de la pharmacologie à sa juste place.

Dans la douleur chronique, le paradoxe est que si, dans la littérature, les traitements médicamenteux peuvent bénéficier d'un niveau de preuves plus élevé, leur importance en pratique reste toujours à relativiser. Alors que le traitement de la douleur aiguë est le plus souvent étiologique et une « couverture antidouleur » pertinente, quand la douleur s'inscrit dans un cadre de « syndrome de douleur chronique », la pertinence d'une approche médicamenteuse peut être questionnée.

Les classiques 3 paliers de l'OMS du traitement de la douleur ne reposent sur aucune base scientifique mais sont largement consensuels et bien ancrés dans la pratique. Il s'agit de recommandations élaborées en 1986 par un comité d'experts internationaux à l'origine pour le traitement des douleurs cancéreuses. L'objectif initial était de diffuser une méthode simple, applicable dans différents pays aussi bien en milieu hospitalier qu'en pratique de première ligne.

Les antalgiques y sont classés en trois paliers selon l'intensité de la douleur. Lorsqu'une douleur est insuffisamment soulagée par un antalgique, il s'agit de passer au palier supérieur. Des associations d'un non-opioïde (palier 1) à un opioïde faible ou fort (palier 2 ou 3) permettraient de renforcer l'effet antalgique. Trente ans plus tard, la pertinence de ces recommandations mérite d'être repensée, en particulier dans le cadre de la douleur chronique.

Gebruik van zwakke opioïden

Het gebruik van zwakke opioïden maakt geen deel uit van de aanbevelingen in de gebruikte richtlijnen. De Canadese richtlijn uit 2012 merkt hoogstens op dat "men in de klinische praktijk de behandeling met opioïden eerst moet starten met zwakke opioïden zoals tramadol of codeïne, voor men overschakelt op sterke opioïden." De onderliggende onderbouwing is zeer zwak.

L'usage des opioïdes faibles

L'usage des opioïdes faibles ne fait pas l'objet de recommandations propres dans nos guides de pratique clinique sources. Tout au plus, le guide Canadien de 2012, note-t-il que « en pratique clinique, les traitements par opioïdes devraient être initiés avec des opioïdes faibles comme le tramadol ou la codéine avant de passer aux opioïdes forts ». Les preuves sous-jacentes sont très faibles.

Concerning metabolism of codeine:

Het is een prodrug die ter hoogte van de cytochroom P450 (CYP2D6) wordt omgezet in morfine.

Verschillen in metabolisatie kunnen de individuele variaties verklaren, zoals overmatig effect bij snelle 'metaboliseerders' van codeïne. Wees bedacht op gelijktijdige inname van CYP2D6-remmers die het pijn-effect verminderen.

Il s'agit d'une prodrogue qui est transformée au niveau du cytochrome P450 (CYP2D6) en morphine.

Une différence dans la métabolisation peut expliquer une variation individuelle, en particulier un effet

excessif observé chez les « métaboliseurs rapides » de la codéine. Il faut être attentif à la prise concomitante d'inhibiteurs du CYP2D6 qui diminuent l'effet antidouleur.

Concerning tramadol:

Tramadol wordt gemetaboliseerd door het iso-enzym 2D6 van het cytochroom P450. Tramadol verlaagt de convulsiedrempel en kan een epileptische aanval uitlokken, vooral in combinatie met andere medicatie die convulsies kunnen uitlokken (bijv. antidepressiva (tricyclische en SSRI's), antipsychotica, centrale stimulantia, chinolonen, theofylline). Anderzijds is tramadol een opioïd met serotonerge werking dat indien samen gebruikt met een andere serotonerg medicijn (bijv. SSRI's) het risico op serotoninesyndroom verhoogt. Hypoglykemieën zijn gemeld bij patiënten behandeld met tramadol; voorzichtigheid is dus geboden bij diabetespatiënten die hypoglykemiërende middelen nemen.

Le tramadol est métabolisé par l'iso-enzyme 2D6 du cytochrome P450. Le tramadol abaisse le seuil convulsif et peut provoquer une crise convulsive notamment en association avec d'autres médicaments convulsivants (par ex. les antidépresseurs (tricycliques ou SSRIs), les antipsychotiques, les stimulants centraux, les quinolones, la théophylline). D'autre part, le tramadol est un opioïde à effet sérotoninergique, l'association à un autre médicament sérotoninergique (ISRS par ex.) augmente le risque de syndrome sérotoninergique. Des hypoglycémies ont été rapportées chez des patients traités par tramadol ; la prudence sera de rigueur chez les patients diabétiques traités par des médicaments hypoglycémiants.

Gebruik van sterke opioïden

Het belang van sterke opioïden bij kankerpijn werd geleidelijk getransponeerd op chronische pijn, wat heeft geleid tot hun gebruik op grote schaal. Hun risico-batenverhouding bij chronische pijn wordt momenteel echter sterk in twijfel getrokken.

L'usage des opioïdes forts

L'intérêt des opioïdes fort dans le cadre de la douleur cancéreuse a été progressivement transposé au domaine de la douleur chronique conduisant à leur utilisation à large échelle. La balance risque/bénéfice en cas de douleur chronique est actuellement fortement remise en question.

- **Stel vóór de start van een behandeling met opioïden in het kader van chronische pijn realistische doelen voorop qua pijnverlichting en vooral qua verbetering van de functionele capaciteit in het dagelijks leven. Overweeg onderbreking van de behandeling als de voordelen niet opwegen tegen de risico's. De behandeling met opioïden mag slechts worden voortgezet bij klinisch significante verbetering van de pijn en de functionele capaciteit. (GRADE 1C).**

- **Préalablement à l'initiation d'un traitement par opioïdes dans le cadre de la douleur chronique, il importe de fixer des objectifs réalistes pour soulager la douleur et surtout pour améliorer la capacité fonctionnelle dans la vie quotidienne. Envisager les modalités d'interruption du traitement si le bénéfice ne l'emporte pas sur les risques. Le traitement opioïde ne devrait être poursuivi que dans le cas d'une amélioration cliniquement significative de la douleur et de la capacité fonctionnelle. (GRADE 1C)**

Toelichting

Als men beslist om sterke opioïden te starten, moeten er strategieën worden voorzien om de behandeling, indien ze niet succesvol is of onaanvaardbare bijwerkingen veroorzaakt, geleidelijk te stoppen. Men kan ook overwegen om bij onvoldoende effect of onaanvaardbare bijwerkingen een ander morfineanalgeticum in te zetten (opioïdrotatie). In dat geval baseert men zich best op de dosisconversietabel. Een equivalentietabel van de verschillende opioïden, uit de SIGN-richtlijn van 2013, is terug te vinden in bijlage 4. Bij chronisch gebruik van een morfineanalgeticum kan een laxativum obstipatie wellicht voorkomen. Het risico op opioïdafhankelijkheid moet met de patiënt worden besproken.

Explications

Si un traitement par opioïdes forts est décidé, il y a lieu de prévoir des stratégies pour interrompre progressivement le traitement si celui-ci s'avère inefficace ou est à l'origine d'effets indésirables inacceptables. On peut également envisager de modifier l'analgésique morphinique (rotation des opioïdes), en cas d'effet insuffisant ou d'effets indésirables inacceptables. Dans ce cas, il vaut mieux se référer au tableau de conversion des doses. Un tableau d'équivalence des différents opioïdes, issu de SIGN 2013, est fourni en annexe 4. En cas d'utilisation chronique d'un analgésique morphinique, il convient probablement de prévenir la constipation au moyen d'un laxatif. Le risque de dépendance aux opiacés doit être évoqué avec le patient.

- **Geef bij opstart van een behandeling met opioïden voor chronische pijn de voorkeur aan opioïden met onmiddellijke afgifte in plaats van aan opioïden met lange werkingsduur. Schrijf de minimale werkzame dosis voor. Drijf bij lagedosistitratie de dagelijkse dosis geleidelijk op. (GRADE 1C)**
- **Lorsqu'un traitement par opioïdes est initié pour une douleur chronique, la préférence doit être accordée à des opioïdes à libération immédiate plutôt que des opioïdes à longue durée d'action. La dose minimale efficace devrait être prescrite. La progression de dose quotidienne doit être réalisée dans le cadre d'une titration à dose limitée. (GRADE 1C)**

Toelichting

Experts (CDC-richtlijn 2016) benadrukken dat wanneer sterke opioïden worden opgestart, artsen:
- de laagst werkzame dosis moeten voorschrijven,
- voorzorgsmaatregelen moeten nemen m.b.t. het risico van overdosering en dit bij alle doses,

- de risico-batenverhouding zorgvuldig moeten beoordelen wanneer 50 mg morfine-equivalenten per dag (MME/dag) worden overschreden,
- een voorschrift van 90 MME/dag dienen te vermijden of te rechtvaardigen,
- bij chronisch gebruik overschakeling op langwerkende preparaten moeten overwegen.

Explications

Les experts (CDC 2016) précisent que, quand des opioïdes forts sont initiés, les cliniciens devraient :

- prescrire la plus petite dose efficace,
- prendre des précautions contre les risques de surdosage à tous les dosages,
- faire une évaluation rigoureuse de la balance risques-bénéfices au-dessus de 50 mg d'équivalents de morphine par jour (MME/jour),
- éviter ou justifier une prescription dépassant 90 MME /jour,
- envisager en cas d'utilisation chronique, un passage à des préparations à longue durée d'action.

- **Informeer patiënten die sterke opioïden voorgeschreven krijgen over de risico's van de meest voorkomende bijwerkingen zoals misselijkheid en obstipatie. (GRADE 1A)**
- **Les patients chez qui des opioïdes forts ont été prescrits doivent être informés du risque d'effets indésirables les plus fréquents tels que les nausées et la constipation. (GRADE 1A)**
- **Sterke opioïden zijn geen optie in de behandeling van neuropathische pijn noch van een acute pijnepisode bij een chronischepijnpatiënt. (GRADE 2B)**
- **Les opioïdes forts ne constituent pas une option pour le traitement de la douleur neuropathique ni pour le traitement d'un épisode douloureux aigu chez un patient souffrant de douleur chronique. (GRADE 2B)**

Toelichting

De 'sterke' opioïden (morfine, oxycodon, fentanyl en buprenorfine in tabletvorm of onder de vorm van huidpleisters of 'patches') zijn doorgaans niet werkzaam voor neuropathische pijn. Het stopzetten gebeurt niet zonder problemen, zeker wanneer ze langdurig werden gebruikt.

Explications

Les opioïdes «forts» (morphine, oxycodone, fentanyl ou buprénorphine, sous forme de comprimés ou sous forme d'emplâtres cutanés, alias «patchs») sont le plus souvent inefficaces dans les douleurs neuropathiques. L'arrêt ne se fait pas sans difficultés, en particulier lorsqu'ils ont été utilisés longtemps.

- **Overweeg bij chronische pijn verwijzing naar een specifiek multidisciplinair programma voor pijnbehandeling. (GRADE 2C)**

- **La référence à un programme spécifique multidisciplinaire de prise en charge de la douleur devrait être envisagée en cas de douleur chronique. (GRADE 2C)**
- **Algemeen komt een multidisciplinaire aanpak waarschijnlijk beter tegemoet aan de verwachtingen van chronischepijnpatiënten. Het is wenselijk dat een specifiek programma voor de behandeling van chronische pijn is ingebed in het dagelijks leven van de patiënt en de eerstelijnstherapeuten bij de aanpak betreft. (GRADE 2C)**

- **De manière générale, une approche multidisciplinaire est probablement mieux à même de rencontrer les attentes de patients douloureux chroniques. Si un programme spécifique de prise en charge de la douleur chronique est proposé, son intégration dans la vie quotidienne du patient et l'implication des thérapeutes de première ligne dans cette prise en charge seraient souhaitables. (GRADE 2C)**

Toelichting

Over het algemeen wordt aangenomen dat wanneer alle zorgverleners rond de patiënt dezelfde uniforme en consistente boodschappen geven, de patiënt in staat is om zijn ziekte beter te begrijpen en beter aan te pakken. Een gemeenschappelijk multidisciplinair doel moet zijn: de verbetering van de 'health literacy' (geletterdheid op vlak van gezondheid) van patiënten, m.a.w. dat ze de juiste informatie kunnen vinden, begrijpen en gebruiken om beslissingen m.b.t. hun gezondheid te nemen. Daarnaast is een multidisciplinaire benadering eveneens gewenst om de therapietrouw te verbeteren. De verwijscriteria naar multidisciplinaire programma's voor de aanpak van pijn (in België meestal tweede-of derdelijns) zijn niet duidelijk. ...

Explication

De manière générale, on s'attend à ce que la délivrance de messages similaires et concordants par l'ensemble des acteurs de santé en contact avec le patient aide celui-ci à mieux comprendre sa maladie et à mieux se prendre en charge. L'amélioration de la littératie en santé, c'est-à-dire de la capacité des individus à trouver, comprendre et utiliser l'information pour prendre des décisions concernant leur santé, doit être un objectif commun multidisciplinaire. D'autre part, une approche multidisciplinaire dans le but d'améliorer l'adhésion thérapeutique est également souhaitée. Les critères de référence vers ces programmes multidisciplinaires de prise en charge de la douleur, le plus souvent en Belgique de deuxième ou troisième ligne, ne sont pas clairs.

5.2.4 CDC 2016

- **Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should**

be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate (recommendation category: A, evidence type: 3).

- **Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety (recommendation category: A, evidence type: 4).**
- **Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy (recommendation category: A, evidence type: 3).**

Important considerations include the following:

- *Be explicit and realistic about expected benefits of opioids, explaining that while opioids can reduce pain during short-term use, there is no good evidence that opioids improve pain or function with long-term use, and that complete relief of pain is unlikely.*
- *Emphasize improvement in function as a primary goal and that function can improve even when pain is still present.*
- *Advise patients about serious adverse effects of opioids, including potentially fatal respiratory depression and development of a potentially serious lifelong opioid use disorder that can cause distress and inability to fulfill major role obligations.*
- *Advise patients about common effects of opioids, such as constipation, dry mouth, nausea, vomiting, drowsiness, confusion, tolerance, physical dependence, and withdrawal symptoms when stopping opioids. To prevent constipation associated with opioid use, advise patients to increase hydration and fiber intake and to maintain or increase physical activity. Stool softeners or laxatives might be needed.*
- *Discuss effects that opioids might have on ability to safely operate a vehicle, particularly when opioids are initiated, when dosages are increased, or when other central nervous system depressants, such as benzodiazepines or alcohol, are used concurrently.*
- *Discuss increased risks for opioid use disorder, respiratory depression, and death at higher dosages, along with the importance of taking only the amount of opioids prescribed, i.e., not taking more opioids or taking them more often.*
- *Review increased risks for respiratory depression when opioids are taken with benzodiazepines, other sedatives, alcohol, illicit drugs such as heroin, or other opioids.*
- *Discuss risks to household members and other individuals if opioids are intentionally or unintentionally shared with others for whom they are not prescribed, including the possibility that others might experience overdose at the same or at lower dosage than prescribed for the patient, and that young children are susceptible to unintentional ingestion. Discuss storage of opioids in a secure, preferably locked location and options for safe disposal of unused opioids.*
- *Discuss the importance of periodic reassessment to ensure that opioids are helping to meet patient goals and to allow opportunities for opioid discontinuation and consideration of*

additional nonpharmacologic or nonopioid pharmacologic treatment options if opioids are not effective or are harmful.

- *Discuss planned use of precautions to reduce risks, including use of prescription drug monitoring program information and urine drug testing. Consider including discussion of naloxone use for overdose reversal.*
- *Consider whether cognitive limitations might interfere with management of opioid therapy (for older adults in particular) and, if so, determine whether a caregiver can responsibly co-manage medication therapy. Discuss the importance of reassessing safer medication use with both the patient and caregiver.*
- **When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to ≥ 50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥ 90 MME/day or carefully justify a decision to titrate dosage to ≥ 90 MME/day (recommendation category: A, evidence type: 3).**

Clinicians should use caution when increasing opioid dosages and increase dosage by the smallest practical amount because overdose risk increases with increases in opioid dosage. Although there is limited evidence to recommend specific intervals for dosage titration, a previous guideline recommended waiting at least five half-lives before increasing dosage and waiting at least a week before increasing dosage of methadone to make sure that full effects of the previous dosage are evident.

- **Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed (recommendation category: A, evidence type: 4).**
- **Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids (recommendation category: A, evidence type: 4).**

Clinicians should evaluate patients to assess benefits and harms of opioids within 1 to 4 weeks of starting long-term opioid therapy or of dose escalation. Clinicians should consider follow-up intervals within the lower end of this range when ER/LA opioids are started or increased or when total daily opioid dosage is ≥ 50 MME/day. Shorter follow-up intervals (within 3 days) should be strongly considered when starting or increasing the dosage of methadone. At follow up, clinicians should assess benefits in function, pain control, and quality of life using tools such as the three-item "Pain

average, interference with Enjoyment of life, and interference with General activity” (PEG) Assessment Scale and/or asking patients about progress toward functional goals that have meaning for them.

Clinicians should also ask patients about common adverse effects such as constipation and drowsiness, as well as asking about and assessing for effects that might be early warning signs for more serious problems such as overdose (e.g., sedation or slurred speech) or opioid use disorder (e.g., craving, wanting to take opioids in greater quantities or more frequently than prescribed, or difficulty controlling use). Clinicians should ask patients about their preferences for continuing opioids, given their effects on pain and function relative to any adverse effects experienced.

Because of potential changes in the balance of benefits and risks of opioid therapy over time, clinicians should regularly reassess all patients receiving long-term opioid therapy, including patients who are new to the clinician but on long-term opioid therapy, at least every 3 months. At reassessment, clinicians should determine whether opioids continue to meet treatment goals, including sustained improvement in pain and function, whether the patient has experienced common or serious adverse events or early warning signs of serious adverse events, signs of opioid use disorder (e.g., difficulty controlling use, work or family problems related to opioid use), whether benefits of opioids continue to outweigh risks, and whether opioid dosage can be reduced or opioids can be discontinued.

Clinicians should re-evaluate patients who are exposed to greater risk of opioid use disorder or overdose (e.g., patients with depression or other mental health conditions, a history of substance use disorder, a history of overdose, taking ≥ 50 MME/day, or taking other central nervous system depressants with opioids) more frequently than every 3 months.

- **Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥ 50 MME/day), or concurrent benzodiazepine use, are present (recommendation category: A, evidence type: 4).**
- **When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs (recommendation category: B, evidence type: 4).**

For more information see “Opioids and substance use disorder”

- **Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible (recommendation category: A, evidence type: 3).**

Benzodiazepines and opioids both cause central nervous system depression and can decrease respiratory drive. Concurrent use is likely to put patients at greater risk for potentially fatal overdose. The clinical evidence review did not address risks of benzodiazepine co-prescription among patients prescribed opioids. However, the contextual evidence review found evidence in epidemiologic series of

concurrent benzodiazepine use in large proportions of opioid-related overdose deaths, and a case-cohort study found concurrent benzodiazepine prescription with opioid prescription to be associated with a near quadrupling of risk for overdose death compared with opioid prescription alone. Experts agreed that although there are circumstances when it might be appropriate to prescribe opioids to a patient receiving benzodiazepines (e.g., severe acute pain in a patient taking long-term, stable low-dose benzodiazepine therapy), clinicians should avoid prescribing opioids and benzodiazepines concurrently whenever possible. In addition, given that other central nervous system depressants (e.g., muscle relaxants, hypnotics) can potentiate central nervous system depression associated with opioids, clinicians should consider whether benefits outweigh risks of concurrent use of these drugs.

5.2.5 NHG 2018

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

Ga na of de patiënt zelf al pijnmedicatie heeft genomen.

Overweeg bij hevige pijn en/of contra-indicaties voor NSAID's direct te starten met een (zwak werkend) opioid, in combinatie met paracetamol. Geef de medicatie op vaste tijden en verhoog zo nodig de dosering op geleide van de pijn (bij hevige pijn snel ophogen). Evalueer bij blijvende klachten of onvoldoende pijnstilling regelmatig het effect, zodat dosering en middel kunnen worden aangepast. Streef naar tijdelijk gebruik van medicatie en overweeg bij adequate pijnstilling na enkele weken de medicatie af te bouwen.

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.*

Stap 3: tramadol (zwak werkend opioid)

Stap 4: sterk werkende opioïden (oraal of pleister)

Stap 5: subcutane of intraveneuze toediening van sterk werkende opiate

A detailed description of step 1 and step 2 are beyond the scope of this work and can be found in the NHG guideline.

Stap 3: tramadol (zwak werkend opioid)

Algemeen. Overweeg tramadol toe te voegen aan paracetamol of NSAID als deze onvoldoende effect hebben. Codeïne wordt niet aanbevolen (ook niet in zetabletten) vanwege onvoldoende effect en frequent optreden van bijwerkingen. Eén op de vijf patiënten ondervindt bijwerkingen van tramadol (duizeligheid, misselijkheid, braken, hoofdpijn, droge mond, obstipatie, zweten, vermoeidheid en slaperigheid). Titreer tramadol bij kwetsbare patiënten langzaam op (bijvoorbeeld door gebruik te maken van druppels) om bijwerkingen te voorkomen. Bij chronisch gebruik is er een risico op afhankelijkheid en onthoudingsverschijnselen bij staken van tramadol (te voorkomen door afbouwen). Ook kan tramadol (off-label) worden toegepast bij

neuropathische pijn. Bij dagdoseringen hoger dan 400 mg, in het bijzonder in combinatie met SSRI's, SNRI's en TCA's, bestaat er risico op serotonerg syndroom. Vaste combinaties van tramadol en paracetamol worden ontraden.

Stap 4: sterk werkende opioïden (oraal of pleister)

Overweeg alleen een sterkwerkend opioïd als er sprake is van ernstige pijn met zoveel invloed op het dagelijks functioneren dat deze situatie moet worden doorbroken en die met de overige behandelingen en optimaal ingestelde medicatie uit de vorige stappen onvoldoende vermindert. Bij de keus voor een opioïd gaat de voorkeur uit naar een oraal morfinepreparaat. Hiermee is ruime ervaring opgedaan. Rectale toediening wordt niet aangeraden vanwege onvolledige en wisselende opname. Bij problemen met orale toediening heeft een fentanylpleister of eventueel parenterale toediening van morfine de voorkeur. Zie tabel 5 voor de doseringsadviezen van morfine en fentanyl.

Tabel 5 Startdoseringen opiaten bij patiënten die niet eerder opiaten gebruikten

Orale startdosering morfine	Rectale startdosering morfine (alleen tijdelijk, als noodoplossing)	Transdermale startdosering fentanyl (werkt na 6-12 uur)
1-2 dd 10-30 mg retard; bij leeftijd > 70 jaar of gewicht < 50 kg 2 dd 10 mg retard	3-4 dd 5-10 mg	pleister 12 microg/uur; na 3 dagen vervangen

Table 6 of the NHG 2018 guideline

De benodigde dosering kan per individu sterk wisselen, afhankelijk van de gewenning en verschillen in respons op en tolerantie voor het opioïd.

De werkgroep beveelt buprenorfine niet aan in de eerste lijn vanwege onvoldoende ervaring zonder bewezen voordelen.

Als verschillende soorten opioïden onvoldoende pijnstilling of onacceptabele bijwerkingen blijven geven, kan bij hoge uitzondering en uitsluitend in overleg met het palliatief team of pijnbehandelcentrum overwogen worden om methadon voor te schrijven. Het voorschrijven van methadon vereist specifieke ervaring in verband met een relevant risico op cumulatie bij gebruik langer dan enkele dagen door grote variatie in eliminatiehalfwaardetijd.

Praktische adviezen zijn:

- Geef voorlichting over de voor- en nadelen van opioïden.
 - Voordelen: effectief bij pijn door kanker, maar minder bewezen effectief bij andere vormen van chronische pijn.
 - Nadelen: kans op ernstige bijwerkingen, zoals problemen in het dagelijks functioneren door sufheid, noodzaak tot gebruik van laxantia en kans op afhankelijkheid en gewenning, waardoor steeds hogere doseringen nodig zijn en meer bijwerkingen mogelijk zijn.
- Schrijf opioïden alleen bij uitzondering voor bij chronische, niet aan kanker gerelateerde pijn als de pijn met de overige behandelingen en optimaal ingestelde medicatie met niet-opioïden

onvoldoende vermindert. *Evalueer de behandeling elke een tot twee weken en stem af of verdere behandeling met opioïden nog noodzakelijk is en of de werkzaamheid opweegt tegen de bijwerkingen.*

- *Schrijf geen opioïden voor aan patiënten met een middelenafhankelijkheid en wees terughoudend bij patiënten met psychische aandoeningen.*
- *Stem bij de start van een opioïd de verwachte gebruikstermijn af met de patiënt. Houd daarvoor een zo kort mogelijke periode aan.*
- *Houd om overmatig gebruik van opioïden te voorkomen de dosering bij chronische, niet aan kanker gerelateerde pijn zo laag mogelijk, bij voorkeur onder de 90 mg morfine-equivalent per dag. Bouw zo snel mogelijk weer af.*
- *Herhaal opioïden bij voorkeur niet volgens automatische herhaling, maar alleen na een consult. Vraag naar de pijnvermindering en stop met het opioïd bij onvoldoende pijnstilling. Bij zorgvuldig ingestelde patiënten kunnen recepten herhaald worden mits dit gebeurt volgens het afgesproken behandelplan met controlemomenten, mogelijkheid tot feedback en bijstelling.*

Tabel 6 Omrekeningstabel opioïdrotatie*

Morfine oraal (mg/24 uur)	Morfine s.c./i.v. (mg/24 uur)	Oxycodon oraal (mg/24 uur)	Oxycodon s.c./i.v. (mg/24 uur)	Fentanyl transdermaal (microg/uur)	Hydromorfon oraal (mg/24 uur)	Hydromorfon s.c./i.v. (mg/24 uur)
30	10	20	10	12	6**	2
60	20	40	20	25	12	4
90	30	60	30	37	18**	6
120	40	80	40	50	24	8
180	60	120	60	75	36	12
240	80	160	80	100	48	16
360	120	240	120	150	72	24
480	160	320	160	200	96	32

Bron: MDR Diagnostiek en behandeling van pijn bij patiënten met kanker, 2016 (richtlijndatabase.nl).

* Als een patiënt overgaat van het ene opioïd naar het andere vanwege bijwerkingen, wordt geadviseerd om 75% van de equivalente 24 uursdosering te geven.

** Deze dosering kan in de praktijk niet gegeven worden, omdat de laagst beschikbare dosering 2 dd 4 mg met vertraagde afgifte is, gevolgd door 8, 16 en 24 mg.

- *Geef voor onderhoudsbehandeling op vaste tijden (vaak tweemaal daags) een dosis in de vorm van een oraal morfinepreparaat met vertraagde afgifte.*
- *Voorkom obstipatie door vanaf de start van het opioïd een laxans zoals lactulose of macrogol toe te voegen (tenzij er sprake is van diarree). Zie hiervoor de NHG-Standaard Obstipatie en/of www.pallialine.nl.*
- *Voeg kortdurend een anti-emeticum toe als er in het begin van de behandeling misselijkheid optreedt of indien een patiënt eerder klachten van opioïdgeïnduceerde misselijkheid en braken heeft gehad. Geef in dat geval metoclopramide of domperidon.*
- *Stop na 1-2 dagen wanneer het gewenste effect niet wordt bereikt en beperk de behandelduur zoals aangegeven. Overweeg bij aanhoudende klachten opioïdrotatie (bijvoorbeeld van morfine naar een ander opioïd zoals fentanyl of oxycodon) of verandering van toedieningsweg (bijvoorbeeld in plaats van oraal of intermitterend subcutaan gebruik*

naar continu subcutaan (pomp) gebruik). Zie hiervoor tabel 6 'Omrekeningstabel Opioidrotatie'.

- Geef bij doorbraakpijn bij kanker en in de palliatieve fase naast de onderhoudsbehandeling een snelwerkend preparaat oraal, oromucosaal, intranasaal of parenteraal als 'rescuemedicatie' bijvoorbeeld als bolus bij een continu subcutaan infuus (afhankelijk van toepasbaarheid en voorkeur van de patiënt). Als de doorbraakpijn situatief gebonden is (bijvoorbeeld bij verzorgen van de patiënt of bij bepaalde activiteiten van de patiënt) kan de doorbraakmedicatie 30 tot 60 minuten tevoren worden gegeven. Geef dan bij voorkeur het kort werkende preparaat van het opioïd dat als onderhoudsbehandeling wordt gebruikt.*
- Voorkom langdurig gebruik bij patiënten met dementie (met uitzondering van palliatieve fase).*
- Geef bij chronische pijn door benigne oorzaak alleen op strikte indicatie sterk werkende opioïden. Vermijd opioïden bij chronische pijn door onbekende oorzaak.*
- Onderschat het risico van chronisch gebruik van sterk werkende opioïden op gewenning en dosisescalatie niet. Er bestaat een dosisafhankelijk risico op (ernstige) bijwerkingen.*
- Indien door afname van de pijn de dosering verlaagd kan worden, doe dit dan geleidelijk om lichamelijke onthoudingsverschijnselen te voorkomen. Halveer de dosering elke twee tot zeven dagen.*

Stap 5: subcutane of intraveneuze toediening van sterk werkende opioïden

Subcutane of intraveneuze toediening van opioïden is aangewezen als met stap 4 onvoldoende pijnstilling kan worden bereikt of als van speciale toedieningswegen een gunstiger effect kan worden verwacht. Als met bovengenoemde methoden onvoldoende pijnstilling bereikt wordt is epidurale of spinale toediening van opioïden mogelijk zinvol. Hiervoor dient de patiënt verwezen te worden naar een anesthesioloog-pijnspecialist.

Management of pain in the palliative setting is beyond the scope of this document. More details can be found in the NHG 2018 guideline.

Neuropathic pain

...Bespreek met de patiënt dat er voordat de meest optimale behandeling duidelijk is mogelijk meerdere geneesmiddelen moeten worden geprobeerd gedurende enkele weken. Paracetamol en NSAID's zijn in de regel niet werkzaam bij 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.

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

Praktische adviezen bij orale medicatie:

...Opioïden (inclusief tramadol) kunnen gewenning en afhankelijkheid geven en worden in beginsel niet geadviseerd bij neuropathische pijn. Overleg zo nodig met de anesthesioloogpijnspecialist.

Als neuropathische pijn onvoldoende reageert op monotherapie, kan een combinatie worden geprobeerd van twee geneesmiddelen met een verschillend werkingsmechanisme die bij neuropathische pijn worden toegepast.

5.2.6 NICE 2017

All neuropathic pain (except trigeminal neuralgia)

- **Consider tramadol only if acute rescue therapy is needed**

Treatments that should not be used (for the purpose of this document only opioids are mentioned)

- **Do not start the following to treat neuropathic pain in non-specialist settings, unless advised by a specialist to do so: morphine and tramadol (this is referring to long-term use, see the previous recommendation for short-term use)**

When it had reviewed evidence for peripheral neuropathic pain and central neuropathic pain, the Guideline Development Group (GDG) concluded it was most appropriate to provide a single set of recommendations for all forms of neuropathic pain (except trigeminal neuralgia), based on the overall analysis combining all types of pain.

The GDG also advised that combination therapies should be further explored, because the effect of adding a treatment onto another treatment may be more practical and effective than switching to a new treatment. The GDG also considered that the use of combination therapies could potentially reduce side effects of particular pharmacological agents through using a combination of lower dosages. However, current evidence is not sufficient to warrant any recommendation on combination therapies.

Morphine - The majority of the analyses showed that morphine appears to reduce pain compared with placebo, but it is associated with significant adverse effects and higher rates of withdrawal due to adverse effects. The GDG also considered the potential risk of opioid dependency. As a result, the GDG agreed it was not appropriate to consider this in non-specialist settings.

Tramadol – the analyses were generally consistent that tramadol is effective at reducing pain compared with placebo. However, the effect estimates were imprecise because only small numbers of patients were involved in the included studies. Also, the included studies had very short study periods (up to 4 weeks), with higher rates of withdrawal due to adverse effects associated with the treatment. The GDG concluded that tramadol should only be considered as a rescue medication when people are awaiting referral to specialist pain services after initial treatment has failed.

Trigeminal neuralgia

No recommendations concerning opioids were provided as they are not recommended in this indication.

5.2.7 ASCO 2016

- **Clinicians should be aware of chronic pain syndromes resulting from cancer treatments, the prevalence of these pain syndromes, risk factors for individual patients, and appropriate treatment options. A list of common cancer pain syndromes can be found in the ASCO 2016 guideline (Table 3) (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)**
- **Clinicians should evaluate and monitor for recurrent disease, second malignancy, or late-onset treatment effects in any patient who reports new-onset pain. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)**
- **Clinicians may prescribe a trial of opioids in carefully selected cancer survivors with chronic pain who do not respond to more conservative management and who continue to experience pain-related distress or functional impairment. Tables 5 and 6 provide guidelines intended to promote safe and effective prescribing. Nonopioid analgesics and/or adjuvants can be added as clinically necessary. (Evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)**

Table 5. Universal Precautions in Chronic Cancer Pain Management		
Steps	Strategies	Comment
1. Assess and stratify risk of opioid misuse	<p>Assess</p> <ul style="list-style-type: none"> Review of medical records including diagnosis Interview (consider risk factors such as age, personal or family history of alcohol or drug abuse, major psychiatric disorder, history of sexual abuse) Examination Screening questionnaires Review of prescription drug monitoring program data Urine drug screening 	<p>All patients should undergo risk assessment</p> <p>Although many questionnaires have been developed to predict aberrant behavior or addiction, the clinical assessment is generally used in practice</p> <p>Risk stratification and adherence monitoring are illustrated in Table 6</p>
2. Decide whether or not to prescribe	<p>Risk of diversion:</p> <ul style="list-style-type: none"> Low → prescribe High and the controlled drug is preferred but not a standard of care → do not prescribe High and the controlled drug is the standard of care and no reasonable alternatives exist → proceed only if controls and adherence monitoring can be established to ensure that diversion is not occurring <p>Risk of drug abuse:</p> <ul style="list-style-type: none"> Low → prescribe Moderate or high: decision to prescribe requires a critical analysis of: <ul style="list-style-type: none"> whether the severity of the pain is meaningfully compromising physical or mental well-being, whether there are reasonable alternatives that may ameliorate pain with manageable risk, and whether the nature of the drug abuse risk is more (eg, relapse of heroin abuse) or less (eg, pattern of early refills) serious 	<p>Proceed only if:</p> <ul style="list-style-type: none"> Prescribing protocol and adherence monitoring commensurate with the risk can be put in place, and The patient is educated about the purpose of these strategies and the plan to modify prescribing or discontinue the drug if abuse occurs <p>Do not prescribe unless warranted by the severity of the pain experience, there are no reasonable alternatives, and the risk of abuse or diversion is manageable</p>
3. Minimize risk	<p>Structure treatment in a manner that:</p> <ul style="list-style-type: none"> establishes an appropriate level of adherence monitoring and helps patients avoid nonadherence <p>Always optimize adjuvant analgesics, nonpharmacologic and interventional approaches; psychological support for treatment of psychiatric illness, anxiety, depression, sleep disorders</p>	<p>Adherence monitoring is illustrated in Table 6</p>
4. Monitor drug-related behaviors	<p>Effectiveness (pain is described as less intense, with a relationship to dose and dosing that is expected, and the pain reduction is associated with the ability to sustain or improve physical or psychological functioning)</p> <p>Adverse effects</p> <p>Adherence monitoring, including compliance with current analgesic and nonopioid analgesic treatments, on the basis of risk assessment</p>	<p>Monitoring of outcomes is consistent with integration of pain management into a palliative care model</p>
5. Respond to aberrant behaviors	<p>A. Reassess and diagnose</p> <ul style="list-style-type: none"> Realize that aberrant drug-related behaviors have a differential diagnosis and that an assessment must be performed to clarify whether behavior indicates addiction, other psychiatric condition associated with impulsive drug use, family issues, desperation or impulsivity driven by uncontrolled pain, or some combination of these factors. Also recognize that diversion is possible and assess for this behavior. <p>B. Consider whether to continue prescribing</p> <ul style="list-style-type: none"> If diversion is occurring or risks now exceed benefit, taper and discontinue <p>C. If diversion is not occurring and the assessment suggests that the benefits of therapy will continue to outweigh the risk if the aberrant behaviors are stopped, restructure prescribing to increase control and adherence monitoring</p> <ul style="list-style-type: none"> Avoid agents with higher abuse liability Prescribe small amounts at short intervals Review prescription drug monitoring data routinely Use pill counts Monitor use of substances through urine/other toxicology screening Require use of one pharmacy Use written agreement Obtain consultation from psychiatry/addiction specialists 	<p>Advanced illness does not free the clinician from the requirement of compliance with laws and regulations</p>
NOTE. Definitions of abuse, addiction, and diversion are listed in the Appendix (online only). Adapted from Portenoy and colleagues. ^{10,60}		

Table 5 of the ASCO 2016 guideline

Table 6. Risk Stratification and Adherence Monitoring			
Action	Low Risk	Moderate Risk	High Risk
Risk stratification*	No history of alcohol abuse or drug abuse, no family history of alcohol or drug abuse No history of a major psychiatric disorder Older age No smoking Stable social support	Remote history of alcohol or drug abuse History of addiction with a sustained period of recovery and a strong system to help sustain recovery Questionable family history of alcohol or drug abuse History of major psychiatric disorder that has been managed effectively Younger age Smoking History of physical or sexual abuse Lack of social support Involvement with others engaging in drug abuse	Recent history, or multiple episodes, of alcohol or drug abuse History of addiction with limited or no system to sustain recovery Strong family history of alcohol or drug abuse History of major psychiatric disorder
Adherence monitoring and mitigation	At least annual adherence monitoring Monitoring should usually include: detailed interviewing about drug-related behavior questioning of family member and record review from other treating physicians check of prescription monitoring program urine drug screen	At least semiannual adherence monitoring (more frequent at higher levels of assessed risk) Monitoring should usually include: detailed interviewing about drug-related behavior questioning of family member and record review from other treating physicians check of prescription monitoring program urine drug screen	Adherence monitoring at least every 2-3 months and more frequent visits Monitoring should usually include: detailed interviewing about drug-related behavior questioning of family member and record review from other treating physicians check of prescription monitoring program urine drug screen pill counts
Respond to aberrant behaviors	Reconsideration of treatment to determine whether nonopioid therapies can be better used	Reconsideration of treatment to determine whether nonopioid therapies can be better used	Reconsideration of treatment to determine whether nonopioid therapies can be better used Refills limited or not permitted Small frequent prescriptions No concurrent use of more than one opioid (eg, no prescription of a second short-acting drug for breakthrough pain in those prescribed a long-acting drug for daily use) Mandated consultation with addiction specialists/psychiatrist

*The level of risk conferred is indicated by the presence of one or more factors itemized in the corresponding risk categories.

Table 6 of the ASCO 2016 guideline

See also the flow charts under “opioids and substance use disorder”

- Clinicians should assess risks of adverse effects of opioids used for pain management. Table 7 lists opioid-related long-term adverse effects. (Evidence-based and informal consensus; benefits outweigh harms; evidence quality: intermediate strength of recommendation: moderate)**

Qualifying statement. Although there is literature describing dysimmune effects and tumor proliferative effects from opioid drugs (both of which may be of particular concern in the cancer survivor population), there is insufficient evidence to determine whether there are clinically important risks. The expert panel believes that further clinical investigation is required to assess these concerns. In the absence of actionable data, physicians should be made aware of these evolving questions, and patients and their families may be informed about them as part of a discussion of the potential harms of long-term opioid therapy, as described in Table 7.

Table 7. Adverse Effects Associated With Long-Term Opioid Use
Persistent common adverse effects
Constipation
Mental clouding
Upper GI symptoms (pyrosis, nausea, bloating)
Endocrinopathy (hypogonadism/hyperprolactinemia)
Fatigue
Infertility
Osteoporosis/osteopenia
Reduced libido
Reduced frequency/duration or absence of menses
Neurotoxicity
Myoclonus
Other changes in mental status (including mood effects, memory problems, increased risk of falls in the elderly)
Risk of opioid-induced hyperalgesia (incidence and phenomenology uncertain, but escalating pain in tandem with dose escalation raises concern)
Sleep-disordered breathing
Increased risk of concurrent benzodiazepine in patients predisposed to sleep apnea
New-onset sleep apnea
Worsening of sleep apnea syndromes
NOTE. Data adapted. ⁶¹⁻⁶³

Table 7 of the ASCO 2016 guideline

Although opioids are the foundation of cancer pain management in moderate to severe acute pain as well as in pain caused by advanced disease, the efficacy of long-term use in survivors has not been well established. The balance between potential risks and benefits must be weighed when considering the long-term use of these agents in people who are surviving cancer. Benefits are no longer simply evaluated on the basis of pain relief but must also include improvements in function, tailored to the abilities of the individual.

- **Clinicians should assess the potential risks and benefits when initiating treatment that will incorporate long-term use of opioids. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)**
- **Clinicians should clearly understand terminology such as tolerance, dependence, abuse, and addiction as it relates to the use of opioids for pain control. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)**
- **Clinicians should incorporate a universal precautions approach to minimize abuse, addiction, and adverse consequences of opioid use such as opioid-related deaths. Clinicians should be cautious in coprescribing other centrally acting drugs, particularly**

benzodiazepines (Table 7). (Evidence-based and informal consensus; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

- **Clinicians should understand pertinent laws and regulations regarding the prescribing of controlled substances. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)**
- **Clinicians should educate patients and family members regarding the risks and benefits of long-term opioid therapy and the safe storage, use, and disposal of controlled substances. Clinicians are encouraged to address possible myths and misconceptions about medication use and should educate patients about the need to be cautious when using alcohol or sedating over-the-counter medications or in receiving centrally acting medications from other physicians. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)**

Education and information about treatment should ideally take into account the patient's literacy level and the need for interpreters and should be provided in a culturally congruent manner.

The ASCO guideline, Prevention and Management of Chemotherapy- Induced Peripheral Neuropathy (CIPN) in Survivors of Adult Cancers, found few high-quality, consistent trials and was unable to make a recommendation regarding any agent for prevention of CIPN. In addition, duloxetine was the only agent recommended by the guideline panel for the treatment of CIPN. Other therapies, although anecdotally beneficial or supported for their use in other neuropathic conditions, could not be recommended, although the guideline committee suggested that it might be reasonable to try these agents in selected patients.

The ratio of benefit to harm of therapy and goals of care are different when comparing the person at the end of life with the long-term survivor. In an attempt to reduce harm, drug–drug interactions with cancer therapies or other treatments should be considered. Cytochrome P450 CYP 3A and CYP2D6 inhibitors can increase concentrations of opioids, such as codeine, oxycodone, hydrocodone, fentanyl, tramadol, and methadone, metabolized by this system. Methadone and buprenorphine can prolong the QT interval, an effect that can be potentiated by many other drugs, notably doxorubicin, nilotinib, pazopanib, sorafenib, and other chemotherapeutic agents.

If pain is severe and disabling, and long-term opioid therapy is being considered, the potential for opioid-related harm over time must also be evaluated. Again, the data are sparse. Persistent adverse effects such as constipation are well recognized, and evolving information about persistent endocrinopathy and risk of sleep-disordered breathing suggests that these conditions must be considered when opioid therapy is initiated and later during the course of treatment. The potential for neurotoxicities, such as persistent mental clouding, increased risk of falls in the elderly, and other phenomena may occur. Opioid-induced hyperalgesia is well described in preclinical models but has uncertain clinical importance; the potential is considered when a patient reports escalating pain in tandem with opioid dose escalation in the absence of identifiable worsening of a pain cause. A more recent line of inquiry is the effect of opioids on immune function and tumor progression, and ultimately, survival. Preclinical studies implicate μ opioids in tumor progression, although studies in humans are lacking. Clearly, there is an urgent need for additional research.

5.2.8 DOH_Ireland 2015

Treatment of cancer pain

Once a comprehensive assessment of a patient's pain has been made including the physical, psychosocial and emotional domains, the various treatment approaches should be considered prior to the formulation of a treatment plan.

Key finding

The WHO analgesic ladder has been extensively validated and shown to be effective in the management of pain in the majority of cancer patients.

- **Cancer patients should have their pain managed in accordance with the World Health Organisation (WHO) Cancer Pain Relief guidance. (recommendation category C)**

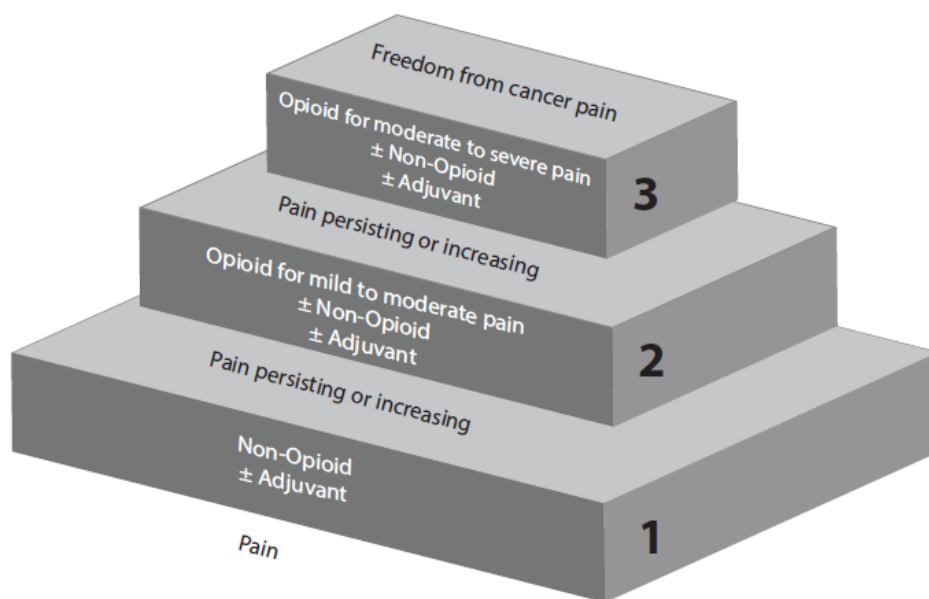


Figure 2 World Health Organisation analgesic ladder from World Health Organisation. Cancer Pain Relief, 2nd ed. Geneva: WHO, 1996 (121)

The fundamental principles of the WHO document are as follows :

1. Oral administration of analgesics:

The oral form of medication should be used whenever possible. Ideally, two types of formulations are required: normal release (for dose titration) and modified release (for maintenance treatment).

2. Analgesics should be given at regular intervals, taking into account the duration of the medication's efficacy (pharmacokinetics). This will ensure a steady level of analgesia in the patient's bloodstream and reduce the need for breakthrough analgesia.

3. Analgesics should be prescribed according to the degree of pain, as indicated by the WHO ladder.

4. Dosing of pain medication should be adapted for the individual.

- Every patient will respond differently to analgesic regimens and there is no standardised dosage for the treatment of pain

5. Analgesics should be prescribed with a constant concern for detail.

In summary:

- By the mouth
- By the clock
- By the ladder
- Individual dose titration
- Attention to detail

How to use the WHO analgesic ladder

Thus, medication is prescribed according to pain severity and the accordingly appropriate 'step' on the ladder.

A patient's pain severity should be regularly assessed and the appropriate analgesia prescribed according to the analgesic ladder; the severity of pain determines the strength of analgesia required, whilst the type and cause of pain will influence the choice of analgesic used. For a patient with chronic pain, both regular and breakthrough analgesia must be prescribed.

Table 4 How to use the WHO Analgesic Ladder
(adapted from SIGN Guideline (2))

WHO analgesic ladder	Score on numerical rating scale	Analgesic of choice
Step 1: mild pain	1 to 2 out of 10	Non-opioid (Paracetamol/ NSAID) +/- Adjuvant
Step 2: mild to moderate pain	3 to 6 out of 10	Weak opioid (Codeine/ Tramadol*) +/- Non-opioid +/- Adjuvant
Step 3: severe pain	7 to 10 out of 10	Strong opioid (Morphine sulphate/Oxycodone/ Hydromorphone/ Fentanyl) +/- Non-opioid +/- Adjuvant

* Unless specific patient-related issues exist, codeine and codeine/paracetamol combinations should be used in cancer pain management in preference to tramadol or tapentadol. See recommendation 7.

Table 4 of the DOH_Ireland 2015 guideline

It is imperative that the clinician selects the strength of opioid analgesic according to the current severity of pain (i.e. the clinician can start at step 3 if the patient has severe pain).

The clinical usefulness of step two has been questioned with the argument that the earlier introduction of a strong opioid is more appropriate. Tassarini et al (2011) undertook a systematic review to analyse the evidence supporting the widespread use of modified analgesic ladders.

- A meta-analysis was performed of four trials comprising 288 patients, of which 88 were treated with the standard three-step approach and 200 were treated with a modified two-step ladder.
- The level of evidence was low or very low for all the trials, resulting in a low strength of the final recommendations.
- Methodological limitations in trial design and conduct, and trial heterogeneity, meant that it was impossible to assess the risk / benefit of the novel two-step approach compared to the standard approach.

Choice of opioids

Opioids for mild to moderate pain

- **Weak opioids may be used in the treatment of mild to moderate pain. They may be used in conjunction with a non-opioid analgesic. Unless specific patient-related issues exist, codeine and codeine/paracetamol combinations should be used in cancer pain management in preference to tramadol or tapentadol. (recommendation category C)**

Codeine, dihydrocodeine and tramadol are examples of weak opioids that are commonly prescribed for use at step two of the WHO ladder. There is an evidence base to support the use of codeine and codeine/paracetamol in cancer pain. There is insufficient evidence to support the use of oral tramadol or tapentadol in preference to codeine/paracetamol for mild to moderate cancer pain.

Codeine phosphate

... the chief analgesic activity of codeine results from its action as a pro-drug of morphine sulphate; 2-10% of codeine is metabolised to morphine sulphate via CYP2D6. CYP2D6 enzyme inhibitors or genetic polymorphisms can reduce morphine sulphate production thus affecting patient analgesic responses. Approximately 7% of Caucasian people, 3% of black people and 1% of Asian people have poor or absent metabolism of codeine, resulting in poor or absent analgesic effect.

Codeine exhibits a 'dose ceiling' effect, above which there is no evidence of additional analgesic effect. Further titration above this however is associated with an increased risk of side-effects. The upper limit of codeine intake should therefore be limited to a maximum of 240mg per day.

Tramadol

In relation to the multi-modal pharmacology of tramadol as both a weak opioid agonist and a serotonin-noradrenaline reuptake inhibitor, a systematic review and meta-analysis examined the pharmacological management of neuropathic pain (in both the cancer and non-cancer settings). This found moderate quality of evidence for the use of tramadol for neuropathic pain.

Combination medications

Codeine/paracetamol combinations have been identified as a useful option in the second step of the analgesic ladder. It has been shown that a combination of codeine 60mg / paracetamol 1g is more effective than paracetamol alone, but studies have shown no benefit with a combination of codeine 8mg / paracetamol 1g when compared to paracetamol alone. (This DOH_Ireland 2015 guideline

refers to the SIGN 2008 guideline which mentions codeine 8mg/ paracetamol 500 mg and not codeine 8mg/ paracetamol 1g).

Opioids for moderate to severe pain

- **Oral morphine sulphate, hydromorphone and oxycodone may be used as first line treatment in the management of moderate to severe cancer pain. (recommendation category B)**
- **Transdermal opioids such as fentanyl and buprenorphine are valid alternatives in selected patients¹. (recommendation category B)**
- **Methadone may be used for the treatment of moderate or severe cancer pain. (recommendation category D)**
- **Methadone use is only advised through the guidance of specialist palliative care professionals. (recommendation category D)**

The available evidence demonstrates that the efficacy and tolerability of morphine sulphate, oxycodone, hydromorphone and methadone are equivalent, and these agents are all valid choices as first and subsequent choice opioids for moderate to severe cancer pain.

Transdermal opioids such as fentanyl and buprenorphine are valid alternatives in selected patients; they may be associated with less constipation and good patient compliance, but their pharmacokinetic and dynamic characteristics present challenges.

Morphine sulphate

Morphine sulphate appears to have no clinical ceiling effect for analgesia. It is metabolised primarily in the liver into the active metabolites morphine sulphate-3-glucuronide (M3G) and morphine sulphate-6-glucuronide (M6G). These metabolites contribute to toxicity, particularly in patients with renal impairment.

The oral route of administration is favoured for reasons of patient acceptability and preference. However, the systemic availability of morphine sulphate by the oral route is poor (35%, ranging from 15-64%) and this can lead to an unpredictable onset of action and great individual variability in dose requirements and responses.

Combination opioid therapy

Fallon et al (2011) performed a systematic review examining the evidence for using two strong opioids simultaneously, so called “combination opioid therapy”. Currently there is a significant gap between the basic scientific work, which potentially supports a role for combination opioid therapy, and clinical practice where combination therapy is used; the available evidence is very limited and of low quality. As such, there is insufficient evidence at present to support the use of combination opioid therapy.

Oxycodone

¹ This guideline does not specify what they consider ‘selected patients’

Oxycodone is metabolised principally to noroxycodone via CYP3A4, with a smaller amount metabolised to oxymorphone via CYP2D6. It is the parent drug however which provides the analgesic effect. Taken orally, oxycodone has a more predictable bioavailability (75%) than morphine sulphate. It is thus more potent than oral morphine sulphate, whilst parenteral bioavailability is similar.

Hydromorphone

Hydromorphone is a semi-synthetic derivative of morphine sulphate with similar pharmacokinetic and pharmacodynamic properties, though it is a more selective mu-opioid receptor agonist ... It is metabolised in the liver to hydromorphone-3-glucuronide (H3G), which has no analgesic activity but does have neuro-excitatory properties. There is wide inter-individual variation in oral bioavailability (37-62%).

Fentanyl

Sequestration occurs in body fats, including epidural fats and CNS white matter. By any route of administration, after systemic redistribution, fentanyl acts supraspinally. It is later metabolised to inactive norfentanyl via CYP3A4 in the liver. ...Use of transdermal fentanyl preparations is associated with a lower occurrence of gastrointestinal side-effects and good patient compliance.

Buprenorphine

Buprenorphine is a highly lipid-soluble opioid which demonstrates multimechanistic pharmacology, acting as a partial mu-opioid receptor agonist and a kappa- and delta-opioid receptor antagonist. It has low oral bioavailability (15%), is metabolised in the liver by CYP3A4 and is highly lipophilic. Buprenorphine is available in transdermal preparations for cancer pain management. Buprenorphine has been shown in in vivo studies to produce the same level of analgesic effect as other strong opioids including morphine and fentanyl.

Following a systematic literature review, Tassinari et al (2011) concluded that to date no definitive data exists to support the extensive use of transdermal opioids in all strong-opioid naïve patients with moderate to severe cancer pain and that the use of slow release oral preparations remains the preferred approach.

An updated systematic review in 2014 demonstrated that there is insufficient evidence to recommend the use of buprenorphine by the sublingual, intramuscular, or subcutaneous routes of administration for cancer pain. When administered transdermally, there is evidence that buprenorphine provides analgesia with possibly fewer side effects than other opioids, in particular regarding nausea. However, there is insufficient evidence to support the use of buprenorphine over any other strong opioid.

Methadone

Methadone is a synthetic opioid with mixed properties; it is a mu-opioid receptor agonist, an NMDA receptor channel blocker and a pre-synaptic blocker of serotonin reuptake. It is absorbed well from all routes of administration, with 80% oral bioavailability. Methadone has a high volume of distribution due to its lipid solubility, and is extensively protein-bound. This results in a long and unpredictable plasma half-life, leading to potential problems with accumulation.

Due to these properties, leading to considerable inter-individual variation, the use of methadone for the treatment of cancer pain is advised only through the guidance of specialist palliative care professionals. Renal and hepatic impairment do not affect methadone clearance.

The available evidence demonstrates that the efficacy and tolerability of hydromorphone, morphine sulphate, oxycodone and methadone are equivalent. These agents are all valid choices as opioids for the treatment of moderate to severe cancer pain. Methadone should be used only under specialist guidance due to its complex pharmacokinetic profile.

Best Practice Point: Pharmacoeconomics

Where there is no evidence of a differential benefit between different medications in terms of efficacy, tolerability or side effect profile, and where clinical expertise allows, the medication with lowest cost base should be used.

Route of administration of opioids

- **The oral route should be used for administration of opioids, if practical and feasible. If a patient is unable to take oral opioids, a number of alternative application routes exist, such as subcutaneous, intravenous, transmucosal, transdermal, topical and spinal routes. (recommendation category A)**

For more details see “Opioid formulations and route of administration”.

Oral opioid dosing schedule

- **As there is no difference between the available oral opioid preparations in terms of analgesic efficacy, oral opioid scheduling should be based on patient preference and ease of compliance. (recommendation category D)**

Oral opioid treatment

- **Oral opioid titration can be adequately and safely commenced and titrated using either oral immediate release preparations, or modified release preparations. (recommendation category C)**

Opioid initiation and titration

Traditionally, when starting morphine sulphate for cancer pain, the recommendation has been to use immediate release (IR) oral morphine sulphate every 4 hours, with the same dose for breakthrough pain. This recommendation is based on the WHO analgesic pain ladder framework and formed part of the 2001 EAPC cancer pain guidelines. Recently this concept has been challenged. ...

The starting dose of analgesia will depend on the severity of pain, the side-effects of present or prior analgesia, and the total amount of analgesia required by the patient previously. Given the present available knowledge, descriptive studies demonstrate that starting with oral morphine sulphate up to and including a dose of 30mg/24hr in opioid naïve patients, or up to and including a dose of 60mg/24hr in those patients titrating from step two opioids, is safe and efficient. For patients converted from another step three opioid, please refer to the table with equianalgesic dosages (see “Rotation of opioids”) to guide management.

Table 6 Titration using immediate release oral preparations

Titration Using Immediate Release Oral Preparations (Using oral morphine sulphate as an example)
<ul style="list-style-type: none">• Use immediate release morphine sulphate, given every 4 hours, and the same dose for breakthrough pain. This rescue dose may be given as often as required and the total daily dose of the morphine sulphate should be reviewed daily.• If pain returns consistently before the next regular dose is due, the regular dose should be increased. Patients stabilised on regular oral morphine sulphate require continued access to a rescue dose to treat breakthrough pain.• When a patient's pain has been controlled with immediate release morphine sulphate, the 24 hour dose can be converted into modified 12 hour release preparation. <p>For example*</p> <ul style="list-style-type: none">• A patient is taking immediate release morphine sulphate 10mg every four hours.• This means that they are taking 60mg of morphine sulphate in 24 hours.• The patient can be commenced on morphine sulphate 30mg twice daily, if using a 12 hourly preparation

**** This conversion is by way of example. Individualised titration is always recommended and is dependent on clinical assessment.***

Table 6 of the DOH_Ireland 2015 guideline

Table 7 Titration using modified release oral preparations

Titration Using Modified Release Oral Preparations (using oral morphine sulphate as an example)
<ul style="list-style-type: none">• Use a modified release preparation, such as a 12 hourly morphine sulphate preparation (e.g. MST®) prescribed twice daily. Co-prescribe an immediate release oral morphine sulphate preparation, to be taken as often as required as a breakthrough dose. See section 2.3.2.2 on appropriate dosage for breakthrough pain prescribing.• After 24 hours, assess the effectiveness of the regimen based on clinical assessment of the patient and calculation of the number of breakthrough analgesic doses required. Titrate the modified release formulation accordingly <p>For example*</p> <ul style="list-style-type: none">• A patient is taking modified release oral morphine sulphate 15mg bd (e.g. MST 15mg bd) and has required 4 breakthrough doses of immediate release oral morphine sulphate 5mg• This means the patient has taken 50mg of morphine sulphate in 24 hours• The patient's modified release oral morphine sulphate should be titrated to 25mg twice daily (also adjust breakthrough dose)• A further assessment of pain and potential dose titration is made after a further 24 hours, and so forth.

Table 7 of the DOH_Ireland 2015 guideline

Alternative routes of administration of opioids

Parenteral routes of opioid administration

- Subcutaneous and intravenous routes may be used where the oral route is not feasible. (recommendation category A)

- The average relative potency ratio of oral morphine sulphate to subcutaneous or intravenous morphine sulphate is between 2:1 and 3:1, with variability between patients. (recommendation category C)

Intravenous infusions of morphine sulphate may be preferred to subcutaneous infusions in patients:

- Who already have an indwelling intravenous line or port system
- With generalised oedema
- Who develop erythema, soreness or sterile abscesses with subcutaneous administration
- With coagulation disorders
- With poor peripheral circulation.

Intravenous administration

Radbruch et al (2011) conclude that both the subcutaneous and intravenous routes are feasible, effective and safe. The intravenous route may be preferable where rapid titration of analgesia in cases of severe uncontrolled pain is required. However, due to the lower risk of complications, the subcutaneous route is generally preferred.

Use of continuous infusions

Indications for the use of continuous infusion include:

- Intractable vomiting
- Severe dysphagia
- Patient too weak to swallow oral medication
- Decreased level of consciousness
- Poor gastrointestinal absorption
- Poor patient compliance.

Transdermal opioids

Key finding

Transdermal fentanyl and buprenorphine patches are valid alternative delivery systems for patients with **stable** pain who require regular opioid analgesia.

- Use of the transdermal route is suitable for patients who have **stable** pain. Patients should be titrated to adequate pain relief with oral or parenteral opioid pain medications prior to the initiation of transdermal patches. Medication for breakthrough pain should also be prescribed. (recommendation category D)

Both fentanyl and buprenorphine are strong opioids that can be administered via transdermal preparations.

...Those studies where the same drug was used but administered through different routes support the finding that efficacy and tolerability are similar between the transdermal route and other routes of opioid administration.

Local symptoms at the application sites of transdermal opioids are reported, such as localised erythema (3 to 27.3%) and pruritis (3.7 to 24.8%). Transdermal absorption may be impaired in cachectic patients.

Transdermal fentanyl

Transdermal fentanyl is effective and well tolerated for the treatment of chronic pain caused by malignant and non-malignant conditions, when administered according to the manufacturer's recommendations. Transdermal fentanyl is a useful analgesic for cancer patients who have stable pain and who are unable to swallow or have gastrointestinal problems. The 72-hour transdermal fentanyl patch forms a depot within the upper skin layers before entering the microcirculation. Therapeutic blood levels are attained 12-16 hours after patch application and decrease slowly with a half-life of 16-22 hours following removal. Patients with chronic pain should be titrated to adequate relief with short-acting oral or parenteral opioids prior to the initiation of transdermal fentanyl, in order to prevent exacerbations of pain or opioid-related adverse effects. Transdermal fentanyl can then be initiated based on the 24- hour opioid requirement, once adequate analgesia has been achieved.

Fentanyl is evenly distributed throughout a drug-in-adhesive matrix, and the release of fentanyl is controlled by the physical characteristics of the matrix. Therefore, it is possible to cut patches with a matrix formulation in half. The administration of half a patch is unlicensed, although the practice is common in clinical settings. The second half of the patch cannot be kept for future use and it must be disposed of immediately and appropriately.

The most accepted approach to commencing transdermal fentanyl is as follows:

- *Calculate the previous 24-hour analgesic requirements*
- *Convert this amount to the equianalgesic oral morphine sulphate dose*
- *Determine the corresponding transdermal fentanyl dose*
- *Initiate treatment using this recommended dose and titrate dosage upwards (no more frequently than every 3 days) until analgesic efficacy is attained.*

There have been several case reports in the literature documenting withdrawal syndromes associated with conversion from oral opioids to transdermal fentanyl. This is due to a 'lag phase' after commencing transdermal fentanyl before which therapeutic concentrations are achieved. This may be as long as 12-18 hours after the initial patch is applied. The SIGN guidelines outline an approach to minimise the risk of this as follows:

When converting from an oral strong opioid to transdermal fentanyl (72 hour patch):

- *if taking 4 hourly oral opioid, continue for 12 hours after applying transdermal patch*
- *if taking 12 hourly oral opioid, give the last dose when the first transdermal patch is applied*
- *for a patient receiving opioids via CSCI, apply the patch and continue the syringe driver for 6 hours after application.*

Medication for breakthrough pain should also be prescribed

Transdermal buprenorphine

When titrating a buprenorphine patch, much like the fentanyl patch, there is a lag phase after the initial application. It can take 12-24 hours for the buprenorphine patch to reach minimal effective concentration.

Transmucosal opioids

Opioid administration via the buccal, sublingual or nasal mucosa as an alternative route of administration was examined systematic review by Radbruch et al (2011). Whilst morphine sulphate's absorption is unpredictable by these routes, highly lipophilic drugs such as fentanyl and buprenorphine can be rapidly absorbed and many new therapeutic systems for transmucosal opioid delivery have been developed in recent years. However, these new systems are indicated only for the treatment of breakthrough pain, and their role in the treatment of continuous pain is limited. Rectal administration of opioids such as morphine sulphate or methadone is not commonly practiced in Ireland, but can be used effectively. Similar efficacy and tolerability with subcutaneous or intravenous application has been described.

Topical (transcutaneous) opioids

Key finding

There is limited evidence to support the use of topical opioids in the management of painful malignant skin and mucosal lesions.

- **Whilst there is support for the use of topical opioids, there is insufficient evidence to make clear recommendations for clinical practice in terms of the ideal opioid to use, starting dose, interval of administration, method of titration, carrier agent or most suitable wounds for this treatment. (recommendation category D)**

The management of painful skin and mucosal lesions presents a therapeutic challenge. The effective use of systemic opioids for such conditions can be complicated by unpredictable bioavailability of the drug within the wound microenvironment, largely due to impaired circulation. These limitations, and the identification of peripheral opioid receptors, have triggered an interest in exploring alternative routes of analgesia, such as topical application.

LeBon et al (2009) performed an extensive systematic review in order to appraise the evidence for such an approach.

Nineteen articles were included in the review, comprising six RCTs and thirteen case reports. Whilst there is support for the use of topical opioids, due to the wide heterogeneity of the studies the authors were unable to make clear recommendations for clinical practice in terms of the ideal opioid to use, starting dose, interval of administration, methods of titration, carrier agent or most suitable wounds for this treatment.

Spinal opioids

Key finding

Spinal opioid therapy may be effective for treating cancer pain where systemic treatment has failed, either due to intolerable side-effects or inadequate analgesia.

- **Available evidence is of low quality and thus only weak recommendations for use of spinal opioids alone or in combination with other drugs can be made. Administering opioids and other medications via spinal delivery systems requires the input of an appropriately qualified specialist. (recommendation category D)**

For more information see “Opioid formulations and route of administration”.

Breakthrough pain

Key finding

Breakthrough pain is common and can have a negative impact on quality of life.

Patients should have breakthrough medication prescribed and this dose should be titrated according to the individual and to the type of breakthrough pain being experienced.

There is a lack of strong evidence to favour one product over another, and choice of drug is likely to come down to drug availability physician familiarity, and patient characteristics. Further studies are required in this area, in particular head to head studies comparing different formulations using validated assessment tools.

- **Breakthrough pain can be effectively managed with either oral immediate release opioids, or buccal/sublingual/intranasal fentanyl preparations.**

More than four episodes of breakthrough pain a day indicates that the current management of the baseline/persistent pain should be reviewed.

As breakthrough pain can vary in severity, duration, aetiology and pathophysiology, it is likely that the required dose will vary and individualised titration for both oral and transmucosal rescue opioids is recommended. (recommendation category A)

Best Practice Point

The dose of breakthrough opioid can be calculated as either:

1/6 of the total 24hr dose (most commonly used calculation)

or,

10%-20% of the total 24hr dose

EXCEPT where fast acting fentanyl preparation are being prescribed. Here, the rescue (breakthrough) dose is independent of the background opioid analgesic dose. Start at lowest available strength, and titrate according to manufacturer's guidance.

There has been lack of consensus in the literature on a formal definition, leading to difficulties when comparing studies and recommending management strategies.

Payne (2007) describes three types of breakthrough pain:

-Incident pain: This is pain that is associated with movement (voluntary or involuntary)

-Idiopathic or spontaneous pain: This has no identifiable cause and tends to last longer than incident pain

-End of dose failure: This occurs prior to the next scheduled dose of analgesia and is often not regarded as true breakthrough pain.

It is important to discern the pattern of the breakthrough pain, as the management may alter accordingly. For example, end of dose failure may be treated by upward titration of the background analgesia, whereas incident pain may be treated by an anticipatory dose of breakthrough analgesia.

The management of breakthrough pain involves the following approaches:

1. Optimise background 'around-the-clock' analgesia

2. Non-pharmacological management:

-Implementing primary therapies: Surgery, radiotherapy and chemotherapy

-Non-pharmacological therapies: These include avoidance of factors known to precipitate pain, engagement in physical therapy, education about physical limitations and exacerbating factors, and patient counselling to reduce anxiety.

3. Pharmacological management:

Patients require continued access to a rescue dose to treat 'breakthrough' pain, as enshrined in the WHO cancer pain framework. It is important to tailor management for the type of breakthrough pain being experienced.

- Pain episodes of uncontrolled background pain should be treated with additional doses of normal release oral formulations

- Incident pain: Treating incident pain involves the pre-emptive use of a shortacting opioid 30 minutes before the precipitating activity

- Idiopathic/ spontaneous: The peak intensity for this type of pain can occur in 3-5 minutes and episodes usually last for under 30 minutes. Therefore, analgesics with a delayed onset are not helpful for this type of pain

- End of dose failure: For end of dose failure, there is a need to alter the around the clock medication to increase the dose or shorten the dosing interval.

Treatment of breakthrough pain

The usual approach to the management of breakthrough pain has been to use supplemental doses of oral immediate release opioids ('rescue' medication), based on the patient's background analgesia, given before or soon after breakthrough pain has started. Traditionally, two approaches were favoured:

- Use of the equivalent four-hourly dose for rescue medication, with subsequent increases or decreases according to clinical effect (this is one sixth of the daily dose)

- Use of short-acting opioid rescue doses of between 10%–20% of the 24 hour oral dose (mg) every 1 hour, as needed.

Breakthrough pain can be effectively managed with either oral immediate release opioids, or buccal/sublingual/intranasal fentanyl preparations. More than four episodes of breakthrough pain a day indicates that the current management of the baseline/persistent pain should be reviewed.

Transmucosal fentanyl preparations

In recent years, a number of transmucosal preparations have been developed specifically to target breakthrough pain. ... Most studies examining the efficacy of transmucosal fentanyl found no correlation between the background opioid dose and the transmucosal or oral rescue doses. As breakthrough pain can vary in severity, duration, aetiology and pathophysiology, it is likely that the required dose will vary and individualised titration for both oral and transmucosal rescue opioids is

recommended. There is a lack of strong evidence to favour one product over another, and choice of drug is likely to come down to drug availability, physician familiarity, and patient characteristics.

Opioid side-effects

- **It is important to anticipate and monitor patients for opioid side-effects and manage these at the earliest opportunity to prevent unnecessary morbidity. (recommendation category D)**
- **The current evidence is too limited to provide evidence-based recommendations for the use of anti-emetics in opioid-induced nausea/vomiting in cancer patients. Choice is therefore based on knowledge of aetiology and expert opinion. (recommendation category D)**
- **In the management of opioid-induced constipation, the combination of a softener and stimulant laxative is generally recommended, and the choice of laxatives should be made on an individual basis. (recommendation category D)**
- **The use of peripheral opioid receptor antagonists (methylnaltrexone) should be restricted to those patients whose treatment is resistant to traditional laxatives. (recommendation category D)**

Dry mouth

Anderson et al (2004) reported that dry mouth is the most common adverse effect of opioids. Concomitantly, many patients may be on other medications that have anticholinergic properties, worsening this symptom. All patients should be educated on the need for, and methods to achieve, good oral hygiene. Frequent administration of oral saliva replacement gels may be helpful.

Nausea and vomiting

Up to 40% of cancer patients with no prior emesis may experience opioid-induced nausea and/or vomiting.

Opioid induced nausea and vomiting mostly occurs on initiation of treatment and tends to subside within 3-5 days. Therefore, it is important to have an anti-emetic available for the patient as needed, especially when commencing opioid treatment.

Constipation

Chronic constipation has been observed in 20-70% of patients treated for chronic cancer pain. Whilst general principles of prevention should be followed, pharmacological treatment is often necessary. More recently, peripheral opioid antagonists such as methylnaltrexone have been introduced for the treatment of opioid-induced constipation (e.g. Relistor®).

The use of subcutaneous methylnaltrexone should be restricted to those patients whose treatment is resistant to traditional laxatives. Combination medications of oral opioids with oral naloxone (e.g. Targin®) have been introduced as a strategy for reducing the incidence of opioid-induced constipation.

Oxycodone combined with Naloxone has been shown to be effective and safe in doses up to 120mg per day and be equianalgesic to oxycodone alone and result in patients using 20% less rescue laxative medication, however studies in cancer patients are limited as are comparisons with strong opioids other than oxycodone. Guidance on the management of constipation in cancer is available in the National Clinical Guideline No 10 Management of Constipation in Adult Patients Receiving Palliative Care.

Respiratory depression

One of the most serious complications of opioid therapy is potential respiratory depression. It rarely occurs in cancer pain management. It is more likely to occur at initiation of therapy, at dose titration, or after opioid switching, especially to methadone.

Neuropsychological opioid side-effects

Key finding

Opioids may cause neuropsychological side-effects, such as sedation, cognitive dysfunction, sleep disturbance, myoclonus, hyperalgesia and delirium. Delirium is a frequent, multi-factorial complication in advanced cancer. Delirium precipitated by opioids is frequently reversible.

- **Opioid reduction or rotation should be considered as a useful strategy to manage opioid side-effects. (recommendation category B)**
- **Given the present available knowledge, no recommendation can be made for or against the use of specific drugs for the relief of opioid-induced myoclonus, sleep disturbance or hyperalgesia. (recommendation category D)**
- **The treatment of delirium firstly involves the search for an identifiable underlying cause and the treatment of this cause. (recommendation category B)**
- **Haloperidol may be recommended for those patients experiencing agitation, hallucinations and perceptual disturbances. Opioid reduction or rotation should be considered. (recommendation category D)**

In a prospective study of 40 patients receiving intermittent narcotic analgesics, Bruera et al (1989) reported that defects in formal cognitive testing occur, particularly on initiation of opioid therapy and in association with dose increments of at least 30%. Cognitive impairment was reported to disappear within one week of the dose increment. The actual patient distress associated with mild cognitive deficits is uncertain, however sedation may be a prelude to the development of delirium and more florid neurotoxicity. Sedation and respiratory depression tend to occur on a continuum. Therefore it is important to monitor patients exhibiting sedation as a result of opioid therapy. This is most likely to occur on initiation of opioids or after dose titration.

... Methylphenidate may have a role for the management of opioid-induced sedation in patients for whom opioid dose reduction or rotation is impractical or inappropriate.

Given the present available knowledge, no recommendation can be made for or against the use of specific drugs for the relief of opioid-induced myoclonus, sleep disturbance or hyperalgesia.

Delirium

...This study found that delirium is a frequent, multi-factorial complication in advanced cancer. Despite its terminal presentation in most patients, delirium is reversible in approximately 50% of episodes. Delirium precipitated by opioids and other psychoactive medications, and dehydration, is frequently reversible with change of opioid or dose reduction, discontinuation of unnecessary psychoactive medication, or hydration, respectively.

The treatment of delirium firstly involves the search for an identifiable underlying cause and the treatment of this cause (for example sepsis, hypercalcaemia, uraemia). Although no studies have assessed the use of most commonly used interventions such as haloperidol in the management of opioid-induced cognitive impairment, a large body of literature attests to its effectiveness for the treatment of agitated delirium in other patient groups, or in delirium caused by other factors. Thus, haloperidol may be recommended for those patients experiencing agitation, hallucinations and perceptual disturbances. Other side-effects of opioids include pruritis, sweating, micturition disturbance and vertigo.

Other side-effects of opioids include pruritis, sweating, micturition disturbance and vertigo.

For the risk of opioid dependence: see “opioids and substance use disorder”.

Opioid toxicity

Key finding

Opioid toxicity may present as subtle agitation, drowsiness, seeing shadows at the periphery of the visual field, vivid dreams, hallucinations, confusion and myoclonic jerks. If untreated, this may progress towards respiratory depression.

- **If toxicity is experienced on a stable dose of an opioid which has been previously tolerated, other factors should be sought and treated such as infection, dehydration, renal impairment or hypercalcaemia. (recommendation category D)**

There is a wide variation in the dose of opioid that is toxic, both between individuals and over time. The ability to tolerate a particular dose depends on the degree of responsiveness of the pain to opioids, prior exposure to opioids, rate of titration of opioids, concomitant medication and renal function. Toxicity can be a frightening and even life threatening experience, but is usually reversible. Opioid toxicity may present as subtle agitation, drowsiness, seeing shadows at the periphery the visual field, vivid dreams, hallucinations, confusion and myoclonic jerks. If untreated, this may progress towards respiratory depression.

Patients may develop toxicity on titration of opioids however, toxicity may occur in patients who are relatively stable on long term opioid therapy. This is known as ‘late opioid toxicity’. Much of this can be explained by the role of morphine sulphate and its metabolites. Morphine sulphate is metabolised in the liver to the active metabolites morphine sulphate-3-glucuronide (M3G) and morphine sulphate-

6-glucuronide (M6G). M6G, which binds to opioid receptors, contributes significantly to the analgesic effect of morphine sulphate and can cause nausea and vomiting, sedation and respiratory depression. Symptoms mediated via M3G are impaired cognitive function, myoclonus, seizures and hyperalgesia. These morphine sulphate metabolites may accumulate secondary to dehydration, impaired renal function, sepsis, hepatic disease and age, as well as the chronic administration of medicines that could inhibit morphine sulphate metabolism by glucuronidation in the liver, such as benzodiazepines and barbiturates.

Management of opioid toxicity

Best Practice Point: Management of opioid toxicity

Renal and hepatic function should be checked and other causes of systemic deterioration excluded e.g. infection, hypercalcaemia. Any reversible precipitating cause should be treated.

Mild opioid toxicity: In mild opioid toxicity; reduce the dose of opioid. Ensure adequate hydration and treat any underlying cause. If agitation/confusion are problematic, consider a neuroleptic such as haloperidol.

Moderate opioid toxicity: If respiratory rate $\geq 8/\text{min}$, oxygen saturations are normal and the patient is not cyanosed and is easily rousable, omit the next dose (or stop infusion/remove patch) of regular opioid immediately, and adopt a 'wait and see' approach. When the situation is more stable, either omit or reduce further doses and re-assess pain before re-introducing regular opioid therapy.

Severe opioid toxicity: If respiratory rate is $8/\text{min}$ or less, oxygen saturations are abnormal or the patient is cyanosed, urgent admission is indicated. Consider reversal of respiratory depression using naloxone; use reversing agents cautiously. The aim is to reverse respiratory depression without compromising pain control. This may not fully reverse sedation. The patient's background analgesia will subsequently need to be reviewed. Seek specialist palliative medical advice for continuing problems, particularly if transdermal patches have been used.

Use of naloxone for reversal of opioid side-effects

(Palliative Adult Network Guidelines 2011 (19), based on the recommendations of the American Pain Society)

If the patient's respiratory rate is $< 8/\text{min}$, the patient is barely rousable/unconscious and/or is cyanosed:

- Dilute a standard ampoule containing naloxone 400 micrograms to 10ml with sodium chloride 0.9% for injection.
- Administer 0.5ml (20micrograms) IV every 2 minutes, until the patient's respiratory status is satisfactory
- Further boluses may be necessary because naloxone is shorter-acting than morphine sulphate and other opioids

Close observation is needed to ensure that the patient is breathing satisfactorily and that pain control is maintained.

If using naloxone, seek specialist advice for management of opioid side-effects and for ongoing cancer pain management.

5.2.9 KCE 2013

Opioids have been used for thousands of years for the treatment of pain (Trescot 2008). Based on their analgesic potency, they have traditionally been classified as weak or strong opioids, however this classification is currently often replaced by the one used in the WHO analgesic ladder. In the WHO

ladder, opioids are divided in those that are used for mild to moderate pain (WHO Step II), and those that are used for moderate to severe pain (WHO Step III).

Examples of WHO Step II opioids include codeine, dihydrocodeine and tramadol, these opioids are characterized by the existence of a ceiling effect implying that escalating the dose beyond a certain level does not increase the analgesic effect anymore. Examples of WHO Step III opioids are morphine, hydromorphone, oxycodone, methadone, fentanyl, buprenorphine (Martindale 2009); typical for these opioids is that their effect increases with dose and that dose increase is only limited by the appearance of hyperalgesia. However, some opioids of this class also exhibit a ceiling effect due to their specific pattern of opioid receptor stimulation.

The most frequent reason for opioid treatment failure is that a dose increase necessary to control pain is limited by intolerable side effects. In usual doses, the commonest adverse effects of opioid analgesics are nausea, vomiting, constipation, drowsiness, and confusion; tolerance to these (except to constipation) generally develops with long term use (Martindale 2009). Constipation should be prevented by the systematic use of laxatives. Other frequent side effects are itching, dry mouth, and myoclonus (at high doses) (Dutch Guideline on cancer pain 2008). The euphoric activity of opioids has led to their abuse. Larger doses of opioids typically produce respiratory depression, which can be life-threatening. Other side effects are difficulties with micturition, an antidiuretic effect, miosis, dizziness, headache, etc.; for a complete overview the reader is referred to standard pharmacological textbooks.

Pharmacological tolerance for an opioid refers to the diminishment of opioid effects caused by repeated exposure to the drug, requiring larger doses to sustain the analgesic effect (Wiffen 2010). A related phenomenon is cross-tolerance, or the tolerance to one opioid that develops as the result of the continued use of another substance with similar pharmacological action (Visser 2010). In practice, cross-tolerance between opioid analgesics is mostly incomplete, due to differences in pharmacodynamics and receptor interaction between opioids (Visser 2010). This incomplete cross-tolerance is one of the explanations of the success of opioid rotation and the combination of two strong opioids (see further).

During chronic opioid therapy, physiological dependence can cause a withdrawal syndrome upon sudden cessation or upon the administration of an antagonist (Wiffen 2010). Another clinical entity is opioid-induced hyperalgesia, which implies that patients, despite increasing doses of the opioid, experience worsening of pain and abnormal symptoms such as pain due to a stimulus which does not normally provoke pain (Visser 2010). Opioid-induced hyperalgesia typically can arise after opioids have been used for a long time.

The treatment of opioid side effects is beyond the scope of this review. General principles are symptomatic treatment; decrease of the opioid dose, associated or not with the introduction of adjuvant analgesics or other analgesic treatment options; switching to another opioid administration route or to another opioid (opioid rotation, see further) (Dutch Guideline on cancer pain 2008).

Pharmacologically, the opioid analgesics are broadly similar but qualitative and quantitative differences are derived from their complex interaction with three main opioid receptor types: mu (μ); kappa (κ); and delta (δ). Other types of opioid receptors have been recognized as well, e.g. sigma (σ); their role remains less well understood. Opioids act at one or more of these receptors. In addition to different affinities for particular receptors, the degree of activation (or efficacy) once bound also differs (Martindale 2009). A full agonist has both affinity for and efficacy at a receptor; an antagonist

has affinity for but no efficacy at a receptor while a partial agonist has affinity, but only partial efficacy (Trescot 2008). The full agonist morphine produces maximum activation at the mu-opioid receptor and its effect increases with dose; dose increase is only limited by the appearance of hyperalgesia. The same holds true for hydromorphone, oxycodone, fentanyl and methadone (Sarzi-Puttini 2012). Partial agonists (also called agonist-antagonists) may demonstrate a ceiling effect in that above a certain dose their effects do not increase proportionally with dose, e.g. buprenorphine (Martindale 2009).

Some opioid analgesics have mixed working mechanisms, exhibiting an additional affinity for non-opioid receptors involved in analgesia (e.g. the Nmethyl-D-aspartate (NMDA) receptor) or involved in related central nervous system pathways (e.g. the neuronal reuptake of norepinephrine and serotonin).

An overview of opioid molecules and their main interaction mechanisms with the opioid receptors is given in Table 13.

Other differences between opioid analgesics may relate to their lipid solubility and pharmacokinetics, speed of onset and duration of action may influence the choice of analgesic (Martindale 2009).

- **The principles of treatment outlined in the WHO analgesic ladder should be followed when treating pain in patients with cancer (very low level of evidence; strong recommendation).**

1. Cancer pain can, and should, be treated.

2. Evaluation and treatment of cancer pain are best achieved by a team approach.

3. The first steps are to take a detailed history, and to examine the patient carefully, to determine if the pain is:

- *Caused by the cancer, related to the cancer, caused by anticancer treatment or caused by another disorder;*
- *Part of a specific syndrome;*
- *Nociceptive, neuropathic, or mixed nociceptive and neuropathic.*

4. Treatment begins with an explanation and combines physical and psychological approaches, using both non-drug and drug treatments.

5. It is useful to have a sequence of specific aims, such as:

- *To increase the hours of pain-free sleep;*
- *To relieve the pain when the patient is at rest;*
- *To relieve pain when the patient is standing or active.*

6. Drugs alone usually give adequate relief from pain caused by cancer, provided that the right drug is administered in the right dose at the right time intervals.

7. 'By mouth': the oral route is the preferred route for analgesics, including morphine.

8. 'By the clock': for persistent pain, drugs should be taken at regular time intervals and not 'as needed'.

9. 'By the ladder':

- *Unless the patient is in severe pain, begin by prescribing a nonopioid drug and adjust the dose, if necessary, to the maximum recommended dose.*
- *If or when the non-opioid no longer adequately relieves the pain, an opioid drug should be prescribed in addition to the nonopioid.*

- *If or when the opioid for mild to moderate pain (e.g. codeine) no longer adequately relieves the pain, it should be replaced by an opioid for moderate to severe pain (e.g. morphine).*

10. *'For the individual': the right dose of an analgesic is the dose that relieves the pain. The dose of oral morphine may range from as little as 5 mg to more than 1000 mg.*

11. *Adjuvant drugs should be prescribed as indicated.*

12. *For neuropathic pain, a tricyclic antidepressant or an anticonvulsant is the analgesic of choice.*

13. *'Attention to detail': it is essential to monitor the patient's response to the treatment to ensure that the patient obtains maximum benefit with as few adverse effects as possible.*

- **The available evidence does not allow to draw firm conclusions on the comparison of analgesic effect or short term side-effects between NSAIDs, and WHO step II or step III opioids in the treatment of moderate to severe cancer pain. Therefore it is not possible to recommend on whether a NSAID or a Step II or Step III opioid should be recommended as first-line treatment option for moderate to severe cancer pain (very low level of evidence).**
- **If paracetamol/NSAIDs no longer adequately relieve(s) the pain, an opioid drug should be considered. In line with the principles of the WHO analgesic ladder, weak opioids (Step II) should be considered in the management of mild to moderate cancer pain after conventional treatment with paracetamol/NSAIDs failed, and patient outcomes should be monitored (very low level of evidence; strong recommendation). This is based on the following evidence. There is conflicting evidence as to the question whether combining a NSAID or paracetamol with a WHO step II opioid is superior to a NSAID or paracetamol alone in patients with cancer pain (very low level of evidence). There are indications that oral codeine and tramadol are effective and well-tolerated drugs as compared to placebo in the management of mild to moderate cancer pain never treated with opioids (low level of evidence).**
- **There are indications that initiating strong opioids (Step III) instead of weak opioids (Step II) for mild to moderate cancer pain after conventional treatment with NSAIDs and/or paracetamol failed, leads to better pain control but at the cost of more side effects (very low level of evidence).**
- **There are indications that NSAIDs as add-on to WHO step III opioids in comparison to step III opioids alone for mild or moderate to severe cancer pain offer no advantage or offer a low clinical advantage (<25% difference) only. It is not possible to draw firm conclusions from the literature on the comparison of short term adverse events in both groups. Therefore the use of NSAIDs as add-on to a stabilized regimen of WHO step III opioids should not be considered as a routine treatment option (very low level of evidence; weak recommendation).**
- **There are indications that paracetamol as add-on to a stabilized regimen of WHO step III opioids for mild cancer pain shows no difference in pain relief as compared to the step III opioids alone. Therefore the use of paracetamol as add-on to a stabilized regimen of WHO step III opioids should not be considered as routine treatment (very low level of evidence; strong recommendation).**

As previously discussed, the WHO ladder approach can help to manage cancer pain for the vast majority of cancer patients, by assisting physicians in the selection of medications according to the level of pain intensity. However, Miguel et al. (2000) proposed a fourth step in the WHO analgesic ladder to address those patients who cannot reach pain relief with the proposed drug scheme, or those who develop undesirable or intolerable side effects. The fourth step consists in 'interventional' procedures including spinal administration of drugs; neurostimulation of the spinal cord, the brain or peripheral nerves; or neuro-ablation including peripheral nerves, visceral block of plexus celiacus or plexus hypogastricus, or other neural structures. Before implementing these invasive analgesic methods as proposed in the Step IV, the risk/benefit ratio should be considered (Miguel 2000).

Table 13 – Comparison among opioids for mild-moderate and severe pain*

Opioid	Main mode of action	Precaution	Typical starting dose (orally) (Leppert (2011) ⁵⁸)
Tramadol	μ-Opioid receptor agonist, 5HT- and NOR-reuptake blocker	Nausea should be prevented by antiemetics; analgesia impaired in CYP2D6 poor metabolizers	25–50 mg q 4–6 h (IR); 50–100 mg q 12 h (CR)
Codeine	μ-Opioid receptor agonist	Constipation should be prevented by laxatives; should not be administered in CYP2D6 ultrarapid metabolizers	30 mg q 4–6 h (IR); 60 mg q 12 h (CR)
Morphine	μ-Opioid receptor agonist	Active metabolites may accumulate and cause adverse effects in renal failure	5–10 mg q 4 h (IR); 20–30 mg q 12 h (CR)
Fentanyl	μ-Opioid receptor agonist	Fever may increase absorption; should not be used for quick dose titration (unstable pain)	One patch 25 μg/h q 72 h; 12.5 μg/h q 72 h for older patients with liver or hepatic impairment
Oxycodone	μ- and κ-Opioid receptor agonist	May accumulate in renal failure	5 mg q 4–6 h (IR); 10–20 mg 12 h (CR)
Buprenorphine	Partial μ-Opioid receptor agonist, weak κ-opioid receptor antagonist	Fever may increase absorption; should not be used for quick dose titration (unstable pain)	One patch 35 μg/h q 84 h; 17.5 μg/h q 84–96 h for older patients with liver or hepatic impairment
Hydromorphone	μ-Opioid receptor agonist	Parent compound and metabolites may accumulate in renal failure	1–2 mg q 4 h (IR); 2–4 mg q 12 h (CR)
Methadone	μ - and δ-Opioid receptor agonist, NMDA-receptor antagonist, NOR- and 5HT-reuptake blocker	Possible QT interval prolongation; numerous drug interactions; long plasma half-life	3–5 mg q 8 h

Source: adapted from Leppert (2011)⁵⁸ - CR controlled-release (i.e. slow release) formulations; IR immediate-release formulations; q every; NOR noradrenaline; 5HT serotonin; NMDA N-methyl-D-aspartate receptors; CYP2D6 cytochrome P450 2D6. - *Note: Typical starting doses for oral opioids can differ slightly from one publication to another. For further information on oral opioid starting doses, see 4.3.1.1.3.1. - *Note: for availability of molecules on the Belgian market, see Table 14.

- Strong interindividual differences in response to opioids are a well-known clinical phenomenon, underpinned by recent scientific insights in genetic variation in opioid metabolism. Therefore, all opioids should be titrated according to individual analgesic response and occurrence of side-effects (very low level of evidence; strong recommendation).
- Based on clinical experience, oral delivery of opioids is effective and simple. Therefore, the oral route should be used for the administration of opioids, if practical and feasible. However, depending on the evolution of the patient's condition and taking into account his/her preferences, the route of administration should be adjusted dynamically and transdermal, subcutaneous, or intravenous opioid administration should be considered. Rarely, intrarectal, intramuscular or intraspinal administration can be considered. Slow release oral opioids cannot be administered by gastric tube since it is not allowed to crush these formulations. However, one slow release oral formulation is an exception since the capsules have been specifically developed to be opened although they should not be crushed (slow release hydromorphone: Palladone Slow Release®) (very low level of evidence; strong recommendation).

Weak opioids

- If paracetamol/NSAIDs no longer adequately relieve(s) the pain, an opioid drug should be considered. In line with the principles of the WHO analgesic ladder, weak opioids (Step II) should be considered in the management of mild to moderate cancer pain after conventional treatment with paracetamol/NSAIDs failed, and patient outcomes should be monitored (very low level of evidence; strong recommendation). This is based on the following evidence. There is conflicting evidence as to the question whether combining a NSAID or paracetamol with a WHO step II opioid is superior to a NSAID or paracetamol alone in patients with cancer pain (very low level of evidence). There are indications that oral codeine and tramadol are effective and well-tolerated drugs as compared to placebo in the management of mild to moderate cancer pain never treated with opioids (low level of evidence). There are indications that initiating strong opioids (Step III) instead of weak opioids (Step II) for mild to moderate cancer pain after conventional treatment with NSAIDs and/or paracetamol failed, leads to better pain control but at the cost of more side effects (very low level of evidence).
- When weak opioids are considered in the management of mild to moderate cancer pain after conventional treatment with paracetamol/NSAIDs failed, codeine and tramadol can be considered as equivalent treatment options, and the choice for one of them should depend on the tolerance of each individual patient (very low level of evidence; weak recommendation). This is based on the following evidence. There are indications that there is no difference in efficacy between tramadol and codeine combined with paracetamol (low level of evidence). RCTs directly evaluating other combinations of weak opioids against each other are not available for this indication.

Strong opioids

- Oral morphine should be considered as the drug of first choice and the gold standard for moderate to severe cancer pain (very low level of evidence; strong recommendation). This is based on the following evidence. There are indications that the effectiveness of oral morphine in the treatment of cancer pain compares well to other available strong opioids (oxycodone, hydromorphone, methadone) when titration to effect is performed (very low level of evidence). There are indications that for oral morphine treatment side effects are common, but that intolerable adverse effects occur in a small number of patients only (4%) and that non-response is infrequent (very low level of evidence).
- Depending on the tolerability of each individual patient, other oral strong opioids in their equi-analgesic dose can be considered as an alternative to oral morphine in the first-line treatment of moderate to severe cancer pain. Likewise, transdermal fentanyl, in an equi-analgesic dose, can be used as an alternative to oral opioids for moderate to severe cancer pain, after a stable opioid regimen has been established (very low level of evidence; strong recommendation). This is based on the following evidence. There are indications that oral morphine, oral oxycodone, oral hydromorphone and transdermal fentanyl, when titration to effect is performed, have a similar efficacy and toxicity in cancer-related pain (very low level of evidence).
- It is not possible to draw conclusions from the literature on the relative efficacy and side-effects of transdermal buprenorphine as compared to oral morphine, to other oral opioids or to transdermal fentanyl for moderate to severe cancer pain. Based on its pharmacological properties and mixed working mechanism, oral² or transdermal buprenorphine might be considered as a treatment option (very low level of evidence; weak recommendation).
- It should be considered to restrict the initiation of a treatment with methadone for analgesic purposes (such as in cancer patients with moderate to severe pain) to medical experts in pain treatment or palliative care. Once optimal dosage has been identified, maintenance treatment can be carried out by another physician (very low level of evidence; strong recommendation). This is based on the following evidence. The pharmacological properties of methadone suggest that it might be useful in the treatment of neuropathic pain. However, based on the available evidence it is not possible to conclude on the superiority of methadone to morphine in patients with neuropathic cancer pain (very low level of evidence). There are indications that oral methadone and morphine have a similar efficacy in the treatment of nociceptive or mixed types of moderate to severe cancer pain (very low level of evidence). Because of its pharmacokinetics and pharmacodynamics, the adverse effects of methadone may become more prominent with repeated dosing. One of its specific although rare adverse effects is prolongation of the QT interval leading to cardiac dysrhythmias, especially at high doses.

² Remark from the reading committee: the term 'oral buprenorphine', as used by this guideline is confusing. There is no 'oral' preparation as such. Sublingual forms are available on the Belgian market. A buccal film is available in other countries.

- Individual patient assessment should determine the appropriate treatment option in cancer patients with neuropathic pain or with a mixed type of pain including neuropathic components, and opioids can be considered alone, or combined with adjuvant analgesics (antidepressants, anticonvulsants) (very low level of evidence; strong recommendation).

Breakthrough cancer pain

- For cancer patients on a stable around-the-clock (ATC) regimen of opioids presenting with breakthrough pain, the first aim should be to optimize the ATC regimen to differentiate between breakthrough pain and end of dose pain (very low level of evidence; strong recommendation).

Breakthrough pain is a transient increase in pain intensity over background pain. It is a common and distinct component of cancer pain that is typically of rapid onset, severe in intensity, and generally self-limiting with an average duration of 30 minutes. Two subtypes of breakthrough pain have been described: incident pain, which is precipitated by factors such as movement and is predictable; and spontaneous pain, which occurs in the absence of a relationship to specific activities, and which is not predictable. It is important to differentiate between breakthrough pain and end of dose failure, the latter resulting from an inadequate analgesic dose or too long an interval between administrations.

- Breakthrough pain in cancer patients on a stable and optimized ATC regimen of opioids can be treated by oral or intranasal fentanyl regardless of which opioid is used for the maintenance therapy³. Although there are indications that oral and intranasal fentanyl might be superior, oral morphine (e.g. as a syrup) can be considered as an effective and cheaper alternative in Belgium (weak recommendation). This is based on the following evidence. For cancer patients on a stable and optimized ATC regimen of opioids, different formulations of oral and intranasal fentanyl are effective and safe as compared to placebo in the treatment of breakthrough cancer pain (low level of evidence). Publications are lacking on the effectiveness and safety in this indication of immediate release oral morphine as well as other forms of oral opioids commonly used for breakthrough pain (oxycodone, hydromorphone). No conclusions can be drawn on whether one form of oral or intranasal fentanyl is superior to another (very low level of evidence). There are indications that oral transmucosal fentanyl citrate and fentanyl pectin nasal spray might be superior to immediate release morphine sulfate (low level of evidence). No conclusions can be drawn on whether one of the other oral opioids is superior to another (very low level of evidence).
- Patients should be informed on the benefits and potential side-effects associated with the use of opioids. Their preferences should be taken into account when deciding on the treatment. (good clinical practice)

Initiating opioids: maintenance therapy and treatment for breakthrough pain

³ At the moment (october 2018), an intranasal fentanyl spray is not available on the Belgian market.

Strong interindividual differences in response to opioids are a well-known clinical phenomenon, underpinned by recent scientific insights in genetic variation in opioid metabolism (Dale 2010, Fallon 2011, Portenoy 2011, Dutch Guideline on cancer pain 2008). Therefore, individualisation of the dose is the key to optimisation of the outcomes of opioid treatment, since the optimal dose cannot be determined in advance. Treatment initiation of the selected opioid should be followed by dose titration. This means looking for the optimal dose by progressively increasing (or reducing) the dose until adequate pain control is reached, and taking into account side effects. Titration is also necessary whenever readjustment of the dose is necessitated by worsening pain. The maintenance opioid therapy should be taken 'by the clock', i.e. at pre-defined regular time intervals. Dosing intervals depend in principle on the half-life elimination time of the opioid, and on the opioid formulation (immediate release, slowrelease, transdermal...) (SIGN 2008, Dutch Guideline on cancer pain 2008, Guideline of the MoH Malaysia 2010).

Breakthrough pain is a transient increase in pain intensity over background pain. It is a common and distinct component of cancer pain that can have a significantly negative impact on quality of life. Other terms that are used for breakthrough pain are episodic pain, transient pain etc. Breakthrough pain is typically of rapid onset, severe in intensity, and generally self-limiting with an average duration of 30 minutes (Zeppetella 2009). Two subtypes of breakthrough pain have been described: incident pain, which is precipitated by factors such as movement and is predictable; and spontaneous pain, which occurs in the absence of a relationship to specific activities, and which is not predictable. It is important to differentiate between breakthrough pain and end of dose failure, which results from an inadequate analgesic dose or too long an interval between administrations; this type of pain can be addressed by adjusting the maintenance (around-the-clock, ATC) dose. The current management for breakthrough pain is 1. optimising ATC pain medication using the WHO ladder, to differentiate between breakthrough pain and end-of-dose pain; and 2. Specific pharmacological interventions for the pain such as supplemental analgesia (also known as rescue medication). Rescue medication is best administered before or soon after breakthrough pain has started, and ideally the medication should have a rapid onset, and a short duration of action (Zeppetella 2009). By their nature, rescue doses are given 'on demand', rather than 'by the clock'. Rescue doses should be prescribed proactively from the start of the maintenance treatment with opioids, as breakthrough pain may occur at any moment.

By way of illustration, information on a typical starting dose for oral administration of some opioids in an opioid-naïve patient is given in Table 13 (based on Leppert 2011). Typical starting doses for oral opioids differ slightly from one publication to another. Conventional practice is to start with a formulation that is active during 4 to 6 hours, rather than with a slowrelease formulation. This should allow background pain to be controlled more rapidly. It allows also easier titration up and down. The around-the-clock opioid formulation used for background pain relief should be supplemented by a short-acting opioid (the rescue medication) for episodes of breakthrough pain, typically at 1/12th to 1/6th of a normal daily dose of the ATC opioid. The analgesic effect of the initial ATC opioid dose can be evaluated after 4-5 times the half-life elimination time of the opioid preparation used; typically 24 hours for morphine, hydromorphone and oxycodone, and 48h for transdermal fentanyl. If the pain persists, the dose is typically increased by 25-50% for moderate pain intensity; and by 50 to 100% for severe pain; however, dose escalation should also take into account the amount of rescue medication that is taken. In conventional practice, the use of 3 to 4 rescue doses within a 24 hour time period is interpreted as a sign that it should be considered to increase the dose of the maintenance opioid therapy by 30%. In case of persisting opioid side effects, the dose can be decreased by 25-50%. It is

beyond the scope of this report to discuss in detail all different aspects of opioid dosing. For further practical considerations on dosing and dosing intervals, dose escalation, or discontinuation of opioids, the reader is referred to reference works, e.g. 'Palliatieve zorg in de praktijk. Zakboekje voor hulpverleners' (2009). Informative peer-reviewed publications are e.g. Vissers 2010, Sarzi-Puttini 2012. For equianalgesic doses, see further.

Equianalgesic opioid doses

The equianalgesic dose of an opioid is the dose that produces equivalent analgesia to the reference compound. Knowledge of this dose is required when there are reasons to administer the same opioid by a different administration route, e.g. parenteral instead of oral administration. In the literature, equianalgesic opioid doses slightly differ between different publications. A second situation is the substitution of one opioid by another (opioid 'rotation'), because of intolerable side effects or poor analgesia despite increasing doses of the first opioid. The success of opioid rotation is based on the fact that cross-tolerance between opioid analgesics is incomplete (Vissers 2010). Because of this incomplete cross-tolerance, the majority of patients needs a lower dosing (conventionally about 33%) than the dose theoretically calculated with an equianalgesic table. For principles underpinning a rational choice of the new opioid during rotation, see Vissers et al. (2010). An example of an opioid equianalgesic table is presented below⁴. An example accompanied by additional practical information can be found in 'Palliatieve zorg in de praktijk. Zakboekje voor hulpverleners' (2009)⁶². For other examples of opioid equianalgesic tables, see Dutch Guideline on cancer pain 2008; Vissers 2010; Sarzi-Puttini 2012. See also Wall and Melzack's Textbook of Pain 2013 (6th edition).

6. EXAMPLE OF OPIOID EQUIANALGESIC TABLE

Morphine		Fentanyl	Oxycodone		Hydromorphone	Tramadol	Buprenorphine
oral	s.c/i.v.	patch	oral	s.c/i.v.	oral	oral	patch
mg/24 hours	mg/24 hours	µg/hour	mg/24 hours	mg/24 hours	mg/24 hours	mg/24 hours	µg/hour
30	10	12	15	7.5	4	150	17.5
60	20	25	30	15	8	300	35
120	40	50	60	30	16	-	70
180	60	75	90	45	24	-	105
240	80	100	120	60	32	-	140
360	120	150	180	90	48	-	-
480	160	200	240	120	64	-	-

Source: adapted from www.pallialine.nl

For rotation from one opioids to another, it is advised to give from $\frac{2}{3}$ to $\frac{3}{4}$ of the equianalgesic dose, because of incomplete cross-tolerance. For further information, the reader is invited to consult the scientific report (see 4.3.1.1.3.).

Inconsistencies in the reporting of conversion ratios make it difficult to interpret results. Moreover, the original equianalgesic tables were based on acute repeated cross-over administration and need to be re-evaluated in the scenario of chronic opioid administration (Mercadante 2011). Therefore, careful interpretation of such tables is mandatory. Further, the proposed opioid dose should be based on a theoretical dose calculation and titrated in accordance with the observed clinical efficacy and the patient's individual characteristics such as age, renal function, side effects etc.

⁴ Tapentadol is a relatively new opioid. It is only recently available in Belgium and is therefore not included in this table, published by the Belgian KCE in 2013.

Morphine

Morphine acts on the central nervous system mainly by strong agonist activity at the mu-opioid receptor, although it also has some minor kappa and delta agonist activity (Martindale 2009). Morphine is available in four oral formulations: morphine solution, immediate release tablets, modified release tablets or capsules, and modified release suspensions. A great flexibility in the management of severe pain is allowed through this wide range of formulations in addition to the various dosages available. Besides its effect on pain, morphine also relieves anxiety, produces drowsiness and allows sleep (Martindale 2009).

Oxycodone

Oxycodone is a semi-synthetic opioid agonist chemically related to codeine. It has agonist activity at the mu-opioid receptor along with a high affinity for the kappa-opioid receptor (Leppert 2011, Mercadante 2010) which makes it suitable for use in opioid rotation schemes. Since many years, its immediate release formulation has been used in combination with paracetamol or aspirin in order to increase analgesic efficacy and to reduce both the amount of opioid required for pain relief and adverse events. These fixed dose combinations should not be used chronically in large doses because of dose-related toxicity from the non-opioid ingredients. Therefore, oxycodone has long been considered to have a 'weak' opioid effect since high doses for strong pain were not possible. However, studies conducted since 1990 have suggested that oxycodone used in single-entity formulations could be as effective as morphine, and since then it has been relaunched in different formulations for use as a strong opioid in moderate to severe pain (Reid 2006). The controlled release formulation of oxycodone provides a biphasic absorption pattern (Cairns 2001). Its adverse effects are the usual opioid-related adverse effects.

Hydromorphone

Hydromorphone is a potent semi-synthetic mu-opioid receptor agonist. It is a strong opioid and related to morphine but with a greater analgesic potency (Martindale 2009). Since a long time it has extensively been used for management of post-operative pain; it has been introduced in recommendations for management of moderate to severe cancer-related pain by the WHO in 1986 (Quigley 2009)⁹. It is available in different formulations. One of its applications is its use as an alternative to morphine for subcutaneous use, since its greater solubility in water allows a smaller dose volume (Leppert 2011). Its adverse effects are the usual opioid-related adverse effects.

Methadone

Methadone is a synthetic opioid acting as a potent agonist at mu-opioid and delta-opioid receptors (Leppert 2011, Nicholson 2008). Dextrorotatory (D-)methadone and levorotatory (L-)methadone are the 2 isomers of the molecule. Although the last isomer is the more potent analgesic, a racemic mixture is used in clinical practice. D-Methadone has also been demonstrated in animal studies to have antagonist activity at the N-methyl-D-aspartate (NMDA) receptor resulting in interest in the clinical application of the drug in neuropathic pain syndromes (Nicholson 2008, Portenoy 2011). It also inhibits the reuptake of serotonin and noradrenalin in the central nervous system, a working mechanism that can also be found in antidepressants. Methadone has a unique pharmacological profile that has to be understood to encourage appropriate use and reduce risk. Its rapid onset of analgesic effect; its long half-life of around 24

hours (range 13 to 100 hours) resulting in infrequent dosing schedules; its lack of active metabolites which suggests reliable use in patients with renal failure; its low rate of induction of tolerance; its increased potency when administered after treatment with another opioid which makes it a candidate for opioid rotation schemes; and its low cost are characteristics that result in its use in the management of pain in profoundly ill patients. The perceived drawbacks of methadone include high potential for accumulation in peripheral tissues leading to delayed toxicity; highly variable pharmacokinetics between individuals and very long half-life in some individuals; possible drug interactions; prolongation of the cardiac QT interval, antidiuresis and respiratory depression; and concerns over safe dose titration and conversion from other opioids in opioid rotation schemes (Nicholson 2008, Portenoy 2011, Martindale 2009).

Besides its use as an analgesic, it is often used as part of the treatment of opioid dependence.

In Belgium, there is only one commercial preparation available for oral methadone at a dose of 5 mg.

Fentanyl

Fentanyl is a potent synthetic μ -opioid receptor agonist. It is a strong opioid with a greater analgesic potency as compared to morphine (Martindale 2009). It is available in parenteral forms, and frequently used as an adjunct to general anaesthesia or in other peri-operative indications. Its highly lipophilic profile led to the development of a variety of transdermal, transbuccal and intranasal preparations for use in chronic pain.

Transdermal patches typically provide continuous administration of fentanyl for 72 hours after each application. They have a lag time of some hours to onset of action after application, require a few days before steady state is reached, and after removal a subcutaneous reservoir remains for up to 24 hours (Trescot 2008). Therefore their use is generally reserved for patients with stable opioid requirements (Quigley 2008). Oral fentanyl developed for the treatment of breakthrough pain is partly absorbed across the buccal mucosa, and partly swallowed with the saliva and absorbed through the gastro-intestinal system. Several forms of oral fentanyl for breakthrough pain exist; e.g. oral transmucosal fentanyl citrate (OTFC), fentanyl buccal tablets (FBT), sublingual fentanyl orally disintegrating tablets (SFODT). Some forms claim to have a more rapid onset of pain relief than others. Intranasal spray fentanyl has the potential to offer a rapid, acceptable route of drug administration because nasal tissues are highly vascularised and easy permeable, but the absorbed drug dose might be variable due to nasal drip. The fentanyl pectin nasal spray (FPNS) is a special formula developed with the aim to avoid the latter problem. The adverse effects of fentanyl are the usual opioid-related adverse effects.

Buprenorphine

Buprenorphine is a semi-synthetic opioid, usually considered to be a strong opioid (Martindale 2009). It acts as a partial agonist of the μ -receptor, implying that it has a high affinity for but low efficacy at this receptor. At the same time it has a kappa-receptor antagonist activity. Opioid partial agonists may have a ceiling to their analgesic effect, such that escalating the dose beyond a certain level does not increase the analgesic effect but yields greater opioid side effects (Trescot 2008, Martindale 2009). It is currently debated whether this is true or not for buprenorphine. It is also debated whether there is a ceiling effect for buprenorphine, or not, to its side effects such as respiratory depression (Martindale 2009). In addition to its activity on the opioid receptors, buprenorphine has been described to interact with other central pain mechanisms, related to neuropathic pain and with the mechanisms involved in the phenomenon of hyperalgesia (Davis 2012). Buprenorphine is

available in several formulations. It has a high liposolubility (but lower intrinsic activity than fentanyl) and therefore is available as sublingual tablets (onset of effect at 30-60 min.) and transdermal patches which have to be replaced after 72 to 96 hours only (Martindale 2009, Trescot 2008). Buprenorphine is used for pain treatment, and also for substitution therapy in the management of opioid dependence, because its working mechanism as a partial agonist is associated with milder withdrawal symptoms (Martindale 2009). However, also due to its partial mu-opioid receptor activity, it may cause withdrawal symptoms when administered in persons on maintenance therapy with pure mu-receptor agonists (Trescot 2008). Its adverse effects are the usual opioid-related adverse effects.

Codeine

Codeine is a methylated morphine derivate that is found naturally, along with morphine, in the poppy seed. It acts as a mu-opioid receptor agonist, but it is considered to be a weak opioid and is much less potent as an analgesic than morphine (Martindale 2009). It demonstrates a ceiling dose-response curve to pain relief; its maximal analgesic effect is typically achieved at a dose of 240 mg/day (SIGN 2008). Besides its use as an analgesic it has also antitussive activity. Codeine is available in several different formulations, oral route of administration is most common. Several preparations combining codeine and non-opioids such as paracetamol, aspirin or a NSAID exist. Cytochrome P450 2D6 (CYP2D6) catalyses the metabolism of codeine to, among other, morphine. It has been suggested that the analgesic effect of codeine may be impaired in patients devoid of CYP2D6 (poor metabolizers) as compared to those with normal activity at this cytochrome (extensive metabolizers) (Leppert 2011, Martindale 2009). On the other hand, adverse effects are unrelated to the conversion to morphine, and are observed in both genotypes. Approximately 7% of Caucasian people, 3% of black people and 1% of Asian people have poor or absent codeine metabolism, resulting in a reduced or absent analgesic effect (SIGN 2008). Drug interactions are possible for other drugs interacting with CYP2D6, a.o. antidepressants. In therapeutic doses codeine is much less liable than morphine to produce adverse effects, although constipation may be troublesome with long-term use (Martindale 2009).

Tramadol

Tramadol is an atypical, centrally acting synthetic opioid agonist. It is available in several different formulations. Its mechanism of action is dual. First, its weak opioid effect is conferred by binding to mu-opioids receptors. Second, tramadol inhibits weakly the neuronal reuptake of norepinephrine and serotonin (Leppert 2011). Tramadol is used both in neuropathic and nociceptive pain (Duehmke 2009). Patients devoid of cytochrome P450 2D6 activity (CYP2D6) (poor metabolizers) need higher tramadol doses than those with normal activity at this cytochrome (extensive metabolizers) (Leppert 2011). Drug interactions are possible for other drugs interacting with CYP2D6, a.o. antidepressants. Tramadol should be used with care in patients susceptible to seizures, since it can lower the threshold for convulsions. It may produce fewer typical opioid adverse effects such as respiratory depression and constipation (Martindale 2009). It may often produce nausea and vomiting after initiation (Tassinari 2011a). Tramadol treatment may have a lower potential for causing tolerance and dependence (Duehmke 2009, Martindale 2009).

Tapentadol is only recently available in Belgium and is therefore not included in KCE 2013.

Other considerations

Strong opioids

In Belgium, there is only one commercial preparation available for oral methadone at a dose of 5 mg. This is a relatively low dosage which makes its use in monotherapy more difficult. (see topic 4 on substance abuse for more details).

Besides the oral and transdermal route of administration, alternative routes can be considered for specific reasons. Subcutaneous or intravenous infusion is often used in the setting of advanced illness. The intramuscular route is not used because it is painful and provides no pharmacological advantage, and the rectal route is considered rarely when the oral route is unavailable and treatment duration will be short. Properly selected patients can benefit from intraspinal therapy. It is beyond the scope of the present review to provide an overview of the literature on these topics.

There is only limited evidence of two trials, that transdermal fentanyl and oral sustained-release morphine show comparable efficacy for moderate to severe cancer pain in patients naive to strong opioids; and it is not possible to conclude on their relative profile of adverse effects (Mercadante 2008, Van Seventer 2003). Based on the available evidence it is not possible to conclude on the relative efficacy and side-effects of transdermal buprenorphine as compared to sustained-released morphine for this patient group (Mystakidou 2005, Pistevou-Gompaki 2004). According to the expert panel (see colophon), clinical practice in this patient group learns that transdermal fentanyl and oral sustained-release morphine show comparable efficacy and side effects. Also, in their experience some patients explicitly prefer transdermal instead of oral formulations, because of its ease of administration. Besides this, it is obvious that transdermal opioids can be an alternative when oral drug administration is difficult or not possible (e.g. vomiting). On the other hand, in cachectic patients transdermal systems might not be effective after 4-8h, since they act through resorption by the subcutaneous fat.

The long duration of action of the available transdermal opioid systems should be taken into account, and therefore transdermal opioids are mostly used after a stable opioid regimen has been established.

Weak opioids

For codeine, the Step II opioid suggested in the WHO analgesic ladder, the consulted expert panel (see colophon) pointed to the fact that in Belgium codeine is only available at a relatively low dose (30mg) as a combination preparation with 500 mg paracetamol. This limits its use as a Step II opioid. The consulted expert panel suggested to add tramadol as a WHO Step II opioid. After initiation tramadol often causes nausea and vomiting but according to the experts, this is a temporary effect. Tramadol has partially an opioid working mechanism, and partially it has other central working mechanisms namely reuptake inhibition of serotonin and norepinephrine. The experts emphasized that for this reason, the opioid side effects of tramadol such as drowsiness and constipation are usually less severe

than for codeine. The experts added that codeine probably also carries a higher risk of addiction given its stronger opioid effect; and because its metabolism differs between individuals some patients react too much or do not respond at all.

Another alternative to the use of the Step II opioids codeine or tramadol could be, according to the consulted expert panel (see colophon), tilidine. In Belgium, tilidine is only available in combination with the opioid antagonist naloxone, to prevent abuse. However, this can hinder good analgesic effect in severe pain, when high tilidine doses might be required. No publications on tilidine corresponding to the inclusion criteria of the present review have been found.

Further, the consulted expert panel suggested to use buprenorphine, as an alternative to Step II opioids if codeine, tramadol or tilidine are not suitable. Buprenorphine is usually considered to be a strong (WHO Step III) opioid.

Breakthrough cancer pain

In Belgium, only a limited choice of reimbursed opioid preparations for breakthrough pain is available (July 2013). Sublingual fentanyl tablets and intranasal fentanyl spray at various doses are available but not reimbursed by the national health insurance system. Sublingual buprenorphine tablets are available and reimbursed; no publications were retrieved in the current review on the efficacy of sublingual buprenorphine tablets in the treatment of breakthrough pain. Further, normal release morphine tablets are available but not reimbursed; immediate release hydromorphone capsules and instant tablets oxycodone are available and reimbursed.

According to the expert panel (see colophon), transmucosal or intranasal fentanyl tends to work faster as compared to the immediate release formulations of the more conventional opioids used for breakthrough pain episodes. This is an important aspect in breakthrough pain relief. Further, it tends to have a shorter duration of action, which is important when one wants to avoid an increase in opioid side effects (e.g. somnolence) due to accumulation with the established maintenance dose of opioids. This is in line with the available evidence for the comparison between transmucosal or intranasal fentanyl and immediate release morphine. According to the stakeholder panel (see colophon), oral morphine e.g. prescribed as a syrup can be a cheap alternative to oral of intranasal fentanyl.

According to the expert panel, the rescue medication should be started at a dose proportional to the total around-the-clock (ATC) opioid dose; and then titrated in the same way that the around-the-clock opioid medication is titrated. However, in the current literature there is not much information on proportional dosing of rapid-onset fentanyl preparations, since most studies have applied a titration process instead of proportional dosing.

Combination of Opioids

- **The available evidence does not allow to conclude on the effectiveness of the concurrent use of two strong opioids for background analgesia in cancer patients with inadequate pain relief and/or intolerable opioid-related adverse effects while using a single strong opioid.**

However, the concurrent use of two carefully selected strong opioids can be a treatment option in some of these patients, after a thorough reassessment of pain management has been performed. It should be considered to restrict the initiation of such treatment to medical experts in pain treatment or palliative care. Once optimal dosage has been identified, maintenance treatment can be carried out by another physician (very low level of evidence; weak recommendation).

The use of combinations of opioids is not advocated by the World Health Organization (WHO) analgesic ladder. However, in clinical practice there can be reasons why strong opioids are used in combination. The topic of adding a short-acting strong opioid, e.g. a fast-acting fentanyl preparation, to a (stable) regimen of another strong opioid in the treatment of breakthrough pain has been discussed before. The rationale for 'combination opioid therapy' in the sense of the concurrent use of two strong opioids for background analgesia, is to improve analgesia, limit the development of opioid tolerance, or decrease opioid side effects by using opioids which together have a lesser effect on the central mu opioid receptors than individually (reducing nausea and vomiting, constipation, respiratory depression). One of the reasons of the potential advantages of opioid combination therapy is the incomplete cross-tolerance between opioids.

The SR dealing with this topic concluded as follows:

Fallon 2011 concluded that there is a paucity of clinical evidence supporting combination opioid therapy in cancer, and that combination opioid therapy is only weakly recommended in the treatment of opioid-responsive cancer pain that is poorly controlled with the use of one strong opioid alone. The authors highlight that other analgesic treatment combinations can be considered as well, such as the combination of opioids with adjuvant analgesics for neuropathic pain, but they considered that topic as out of scope for their review.

According to the expert panel (see colophon), there is clinical evidence that points to the usefulness of adding a second strong opioid for background analgesia in cancer patients with inadequate pain relief and/or intolerable opioid-related adverse effects while using a single strong opioid. Addition of a second strong opioid can also be considered when one wants to prevent opioid-related hyperalgesia. The second strong opioid should be selected carefully, e.g. no second pure mu-receptor agonist should be added, but rather an opioid with a mixed working mechanism, e.g. methadone, buprenorphine.

5.3 Opioid formulations and route of administration

5.3.1 Summary

The use of different pharmaceutical formulations and routes of administration

The oral route should be used for opioids if practical and feasible (NPC_Canada 2017, NHG 2018, DOH_Ireland 2015, KCE 2013).

Immediate-release opioids instead of extended-release/long-acting opioids are recommended when starting opioids (NPC_Canada 2017, WOREL 2017, CDC 2016, DOH_Ireland 2015). However, the DOH_Ireland 2015 guideline also states that oral opioid titration can be adequately and safely

commenced and titrated using either oral immediate release preparations, or modified release preparations.

The guidelines recommend around-the-clock treatment with controlled release formulations for continuous and stable pain.

There is no difference in analgesic efficacy between the different oral preparations (4h, 12h, 24h dosing of morphine sulphate) (DOH_Ireland 2015). Oral opioid scheduling should be based on patient preferences and ease of compliance (DOH_Ireland 2015).

Opioid administration via the buccal, sublingual or nasal mucosa is indicated only for the treatment of breakthrough pain. Any role in the treatment of continuous pain is limited (DOH_Ireland 2015).

Breakthrough pain can be effectively managed with either oral immediate release opioids, or buccal/sublingual/intranasal fentanyl preparations. (DOH_Ireland 2015)

Alternative routes for oral administration of opioids

An alternative route of administration might be needed for various reasons like the inability to take oral opioids, the patient's condition and preferences, and non-compliance.

Subcutaneous, intravenous, rectal and transdermal routes are all useful alternatives for opioid administration, where oral treatment is not possible (DOH_Ireland 2015).

Patients should be titrated to adequate pain relief prior to the initiation of transdermal patches (DOH_Ireland 2015).

The NHG 2018 guideline has a preference for a fentanyl patch or if required parenteral morphine. The guideline does not recommend buprenorphine in primary care due to limited experience and evidence for any advantage.

The guideline does not recommend the rectal route.

The DOH_Ireland 2015 guideline recommends transdermal opioids such as fentanyl and buprenorphine as valid alternatives in selected patients⁵. Transdermal opioids are useful alternatives, where oral treatment is not possible in patients with stable pain. The efficacy and tolerability of transdermal opioids are similar to the same opioid used in other routes of administration. However, they may be associated with less constipation and good patient compliance. Their pharmacokinetic and dynamic characteristics, however, do present challenges. An increased skin blood flow (due to transpiration, fever, or a hot shower) can lead to an increased risk for side effects related to transdermal opioids (NHG 2018, KCE 2013). (See "Management of chronic pain with opioids").

Transdermal opioids might not be effective in cachectic patients due to impaired absorption (DOH_Ireland 2015, KCE 2013).

⁵ This guideline does not specify the term 'selected patients'

Intranasal drug delivery might be an option in patients with oral problems such as xerostomia, which is common in patients with advanced cancer (KCE 2013).

Subcutaneous or intravenous infusion is often used in the setting of advanced illness. (KCE 2013)
Both the subcutaneous and intravenous routes are feasible, effective and safe. The intravenous route may be preferable where rapid titration of analgesia in cases of severe uncontrolled pain is required. However, due to the lower risk of complications, the subcutaneous route is generally preferred. (DOH_Ireland 2015)

The intramuscular route and rectal route are rarely used (DOH_Ireland 2015, KCE 2013).

For more information on spinal opioids see for example the DOH_Ireland 2015 guideline.

5.3.2 NPC_Canada 2017

In patients with continuous pain including pain at rest, clinicians can prescribe controlled release opioids both for comfort and simplicity of treatment. Activity related pain may not require sustained release treatment and opioid therapy may be initiated with immediate release alone.

The benefit and safety of controlled release or sustained release over immediate release preparations is not clearly established. Some patients, when switching from immediate release to comparable dose sustained release, require larger doses in order to acquire a similar analgesic effect. The release profile of all sustained or controlled release preparations is not the same and may vary for the same drug among patients. Individuals misusing opioids favour immediate release opioid preparations, regardless of the route of administration.

5.3.3 WOREL 2017

- **Geef bij opstart van een behandeling met opioïden voor chronische pijn de voorkeur aan opioïden met onmiddellijke afgifte in plaats van aan opioïden met lange werkingsduur. Schrijf de minimale werkzame dosis voor. Drijf bij lagedosistitratie de dagelijkse dosis geleidelijk op. (GRADE 1C)**

- **Lorsqu'un traitement par opioïdes est initié pour une douleur chronique, la préférence doit être accordée à des opioïdes à libération immédiate plutôt que des opioïdes à longue durée d'action. La dose minimale efficace devrait être prescrite. La progression de dose quotidienne doit être réalisée dans le cadre d'une titration à dose limitée. (GRADE 1C)**

This recommendation is based on the CDC guideline.

5.3.4 CDC 2016

- **When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids (recommendation category: A, evidence type: 4).**

Experts agreed that for patients not already receiving opioids, clinicians should not initiate opioid treatment with ER/LA opioids and should not prescribe ER/LA opioids for intermittent use. ER/LA opioids should be reserved for severe, continuous pain and should be considered only for patients who have received immediate-release opioids daily for at least 1 week.

Because dosing effects of transdermal fentanyl are often misunderstood by both clinicians and patients, only clinicians who are familiar with the dosing and absorption properties of transdermal fentanyl and are prepared to educate their patients about its use should consider prescribing it.

5.3.5 NHG 2018

- *Overweeg bij goede pijnstilling met tramadol deze om te zetten naar een preparaat met gereguleerde afgifte in doseringen 2 dd 50 tot 100 mg of 1 dd 400 mg.*

See 'step 4' in the previous chapter on 'Management of chronic pain with opioids'.

See 'step 5' in the previous chapter on 'Management of chronic pain with opioids'.

5.3.6 NICE 2017

No specific recommendations were provided

5.3.7 ASCO 2016

No specific recommendations were provided

5.3.8 DOH_Ireland 2015

Route of administration of opioids

Oral opioids have been recommended as the mainstay of cancer pain management. If a patient is unable to take oral opioids, a number of alternative application routes exist, such as subcutaneous, intravenous, transmucosal, transdermal, topical and spinal routes.

Radbruch et al (2011) performed a systematic literature review on the use of alternative routes for opioid administration and found 18 relevant studies. The best evidence (from one systematic review and three RCTs) was found for subcutaneous administration of morphine sulphate or other opioids. There was less evidence available for other routes of administration. However, the review found no significant difference in efficacy or side-effects between the alternative application routes

investigated. Thus, subcutaneous, intravenous, rectal and transdermal routes are all useful alternatives for opioid administration, where oral treatment is not possible.

Choice of opioids

- **Oral morphine sulphate, hydromorphone and oxycodone may be used as first line treatment in the management of moderate to severe cancer pain. (recommendation category B)**
- **Transdermal opioids such as fentanyl and buprenorphine are valid alternatives in selected patients. (recommendation category B)**

Route of administration of opioid

Key finding

The oral route should be used for administration of opioids, if practical and feasible. Alternative routes are found to be as effective from an efficacy and side effect profile perspective.

- **The oral route should be used for administration of opioids, if practical and feasible. If a patient is unable to take oral opioids, a number of alternative application routes exist, such as subcutaneous, intravenous, transmucosal, transdermal, topical and spinal routes. (recommendation category A)**

Oral administration of opioids

Morphine sulphate, oxycodone and hydromorphone can be administered as immediate (IR) or modified release (MR) (sometimes called ‘sustained release’ or SR). Peak plasma concentrations normally occur within one hour of administration of an immediate release morphine sulphate preparation, with reasonably rapid onset of analgesia, which then lasts for about 4 hours. In contrast, modified release formulations produce a delayed peak plasma concentration after 2-6 hours, and analgesia lasts for 12 to 24 hours.

In terms of analgesic efficacy, there is no difference between four-hourly, twelve-hourly and twenty-four-hourly dosing of morphine sulphate, oxycodone or hydromorphone preparations, once they are correctly administered.

Oral opioid treatment

- **Oral opioid titration can be adequately and safely commenced and titrated using either oral immediate release preparations, or modified release preparations. (recommendation category C)**

For more information on titration using immediate release and modified release oral preparations, see “Management of chronic pain with opioids”.

Parenteral routes of opioid administration

- **Subcutaneous and intravenous routes may be used where the oral route is not feasible. (recommendation category A)**

- The average relative potency ratio of oral morphine sulphate to subcutaneous or intravenous morphine sulphate is between 2:1 and 3:1, with variability between patients. (recommendation category C)

Intravenous administration

Radbruch et al (2011) conclude that both the subcutaneous and intravenous routes are feasible, effective and safe. The intravenous route may be preferable where rapid titration of analgesia in cases of severe uncontrolled pain is required. However, due to the lower risk of complications, the subcutaneous route is generally preferred.

Use of continuous infusions

Indications for the use of continuous infusion include:

- Intractable vomiting
- Severe dysphagia
- Patient too weak to swallow oral medication
- Decreased level of consciousness
- Poor gastrointestinal absorption
- Poor patient compliance.

Continuous subcutaneous infusion of opioids is simple to administer and as effective as continuous intravenous infusion. Syringe driver infusion pumps may be used to avoid the need for regular bolus injections for those on regular opioids, where the oral route is no longer appropriate.

Transmucosal opioids

Opioid administration via the buccal, sublingual or nasal mucosa as an alternative route of administration was examined systematic review by Radbruch et al (2011). Whilst morphine sulphate's absorption is unpredictable by these routes, highly lipophilic drugs such as fentanyl and buprenorphine can be rapidly absorbed and many new therapeutic systems for transmucosal opioid delivery have been developed in recent years. However, these new systems are indicated only for the treatment of breakthrough pain, and their role in the treatment of continuous pain is limited. Rectal administration of opioids such as morphine sulphate or methadone is not commonly practiced in Ireland, but can be used effectively. Similar efficacy and tolerability with subcutaneous or intravenous application has been described.

Spinal opioids

Key finding

Spinal opioid therapy may be effective for treating cancer pain where systemic treatment has failed, either due to intolerable side-effects or inadequate analgesia.

- Available evidence is of low quality and thus only weak recommendations for use of spinal opioids alone or in combination with other drugs can be made.
Administering opioids and other medications via spinal delivery systems requires the input of an appropriately qualified specialist. (recommendation category D)

Topical opioids

Key finding

There is limited evidence to support the use of topical opioids in the management of painful malignant skin and mucosal lesions.

- **Whilst there is support for the use of topical opioids, there is insufficient evidence to make clear recommendations for clinical practice in terms of the ideal opioid to use, starting dose, interval of administration, method of titration, carrier agent or most suitable wounds for this treatment. (recommendation category D)**

The management of painful skin and mucosal lesions presents a therapeutic challenge. The effective use of systemic opioids for such conditions can be complicated by unpredictable bioavailability of the drug within the wound microenvironment, largely due to impaired circulation. These limitations, and the identification of peripheral opioid receptors, have triggered an interest in exploring alternative routes of analgesia, such as topical application.

LeBon et al (2009) performed an extensive systematic review in order to appraise the evidence for such an approach.

Nineteen articles were included in the review, comprising six RCTs and thirteen case reports. Whilst there is support for the use of topical opioids, due to the wide heterogeneity of the studies the authors were unable to make clear recommendations for clinical practice in terms of the ideal opioid to use, starting dose, interval of administration, methods of titration, carrier agent or most suitable wounds for this treatment.

Spinal opioids**Key finding**

Spinal opioid therapy may be effective for treating cancer pain where systemic treatment has failed, either due to intolerable side-effects or inadequate analgesia.

- **Available evidence is of low quality and thus only weak recommendations for use of spinal opioids alone or in combination with other drugs can be made. Administering opioids and other medications via spinal delivery systems requires the input of an appropriately qualified specialist. (recommendation category D)**

Since endogenous opioids and opioid receptors were first isolated in the central nervous system in the 1970s, attempts have been made to optimise opioid therapy by central delivery of opioids. In those patients whose pain is refractory to systemic opioid treatments, there may be specific reasons that a patient may benefit from neuraxial (epidural, intrathecal and intracerebroventricular) administration of opioids, such as:

-Unacceptable side-effects despite successful analgesia with systemic opioids

-Unsuccessful analgesia despite escalating doses and use of sequential systemic opioids

-Intolerable neuropathic pain which may be amenable to spinal adjuvants

-Incident pain which may benefit from numbness (local anaesthetic). Intrathecal opioids act by binding to mu and kappa receptors in the substantia gelatinosa of the spinal cord. This is achieved to a lesser extent with epidural opioids which exert both a systemic effect (10%) and an intrathecal effect (90%). There is growing evidence favouring the intrathecal route of administration due to

better long term pain outcomes, the lower dose required, the fewer systemic side-effects and the lower complication rates.

Breakthrough pain

- **Breakthrough pain can be effectively managed with either oral immediate release opioids, or buccal/sublingual/intranasal fentanyl preparations. More than four episodes of breakthrough pain a day indicates that the current management of the baseline/persistent pain should be reviewed. As breakthrough pain can vary in severity, duration, aetiology and pathophysiology, it is likely that the required dose will vary and individualised titration for both oral and transmucosal rescue opioids is recommended. (recommendation category A)**

Breakthrough pain can be effectively managed with either oral immediate release opioids, or buccal/sublingual/intranasal fentanyl preparations. (See also “management of chronic pain with opioids)

5.3.9 KCE 2013

Opioid route of administration

Based on clinical experience, oral delivery of opioids is effective and simple. Most guidelines recommend that the oral route should be used for the administration of opioids, if practical and feasible (SIGN 2008, Dutch Guideline on cancer pain 2008, Guideline of the MoH Malaysia 2010). In advanced illness, oral opioids can be administered by gastric tube, with the exception of sustained release oral opioids because it is not allowed to crush these formulations. However, one slow release oral formulation is an exception since the capsules have been specifically developed to be opened although they should not be crushed (slow release hydromorphone: Palladone Slow Release®). Transdermal opioids can be an alternative when oral drug administration is difficult or not possible (e.g. vomiting), or for non-compliant patients. On the other hand, in cachectic patients transdermal systems might not be effective after more than 4-8h, since they act through resorption by the subcutaneous fat. Transdermal patches typically provide continuous administration of the opioid for many hours after each application, e.g. 72 hours for fentanyl. They have a lag time of some hours to onset of action after application, require a few days before steady state is reached, and after removal a subcutaneous reservoir remains for a long time (e.g. up to 24 hours for fentanyl) (Trescot 2008). Therefore the use of patches is generally reserved for patients with stable opioid requirements (Quigley 2008).

Intranasal drug delivery might have advantages as compared to the oral transmucosal route since the use of the latter might be compromised by oral problems such as xerostomia, which is common in patients with advanced cancer. Also, first-passage through the liver after gastrointestinal absorption is avoided, but the absorbed drug dose might be variable due to nasal drip.

Besides the oral, transdermal or intranasal route of administration, alternative routes can be considered for specific reasons. It is beyond the scope of the present review to provide an overview of the literature regarding these alternative routes of administration. Subcutaneous or intravenous

infusion is often used in the setting of advanced illness. The intramuscular route is rarely used because it is painful and provides no pharmacological advantage. The rectal route is also considered rarely, when the oral route is unavailable and treatment duration will be short (Portenoy 2011). Properly selected patients can benefit from intraspinal therapy (KCE report n° 189). For further practical considerations on doses in different routes of administration, the reader is referred to reference works, e.g. 'Palliatieve zorg in de praktijk. Zakboekje voor hulpverleners' (2009).

5.4 Opioids in adolescents, older patients and patients with renal or hepatic insufficiency

5.4.1 Summary

The guidelines only focus on opioid use in adults.

CDC 2016 states that there is only limited available evidence concerning long-term opioid therapy in **adolescents**. The risk of misusing their prescribed opioids is estimated at 20% among adolescents (CDC 2016). The use of prescribed opioids at a younger age is associated with an increased risk of later opioid misuse (CDC 2016).

A start low and go slow approach for dosing opioids is generally recommended in the **elderly** (NHG 2018). Clinicians should use additional caution and increased monitoring to minimize risks of opioids prescribed for patients aged ≥ 65 years (CDC 2016). On the other hand, inadequate pain treatment among this population has been documented (CDC 2016).

The use of dose conversion tables for opioid rotation (see section "rotation of opioids") should be used with caution, particularly in the **elderly and in patients with renal or hepatic impairment** (WOREL 2017).

The guidelines recommend additional caution and increased monitoring to minimize risks of opioids prescribed for patients with **renal or hepatic insufficiency** (CDC 2016, NHG 2018, DOH_Ireland 2015).

Clinicians should use additional caution with ER/LA opioids and consider a longer dosing interval when prescribing to patients with **renal or hepatic dysfunction** (CDC 2016, NHG 2018).

In mild to moderate **renal impairment** (eGFR 30-89 ml/ min/1.73 m²), all opioids appropriate for cancer pain can be used, with consideration of reduced dose or frequency at lower eGFR levels (DOH_Ireland 2015). Specialist advice should be sought when prescribing opioids in moderate to severe renal impairment disease (DOH_Ireland 2015). Alfentanil and fentanyl are recommended by some guidelines as the safest opioids of choice in patients with stages 4 or 5 kidney disease (eGFR < 30 ml/ min/1.73 m²) (DOH_Ireland 2015, KCE 2013).

In **liver disease**, any opioids should be initiated at lower doses and prescribed with extended dosing intervals (DOH_Ireland 2015). The KCE 2013 review recommends to avoid oxycodone, codeine, methadone, tramadol and oxymorphone in liver impairment. In advanced liver impairment, dosage recommendations should be patient specific and specialist advice should be sought (DOH_Ireland

2015). The transdermal route and sustained release preparations should be avoided in this population (DOH_Ireland 2015) otherwise close monitoring is needed (KCE 2013).

5.4.2 NPC_Canada 2017

No specific recommendations were provided

5.4.3 WOREL 2017

A number of dose conversion charts are available and can be useful, but there is significant inter-individual variability and they should be used with caution, particularly in the elderly, if there are significant other co-morbidities (e.g. hepatic or renal impairments; or with polypharmacy).

5.4.4 CDC 2016

*Clinicians should use additional caution and increased monitoring to minimize risks of opioids prescribed for patients with **renal or hepatic insufficiency**, given their decreased ability to process and excrete drugs, susceptibility to accumulation of opioids, and reduced therapeutic window between safe dosages and dosages associated with respiratory depression and overdose (contextual evidence review).*

*Clinicians should use additional caution with ER/LA opioids and consider a longer dosing interval when prescribing to patients with **renal or hepatic dysfunction** because decreased clearance of drugs among these patients can lead to accumulation of drugs to toxic levels and persistence in the body for longer durations.*

*Inadequate pain treatment among **persons aged ≥65 years** has been documented. Pain management for older patients can be challenging given increased risks of both nonopioid pharmacologic therapies and opioid therapy in this population. Given reduced renal function and medication clearance even in the absence of renal disease, patients aged ≥65 years might have increased susceptibility to accumulation of opioids and a smaller therapeutic window between safe dosages and dosages associated with respiratory depression and overdose. Some older adults suffer from cognitive impairment, which can increase risk for medication errors and make opioid-related confusion more dangerous. In addition, older adults are more likely than younger adults to experience co-morbid medical conditions and more likely to receive multiple medications, some of which might interact with opioids (such as benzodiazepines). Clinicians should use additional caution and increased monitoring to minimize risks of opioids prescribed for patients aged ≥65 years. Experts suggested that clinicians educate older adults receiving opioids to avoid risky medication-related behaviors such as obtaining controlled medications from multiple prescribers and saving unused medications. Clinicians should also implement interventions to mitigate common risks of opioid therapy among older adults, such as exercise or bowel regimens to prevent constipation, risk assessment for falls, and patient monitoring for cognitive impairment.*

The recommendations do not address the use of opioid pain medication in children or adolescents aged <18 years. The available evidence concerning the benefits and harms of long-term opioid therapy in children and adolescents is limited, and few opioid medications provide information on the label regarding safety and effectiveness in pediatric patients. However, observational research shows significant increases in opioid prescriptions for pediatric populations from 2001 to 2010, and a large proportion of adolescents are commonly prescribed opioid pain medications for conditions such as headache and sports injuries (e.g., in one study, 50% of adolescents presenting with headache received a prescription for an opioid pain medication). Adolescents who misuse opioid pain medication often misuse medications from their own previous prescriptions, with an estimated 20% of adolescents with currently prescribed opioid medications reporting using them intentionally to get high or increase the effects of alcohol or other drugs. Use of prescribed opioid pain medication before high school graduation is associated with a 33% increase in the risk of later opioid misuse. Misuse of opioid pain medications in adolescence strongly predicts later onset of heroin use. Thus, risk of opioid medication use in pediatric populations is of great concern. Additional clinical trial and observational research is needed, and encouraged, to inform development of future guidelines for this critical population.

5.4.5 NHG 2018

Over het algemeen zal bij kwetsbare ouderen een lagere dosis gegeven moeten worden en langzamer een spiegel opgebouwd moeten worden.

For tramadol the following was mentioned:

- *Start bij kwetsbare ouderen in een lagere dosering (10 tot 25 mg) bijvoorbeeld in de vorm van druppels (2,5 mg per druppel) en verhoog vervolgens langzaam de dosis: 1 tot 4 dd 4 tot 10 druppels (10 tot 100 mg/dag).*
- *Verleng bij lever- en/of nierfunctiestoornis (eGFR < 30 ml/min/1,73 m²) het doseringsinterval naar 12 uur en geef maximaal 2 dd 100 mg.*

Tabel 5 Startdoseringen opiaten bij patiënten die niet eerder opiaten gebruikten

<i>Orale startdosering morfine</i>	<i>Rectale startdosering morfine (alleen tijdelijk, als noodoplossing)</i>	<i>Transdermale startdosering fentanyl (werkt na 6-12 uur)</i>
1-2 dd 10-30 mg retard; bij leeftijd > 70 jaar of gewicht < 50 kg 2 dd 10 mg retard	3-4 dd 5-10 mg	pleister 12 microg/uur; na 3 dagen vervangen

5.4.6 NICE 2017

No specific recommendations were provided.

5.4.7 ASCO 2016

No specific recommendations were provided.

5.4.8 DOH_Ireland 2015

Opioids in renal impairment

Key finding

The quality of evidence for the safe and effective use of opioids for the relief of cancer pain in patients with renal impairment is low.

The available evidence is suggestive of significant differences between the activities of opioid metabolites and therefore their relative risk profiles in patients with impaired renal function.

- **In renal impairment, all opioids should be used with caution, and with consideration of reduced doses and/or frequency of administration.**

Specialist advice should be sought when prescribing opioids in moderate to severe renal impairment.

The presence of renal impairment should not be a reason to delay the use of an opioid for those with cancer pain, when needed.

Close monitoring of pain and for signs of opioid toxicity is required.

Alfentanil and fentanyl are the safest opioids of choice in patients with stages 4 or 5 kidney disease (estimated glomerular filtration rate <30 ml/ min/1.73 m²).

Paracetamol is considered the non-opioid analgesic of choice for mild-to-moderate pain in patients with renal impairment.

Adjuvant analgesics may require dose adjustment in patients with renal impairment. (recommendation category D)

Renal impairment in cancer

The accuracy of formulae to derive estimated GFR (eGFR) or CrCl measurements is lessened in the presence of oedema, cachexia, low protein states and acute renal failure, all seen frequently in cancer patients.

Declining kidney function is commonly seen in cancer patients due to disease, advancing age, reduced oral fluid intake and concomitant drug therapy. In such patients, medication side-effects can mimic the symptoms of opioid toxicity or terminal decline. Dehydration and renal impairment increase the potential for opioid toxicity or other drug side-effects by:

- Allowing the build-up of active drug metabolites*
- Decreasing plasma protein binding capacity due to protein loss, or altered protein binding caused by uraemia*
- Causing changes in hydration, affecting the distribution of drugs in the body*
- Reducing oral absorption of drugs due to vomiting, diarrhoea and gastrointestinal oedema*

-Increasing permeability of the blood brain barrier (in uraemia) which may exaggerate unwanted central nervous system side-effects.

Guidance for opioid prescribing in renal impairment

In patients with poor or deteriorating kidney function, the following factors should be taken into consideration to prevent or manage toxicity:

- Choice of opioid*
- Consideration of dose reduction and/or an increase in the dosage interval*
- Change from modified release to an immediate release oral formulation*
- Frequent clinical monitoring and review.*

The presence of renal impairment should not be a reason to delay the use of an opioid for those with cancer pain when needed.

Dose adjustment recommendations should only be used as an initial guide, and further dose adjustments should be based on the clinical condition of the patient.

Codeine

Codeine is metabolised to morphine sulphate and its metabolites, which can accumulate in patients with renal impairment. Renal excretion of codeine and its metabolite codeine-6-glucuronide is reduced in patients with renal impairment; therefore caution with its use is required.

Tramadol

Tramadol inhibits noradrenaline and serotonin uptake in addition to its weak opioid receptor activity. There is potential for serotonin-type side-effects and opioid adverse effects in patients with or without renal impairment. Tramadol is extensively metabolised in the liver to one active metabolite, O-demethyl tramadol. Unchanged tramadol and the active metabolite are both eliminated mainly by the kidneys and will accumulate in renal impairment, requiring dose reduction and an increase in the dosing interval according to the degree of impairment.

Morphine sulphate

Morphine sulphate toxicity is well reported in patients with poor renal function and is due to the accumulation of morphine sulphate-3-glucuronide (M3G) and morphine sulphate-6-glucuronide (M6G). Morphine sulphate is metabolised primarily in the liver and the metabolites are largely excreted by the kidneys.

Dose reductions and decreased frequency of administration should be considered depending on the degree of renal impairment. Toxicity caused by the accumulation of metabolites in cerebrospinal fluid can take several days to resolve after morphine sulphate is discontinued.

Oxycodone

Oxymorphone and noroxycodone, the principal metabolites of oxycodone, are excreted renally. The contribution of these metabolites to the pharmacological activity of oxycodone is uncertain, but thought to be small. Reduced excretion of oxycodone in renal impairment has been reported.

... The authors conclude that oxycodone should be used with care in patients with renal impairment. In severe renal impairment (eGFR<30 ml/min/1.73m²) start with small doses and slowly titrate.

Hydromorphone

Hydromorphone is metabolised in the liver, principally to hydromorphone-3- glucuronide. All metabolites are excreted renally.

... Evidence for the safety of hydromorphone in renal impairment is inconsistent. However, hydromorphone is used in many units that deal with renal impairment frequently, and there are many reports of its successful use in such patients, when titrated carefully.

Fentanyl

Fentanyl is metabolised in the liver to compounds thought to be inactive and nontoxic, with less than 10% excreted unchanged in urine. Some reviews have reported studies concluding that no dose adjustment is needed in patients with renal impairment. However, an increased elimination half-life has been reported in critically ill patients with renal failure. It would be prudent to monitor patients with renal failure for signs of gradual accumulation of fentanyl and its metabolites.

Alfentanil

Alfentanil is a synthetic derivative of fentanyl. It is less potent than fentanyl and is metabolised in the liver, with urinary excretion of the metabolites (which are thought to be inactive).

...The authors conclude that the evidence for the safe use of alfentanil in patients with renal impairment is limited to retrospective reports of adequate analgesia and improved symptoms in patients switched from other opioids due to poor tolerability.

Buprenorphine

Buprenorphine is metabolised mainly to norbuprenorphine, which is the only metabolite thought to have analgesic activity. Unchanged buprenorphine is mainly excreted in the faeces and its metabolites are mainly excreted in the urine.

Buprenorphine is considered generally safe to use in renal impairment as its pharmacokinetics are largely unchanged. However, there remains relatively little experience with this drug in cancer pain.

Methadone

Methadone is primarily excreted in the faeces, with approximately 20% excreted unchanged in urine. Methadone tends to accumulate in tissues with chronic use, has a long half-life and is highly protein bound. These factors make methadone use for analgesia potentially complex, even in the absence of renal failure. Due to its long half-life, methadone should be dose reduced in renal impairment. It is recommended that methadone should only be used under experienced specialist supervision because of the risks of accumulation and toxicity.

Opioid metabolites in patients with renal impairment

Given that the quality of evidence for the safe and effective use of opioids for the relief of cancer pain in patients with renal impairment is low, any recommendations made must do so on the basis of pharmacokinetic data, extrapolation from noncancer pain studies and from clinical experience. The evidence however is suggestive of significant differences in risk between opioids, as summarised in Table 14.

Table 14 Risk stratification of opioids

Drug	Recommendations in patients with cancer and renal impairment	Comment
Codeine	If judged appropriate to use, then do so with caution.	Metabolised to morphine sulphate and codeine-6-glucuronide, which accumulate in renal impairment. No clinical studies of use in cancer pain and renal impairment (RI) identified. However, there have been reports of severe hypotension, respiratory arrest and profound narcolepsy in patients with advanced RI in the general population (413). The manufacturer advises that codeine is used cautiously, at a reduced dose, in patients with RI and avoided in patients with severe RI (414). However, codeine is used in practice in some renal units (415).
Tramadol	If judged appropriate to use, then do so with caution.	Metabolised extensively in the liver. Unmetabolised tramadol and its metabolites may accumulate in RI. No clinical studies identified in cancer pain and RI population but expert opinion suggests that when using weak opioids, tramadol should be used in preference to codeine. The manufacturer recommends that the dosage interval should be increased to 12 hours if CrCl is less than 30ml/min (416). Modified release preparations should be avoided (413). In severe RI (CrCl <10ml/min), tramadol is not recommended due to prolonged elimination (416).
Morphine sulphate	If judged appropriate to use, then do so with caution.	Active metabolites produced via hepatic metabolism (morphine-3-glucuronide and morphine-6-glucuronide) accumulate in renal impairment. Studies demonstrate an increased risk of adverse events in renal impairment.
Oxycodone	If judged appropriate to use, then do so with caution.	Metabolised to oxymorphone and noroxycodone in liver. Excreted renally. Inconsistent evidence regarding safety in renal impairment. The manufacturer contraindicates its use in severe RI (CrCl <10ml/min) (417).
Hydromorphone	If judged appropriate to use, then do so with caution.	Metabolised in the liver to hydromorphone-3-glucuronide. All metabolites excreted renally. Evidence for the safety of hydromorphone in renal impairment is inconsistent. However, hydromorphone is used in a number of units that deal with renal impairment frequently, and there are reports of its successful use in such patients, when titrated carefully.
Fentanyl	May be used in renal impairment. Opioid of choice, along with alfentanil, in severe RI	Metabolised in the liver to metabolites that are thought to be inactive. Limited clinical evidence supports use with careful oversight.
Alfentanil	May be used in renal impairment. Opioid of choice, along with fentanyl, in severe RI	Metabolised in the liver to metabolites that are thought to be inactive. Limited clinical evidence supports use with careful oversight.
Buprenorphine	If judged appropriate to use, then do so with caution.	Metabolised to norbuprenorphine and norbuprenorphine-3-glucuronide, which are excreted in the urine; unchanged buprenorphine is mainly excreted in the faeces. Limited amount of evidence for use in RI in general population (413) and cancer population (412). The manufacturers of the buprenorphine patch suggest no dose changes are required (417) whereas RI is listed as a precaution for the 2mg sublingual tablets (419).
Methadone	If judged appropriate to use, then do so with caution in the specialist setting only	Primarily excreted in the faeces, with 20% excreted unchanged in the urine. No clinical studies identified and pharmacology is complex.

Table 14 of the DOH_Ireland 2015 guideline

Dosage recommendations

Mild to moderate renal impairment

Estimated glomerular filtration rate (eGFR) 30–89ml/min/1.73m² (mild to moderate renal impairment)

- *All opioids that are appropriate for cancer pain can be used, with consideration of reduced dose or frequency at lower eGFR levels.*
- *Monitor for changes in renal function and consider a pre-emptive change of opioid in rapidly deteriorating renal function.*
- *Assess for any reversible factors.*
- *Be aware that estimations of GFR may be less accurate in the presence of cachexia, low protein states, oedema and with acute renal failure. An estimated GFR at the lower end of the moderate renal impairment range should therefore prompt consideration of a change of opioid to one considered safer in renal impairment.*

Severe and end stage renal impairment

Estimated glomerular filtration rate (eGFR) <30ml/min/1.73m² (end-stage renal failure and severe renal impairment).

- *Due to the delay in the onset and offset of action, the transdermal route should be avoided if stable pain control has not been achieved. Even with stable pain control, careful consideration is needed due to the potential for delayed toxicity.*
- *Methadone may be useful if used by those experienced in its use for pain management.*
- *Remifentanyl needs further assessment as to their suitability for use in cancer pain and renal impairment.*
- *If fentanyl or alfentanil is not available, alternative opioids may be used at reduced doses and frequency of administration, and with careful monitoring. If it is not appropriate or practical to use injectable, buccal, sublingual or nasal preparations for PRN use, then alternative opioids may need to be used (at reduced doses and frequencies). However this is likely to represent a risk of toxicity.*

Table 15 Dosage recommendations

(Adapted From Renal Drug Database for opioids in patients with renal impairment (420) and UK Medicines Information)(415)

Opioid	GFR
Codeine	<ul style="list-style-type: none"> • 20-50ml/min: dose as in normal renal function • 10-20ml/min: 30mg up to every 4 hours. Increase if tolerated • < 10ml/min: 30mg up to every 6 hours. Increase if tolerated
Tramadol	<ul style="list-style-type: none"> • 20-50ml/min: Dose as in normal renal function • 10-20ml/min: 50-100mg every 8 hours initially and titrate dose as tolerated • <10ml/min: 50mg every 8 hours initially and titrate dose as tolerated
Morphine	<ul style="list-style-type: none"> • 20-50ml/min: 75% of normal dose • 10-20ml/min: Use small doses (50% of dose), eg. 2.5-5mg and extended dosing intervals. Titrate according to response • <10ml/min: Use small doses. Eg. 1.25-2.5mg and extended dosing intervals. Titrate according to the response <p>Avoid slow release oral preparations as any side effects may be prolonged</p>
Oxycodone	<ul style="list-style-type: none"> • 20-50ml/min: Start with 75% of dose. Dose as in normal renal function • 10-20ml/min: Start with 75% of dose. Dose as in normal renal function • <10ml/min: Start with small doses e.g. 50% of dose <p>Has been used in CKD 5 patients; start with lowest dose and gradually increase dose according to response.</p>
Hydromorphone	<ul style="list-style-type: none"> • 20-50ml/min: Dose as in normal renal function • <10-20ml/min: Reduce dose – start with lowest dose and titrate according to response
Fentanyl	<ul style="list-style-type: none"> • 20-50ml/min: 75% of normal dose. Titrate according to response • 10-20ml/min: 75% of normal dose. Titrate according to response • <10ml/min: 50% of normal dose. Titrate according to response
Alfentanil	<ul style="list-style-type: none"> • <10-50ml/min: Dose as in normal renal function
Buprenorphine	Transdermal: Dose as in normal renal function
Methadone	<ul style="list-style-type: none"> • 10-50ml/min: Dose as in normal renal function • <10ml/min: 50-75% of normal dose, and titrate according to response

Table 15 of the DOH_Ireland 2015 guideline

The use of opioids in patients receiving dialysis

The use of opioids in patients undergoing dialysis is a complex issue. The type of dialysis and whether an opioid and its metabolites are dialyzable needs to be taken into consideration. The evidence base for the use of opioids in patients receiving dialysis has not been systematically reviewed, but King et al (2011) do provide some guidance based on clinical experience and a non-formalised review of available evidence. Beyond this, the evidence base consists largely of case reports and clinical experience. Clinical practice varies amongst nephrologists and specialist advice should be sought. Specialist reference sources such as The Renal Drug Handbook or Renal Drug Database are useful resources. Factors such as the need for additional analgesia around the time of dialysis should be considered. Regular and close monitoring is required when dose adjustments are made to the patient's opioid.

Opioids in hepatic impairment

Key finding

There is very limited evidence available to evaluate the use of opioids in patients with liver impairment. Liver disease can alter the pharmacokinetics of opioids.

- **In advanced liver impairment:**
Opioids should be used with caution in patients with advanced liver disease. Dosage recommendation should be patient specific and specialist advice sought.
The transdermal route should be avoided, as drug absorption can be variable and unpredictable.
Sustained release preparations should be avoided. (recommendation category C)

General measures

The therapeutic index of any opioid is narrower in the setting of liver disease, and opioids should therefore be initiated at lower doses and prescribed with extended dosing intervals.

Opioid metabolism and use in hepatic impairment

The liver plays a pivotal role in the biotransformation of most opioids. The pharmacodynamic effects of these drugs may be affected in patients with liver impairment. The enzymatic system of the liver is central to opioid metabolism and clearance. Other factors such as hepatic blood flow, plasma protein binding and the presence of a porto-systemic shunt may also have a significant effect. Predicting impaired drug clearance can be difficult as there is no biochemical marker or formula that can accurately do so. The presence of altered liver function tests in conjunction with the clinical presence of hepatic decompensation, such as the presence of jaundice, ascites, or encephalopathy, may alert the prescriber to the potential for altered drug metabolism. The Child–Pugh score and the Model for End-Stage Liver Disease (MELD) can be used to assess the severity of hepatic dysfunction; however, these only offer a rough guide and cannot be used specifically to predict the ability of the liver to metabolise opioids. There is a lack of reliable information on the behaviour of commonly used palliative care medicines in patients with liver disease. Consequently, advice regarding drug treatment should be patient specific. In general, the therapeutic index of any opioid is narrower in cirrhosis or liver disease than in healthy individuals. In these patients, opioids should be initiated at lower doses and titrated slowly using extended dosing intervals. Furthermore, ascites provides a reservoir (third space) for hydrophilic opioids (morphine sulphate, oxycodone, hydromorphone) which delays their clearance.

Codeine

The data available on the use of codeine in liver disease is limited. The analgesic activity of codeine is primarily achieved through its metabolism to morphine sulphate by the hepatic enzyme CYP2D6. The activity of this enzyme is reduced in advanced liver disease, resulting in a reduced rate of conversion of codeine to morphine sulphate. This may be the reason for its reduced analgesic activity in these patients.

Tramadol

In moderate liver disease, the level of tramadol's active opioid metabolite (O-desmethyl tramadol) is reduced and its duration of action is prolonged. In severe liver disease, tramadol's bioavailability increases and its half-life can be as long as 13-22 hours. The half-life of sustained release tramadol can be even longer. The use of tramadol should therefore be avoided in hepatic failure and advanced cirrhosis.

Morphine sulphate

Advanced liver disease is associated with an increase in the oral bioavailability of morphine sulphate of up to 200%. This can lead to an increase in plasma levels and possible accumulation. A prolonged duration of action can be seen in association with a prolonged prothrombin time, hypoalbuminaemia, encephalopathy, ascites and jaundice. Oral bioavailability increases in cirrhosis due to reduced first pass metabolism. A possible increased bioavailability in early liver disease means that lower doses should be used with initial dosing, but at usual dosage intervals.

Oxycodone

The liver has a significant role in the metabolism of oxycodone. Oxycodone is extensively metabolised by the CYP2D6 enzyme in the liver to noroxycodone, oxymorphone and their glucuronides. As such, the clearance of oxycodone is decreased in hepatic failure. In advanced liver disease, immediate release oxycodone has a prolonged half-life which is similar to that of sustained-release oxycodone in healthy individuals.

The manufacturers of oxycodone recommend that in a setting of hepatic impairment, controlled release oxycodone should be initiated at 1/3 to 1/2 of normal starting dose with subsequent slow and careful dose titration.

Hydromorphone

Hydromorphone has a greater bioavailability in patients with cirrhosis, with reduced first-pass clearance but no increase in the half-life. Hydromorphone should be initiated at a lower dose in patients with moderate hepatic impairment, as it is primarily metabolised by the liver and thus increased opioid exposure may occur in patients with moderate hepatic impairment. Based on this information, it may be deduced that dosage intervals do not have to be significantly extended except in late-stage cirrhosis and overt hepatic failure.

Fentanyl

The half-life of a single bolus dose of fentanyl is short because of rapid distribution throughout the body. However, this half-life increases with prolonged infusion once fat and muscle stores are saturated, and hepatic elimination becomes rate limiting. Initial single-dose bolus studies of fentanyl pharmacokinetics reported that fentanyl is relatively unaltered by liver disease. However, at high doses, in cirrhosis and in severe liver disease, the duration of action is markedly prolonged.

Transdermal Fentanyl

Transdermal fentanyl has not been adequately studied in hepatic failure. Hepatic failure alters skin permeability and regional blood flow to the skin, which influences drug absorption. Therefore, the transdermal route should also be avoided as drug absorption from that route could be unpredictable.

Alfentanil

Alfentanil demonstrates complex pharmacokinetics. In liver failure associated with hypoalbuminemia, reduced protein binding leads to prolonged and pronounced analgesia per dose.

Methadone

The influence of chronic liver disease on methadone metabolism has not been well studied. Methadone is 90% protein bound and its elimination half-life in normal liver function varies from 7 to 57 hours. With impairment of liver function there may be a three- to four-fold increase in the elimination half-life, which could lead to further accumulation and potentially fatal adverse effects. Methadone is commonly used for opioid maintenance therapy in subjects with a high prevalence of liver disease. Steady state pharmacokinetics in this population do not appear to differ from that of the healthy population. However, in patients with hepatitis C, reports suggest that methadone requirements may actually be greater than anticipated. This is because hepatitis C reportedly stimulates CYP3A4, an enzyme that is responsible for the metabolism of methadone. As in the general population, in patients with hepatic impairment, inter-individual variability in the pharmacokinetics of methadone as well as its long half-life limit its utility.

Buprenorphine

Buprenorphine pharmacokinetics have been inadequately studied in patients with hepatic impairment. At this time there is insufficient evidence to permit a recommendation to be made regarding the use of buprenorphine for management of cancer pain in patients with hepatic failure.

Table 16 The Effects of Liver Disease on Opioid Pharmacokinetics
(Table reproduced from Opioids in Cancer Pain, Oxford, 2nd Ed) (426)

Opioid	Bioavailability	Activation	Clearance
Codeine	-	+	+++
Tramadol	-	+	+++
Morphine sulphate	++	-	+
Oxycodone	+	-	+++
Hydromorphone	++	-	+
Fentanyl	+	-	+++
Alfentanil	+	-	++
Methadone	-	-	+

Key: - no effect; + minimal effect; ++ moderate effect; +++strong effect

Table 16 of the DOH_Ireland 2015 guideline

Recommendations on the use of analgesics in liver disease

Table 17 Recommendations on the use of analgesics in liver disease
(Adapted from PANG(19) and Hanna (37))

Drug	Recommendations in liver disease	Comment
Codeine	Avoid use	In moderate hepatic impairment, codeine will have unpredictable efficacy and adverse effects.
Tramadol	Use with caution Avoid in severe	In moderate hepatic impairment, tramadol will have unpredictable efficacy and adverse effects. If use cannot be avoided, increase the dosage interval.
Morphine sulphate	Use with caution	Moderate impairment – use lower doses and extend dosing interval. In severe, hepatic impairment, oral bioavailability may equal that of intravenous.
Oxycodone	Use with caution Avoid in severe	Moderate impairment – use lower doses with a minimum dosing interval of 6 hourly for normal release products.
Targin® (Oxycodone/ naloxone)	Use with caution Avoid in moderate to severe liver disease	Naloxone component may be systemically absorbed and precipitate pain and opioid withdrawal.
Hydromorphone	Use with caution	Dosage reduction necessary. In severe hepatic impairment oral bioavailability may increase significantly. Monitor patient carefully for adverse effects.
Fentanyl	Use with caution	Avoid transdermal products. Single doses appear unaltered by liver disease. May be suitable for the treatment of breakthrough pain.
Alfentanil	Use with caution	Dosage reduction necessary.
Methadone	Not advised	Not advised in moderate liver failure due to the risk of accumulation and fatal adverse effects.

Table 17 of the DOH_Ireland 2015 guideline

5.4.9 KCE 2013

Renal impairment and opioids

Deteriorating kidney function occurs approximately in 60 % of cancer patients (creatinine clearance < 90 ml/min). The prevalence of moderate to severe renal impairment is 4 times greater in cancer patients than in the general population (King 2011). Moreover, often dialyzed patients have a increasing risk to develop cancer (Dutch Guideline on cancer pain 2008).

Codeine and dihydrocodeine

Cancer patients with renal impairment have reduced clearance of codeine, dihydrocodeine and their metabolites. In addition, codeine is metabolized in morphine (see below)... However, Dean et al (2004) discouraged the use of codeine because of the accumulation of its active metabolites and severe adverse events reported in patients with renal impairment.

Morphine

Based on pharmacokinetic evidence reported in King 2011, the Dutch guideline on cancer pain 2008 and SIGN 2008, morphine is converted principally to 2 active metabolites (M3G: morphine-3-glucuronide and M6G: morphine-6-glucuronide). The accumulation of these 2 metabolites are probably responsible for adverse events but conflicting evidence was reported. ... However, all these studies failed to prove a relationship between the concentration of the metabolites (M3G and M6G) with pain intensity, toxicity or need to switch. Only two studies (Wood 1998 and Ashby 1997) highlighted a statistically significant relationship between nausea/vomiting with M3G and M6G.

Oxycodone

Oxycodone and its principal metabolites are excreted by the kidneys. Renal impairment reduces the excretion but the clinical effects of metabolite accumulation is unknown. King et al (2011) identified a prospective observational study (Narabayashi 2008) that reported a higher adequate pain control when morphine is switched for oxycodone in a small sample of patients (9 cancer patients with renal impairment were compared with 18 without impairment).

Hydromorphone

Hydromorphone and its metabolites are excreted renally. The evidence about their toxicity in case of renal impairment is inconsistent.

Methadone

Dutch Guideline on cancer pain 2008 recommended methadone as an alternative of morphine for patients with renal impairment based on pharmacokinetic data). On the same basis, no dosage adjustment is needed.

Fentanyl

After liver metabolism, the metabolites of fentanyl are inactive and nontoxic. Therefore, SIGN 2008 reported two studies (Mercadante 2004 and Launay-Vacher 2005) that concluded that there is no need to adjust dose for patients with renal impairment. King 2011 reported another retrospective study in 53 cancer patients with renal impairment reporting 85 % complete or partial pain relief and 57 % complete or partial improvement of adverse events (Mazzacato 2006). Dutch Guideline on cancer pain 2008 recommended also fentanyl as an alternative of morphine for patients with renal impairment.

Synthetic derivatives of fentanyl

Sufentanil and alfentanil are synthetic derivatives from fentanyl. Alfentanil is used for intravenous, epidural, intrathecal or intramuscular administration; sufentanil is used for intravenous and epidural administration or rarely for intrathecal, intranasal or sublingual administration (Martindale 2009). Sufentanil is an analogue to fentanyl for which the metabolism in humans is not clearly documented. Its use is only mentioned in King 2011. The authors found a retrospective study in 48 patients published as a letter (White 2008) and reported a generally favourable result (no additional

information provided). Alfentanil is a short acting analgesic derivative from fentanyl. This synthetic component is excreted in the urine in form of inactive compounds. King et al (2011) retrieved 2 publications. The first was a retrospective series of 4 patients published as a letter and reported an improvement in agitation when alfentanil was used (Kirkham 1995). The second publication in a retrospective study including cancer and non- cancer patients and concluded a decrease of side effects with alfentanil in comparison with other opioids (Urch 2004).

Pethidine

Pethidine is considered only by King 2011. A retrospective study in 67 patients (19 of whom had cancer) reported a higher concentration of norpethidine, a metabolite of pethidine known for its CNS toxicity (Kaiko 1983). Pethidine is generally not recommended because of its high risk of toxicity (King 2011, Portenoy 2011).

Buprenorphine

Only SIGN 2008 reported that buprenorphine can be considered as safe for renal impaired patients because of its largely unchanged pharmacokinetics (Mercadante 2004 and Launay-Vacher 2005).

Tramadol

King et al (2011) did not find any study concerning the use of tramadol in cancer pain treatment for renal impaired patients. SIGN 2008 and Dutch Guideline on cancer pain 2008 advised however to reduce the dosage and to increase the dosing interval according to the degree of impairment.

Patients undergoing renal dialysis

Dean et al (2004) recommended not to use morphine and codeine in patients with severe renal impairment (creatinine clearance <20 ml/min). Hydromorphone is theoretically excreted by dialyze and can be used for this population group (Dutch Guideline on cancer pain 2008). Methadone and fentanyl are excreted by dialyze and can be a good alternative of morphine in dialyzed patients (Dutch Guideline on cancer pain 2008).

Conclusions

King 2011 et al concluded that it was impossible to formulate recommendations because of the lack of good quality studies including renal impaired cancer patients. Based on pharmacokinetic data, extrapolation from non-cancer pain studies and from clinical experience, the authors stratified the risk of opioid use in renal impairment according to the activity of opioid metabolites, potential for accumulation and reports of successful or harmful use. King 2011 et al concluded that fentanyl, alfentanil and methadone are identified, with caveats, as the least likely to cause harm when used appropriately. Morphine may be associated with toxicity in patients with renal impairment. This toxicity can be satisfactorily dealt with by increasing the dosing interval or reducing the 24 hour dose or by switching to an alternative opioid. The use of hydromorphone in renal impaired cancer patients was associated with toxicity. However, switching from morphine to hydromorphone suggested a greater analgesia and reduced adverse effects in one study.

Liver impairment and opioids

The liver plays a pivotal role in the metabolism of most opioids. Liver dysfunction can affect the

analgesic efficacy and the toxicity of opioids. The authors recommended to avoid oxycodone, codeine, methadone, tramadol and oxymorphone.

Morphine and hydromorphone have to be used cautiously with an increasing dosing interval. Fentanyl appears to be safe without dose adjustment. The authors highlighted however that monitoring is needed when transdermal fentanyl is used.

5.5 Rotation of opioids

5.5.1 Summary

5 guidelines provide guidance on opioid rotation (NPC_Canada 2017, WOREL 2017, NHG 2018, DOH_Ireland 2015, KCE 2013).

Opioid rotation may be useful in some patients with uncontrolled pain, intolerable side effects and/or the need to switch to a new route of opioid administration (e.g. transdermal). It might also be useful to facilitate a dose reduction.

4 guidelines provide conversion tables with approximations of equianalgesic opioid doses (NPC_Canada 2017, WOREL 2017, NHG 2018, DOH_Ireland 2015). These tables should be used with caution due to significant inter-individual variability. The relative potency ratios are not fixed but are affected by the clinical context of the switch and the setting of care. Careful monitoring during opioid rotation is required to avoid either under-dosing, leading to uncontrolled symptoms, or over-dosing, leading to undesirable side-effects (DOH_Ireland 2015).

Opioid rotation should only be performed by those with relevant clinical expertise (DOH_Ireland 2015).

5.5.2 NPC_Canada 2017

- **The guideline suggests rotation to other opioids rather than keeping the opioid the same for patients with chronic noncancer pain who are currently using opioids, and have persistent problematic pain and/or problematic adverse effects. (Weak recommendation)**

Rotation in such patients may be done in parallel with, and as a way of facilitating, dose reduction.

Practical Info

Opioid rotation may be useful in some patients with uncontrolled pain, intolerable side effects and/or the need to switch to a new route of opioid administration (e.g. transdermal). One common scenario for opioid rotation is the switch from morphine to any other conventional opioid because active morphine metabolites can result in drowsiness and confusion – especially in the setting of renal failure. Recognizing that equianalgesic tables provide only a rough approximation of equivalent

opioid potency, calculate the equianalgesic dose of the new opioid based on Table 5 and reduce the calculated dose by 25-50% to minimize the risk of inadvertent overdose. For patients in whom the rationale for opioid rotation is severe uncontrolled pain, administration of the equianalgesic dose without dose reduction may be reasonable. Rotation from conventional opioids to methadone is more complicated and is best carried out by experienced practitioners.

Clinicians may consider the following guidance when opioid rotation is used as a strategy to reduce dose:

1. Decrease the total daily dose of the current oral opioid 10-30% while starting the new oral opioid at the lowest total daily dose for the formulation
2. Decrease the total daily dose of the current opioid 10-25% per week while titrating up the total daily dose of the new opioid weekly by 10-20% with a goal of switching over 3-4 weeks

Practitioners may wish to use the Switching Opioids Tool as a guide when rotating opioids:

http://nationalpaincentre.mcmaster.ca/opioidmanager/documents/opioid_manager_switching_opioids.pdf

Table 5: Opioid conversion table

Opioids*	To convert to oral morphine equivalent, multiply by:	To convert from oral morphine, multiply by:	50 MED equivalent dose	90 MED equivalent dose
Oral preparations (mg/d)				
Codeine	0.15 (0.1-0.2)	6.67	334 mg/d	600 mg/d
Hydromorphone	5.0	0.2	10 mg/d	18 mg/d
Morphine	1.0	1	50mg/d	90mg/d
Oxycodone	1.5	0.667	33 mg/d	60 mg/d
Tapentadol	0.3-0.4	2.5-3.33	160	300
Tramadol	0.1 -0.2	6	300	540**

*Conversion ratios for opioids are subject to variations in kinetics governed by genetics and other drugs.

** The maximum recommended daily dose of tramadol is 300 mg - 400 mg depending on the formulation.

Table 5 of the NPC_Canada 2017 guideline

5.5.3 WOREL 2017

Als men beslist om sterke opioïden te starten, moeten er strategieën worden voorzien om de behandeling, indien ze niet succesvol is of onaanvaardbare bijwerkingen veroorzaakt, geleidelijk te stoppen. Men kan ook overwegen om bij onvoldoende effect of onaanvaardbare bijwerkingen een ander morfineanalgeticum in te zetten (opioïdrotatie). In dat geval baseert men zich best op de dosisconversietabel. Een equivalentietabel van de verschillende opioïden, uit de SIGN-richtlijn van 2013, is hieronder terug te vinden.

Si un traitement par opioïdes forts est décidé, il y a lieu de prévoir des stratégies pour interrompre progressivement le traitement si celui-ci s'avère inefficace ou est à l'origine d'effets indésirables

inacceptables. On peut également envisager de modifier l'analgésique morphinique (rotation des opioïdes), en cas d'effet insuffisant ou d'effets indésirables inacceptables. Dans ce cas, il vaut mieux se référer au tableau de conversion des doses. Un tableau d'équivalence des différents opioïdes, issu de SIGN 2013, est fourni ci-dessous.

Box 2: Suggested dose conversion ratios		
(converting from) Current opioïd	(converting to) New opioïd and/or new route of administration	Divide 24 hour dose* of current opioïd (column 1) by relevant figure below to calculate initial 24 hour dose of new opioïd and/or new route (column 2)
Example 120 mg oral morphine in 24 hours	subcutaneous diamorphine	Divide by 3 (120 mg / 3 = 40 mg subcutaneous diamorphine in 24 hours)
ORAL TO ORAL ROUTE CONVERSIONS		
oral codeine	oral morphine	Divide by 10
oral tramadol	oral morphine	Divide by 5
oral morphine	oral oxycodone	Divide by 2
oral morphine	oral hydromorphone	Divide by 7.5
ORAL TO TRANSDERMAL ROUTE CONVERSIONS		
oral morphine	transdermal fentanyl	Refer to manufacturer's information**
oral morphine	transdermal buprenorphine	Seek specialist palliative care advice
ORAL TO SUBCUTANEOUS ROUTE CONVERSIONS		
oral morphine	subcutaneous morphine	Divide by 2
oral morphine	subcutaneous diamorphine	Divide by 3
oral oxycodone	subcutaneous morphine	No change
oral oxycodone	subcutaneous oxycodone	Divide by 2
oral oxycodone	subcutaneous diamorphine	Divide by 1.5
oral hydromorphone	subcutaneous hydromorphone	Seek specialist palliative care advice
OTHER ROUTE CONVERSIONS RARELY USED IN PALLIATIVE MEDICINE		
subcutaneous or intramuscular morphine	intravenous morphine	No change
intravenous morphine	oral morphine	Multiply by 2
oral morphine	intramuscular morphine	Divide by 2
<p>Conversion ratios between strong opioids: Strong evidence for converting between opioids is lacking, with the majority of studies being single dose, small sample size pharmacokinetic studies, usually in healthy volunteers (see section 12.2). A number of dose conversion charts are available and can be useful, but there is significant inter-individual variability and they should be used with caution, particularly in the elderly; if there are significant other co-morbidities (eg hepatic or renal impairment); or with polypharmacy.</p> <p>* The same units must be used for both opioids or routes, eg mg morphine to mg oxycodone</p> <p>** The conversion ratios of oral morphine:transdermal fentanyl specified by the manufacturer(s) vary from around 100:1 to 150:1</p>		

Box 2 of the WOREL 2017 guideline

5.5.4 CDC 2016

No specific recommendations were provided.

5.5.5 NHG 2018

Switch bij opioïdrotatie vanwege het optreden van bijwerkingen naar 75% van de equivalente 24 uursdosering van het alternatief.

Geef bij rotatie vanwege onvoldoende pijnstilling de equivalente dosering van het alternatief.

Gedurende de eerste dag na het aanbrengen van een pleister is het noodzakelijk het opioïd met vertraagde afgifte in halve dosering oraal erbij te geven.

For more details, see also step 4 in the section “Management of chronic pain with opioids”.

Tabel 6 Omrekenings opiaatrotsatie*

Morfine oraal (mg/24 uur)	Morfine s.c./i.v. (mg/24 uur)	Oxycodon oraal (mg/24 uur)	Oxycodon s.c./i.v. (mg/24 uur)	Fentanyl transdermaal (microg/uur)	Hydromorfon oraal (mg/24 uur)	Hydromorfon s.c./i.v. (mg/24 uur)
30	10	20	10	12	6**	2
60	20	40	20	25	12	4
120	40	80	40	50	24	8
180	60	120	60	75	36	12
240	80	160	80	100	48	16
360	120	240	120	150	72	24
480	160	320	160	200	96	32

Bron: MDR Diagnostiek en behandeling van pijn bij patiënten met kanker, 2016 (richtlijnen database.nl).

* Bij het overgaan van het ene opiaat naar het andere vanwege bijwerkingen wordt geadviseerd om 75% van de equivalente 24-uursdosering te geven.

** Deze dosering kan in de praktijk niet gegeven worden omdat de laagst beschikbare dosering 2 dd 4 mg met vertraagde afgifte is.

5.5.6 NICE 2017

No specific recommendations were provided.

5.5.7 ASCO 2016

No specific recommendations were provided.

5.5.8 DOH_Ireland 2015

Key finding

Opioid rotation utilises inter-individual variability and the phenomenon of incomplete cross tolerance in order to maximise the analgesic effect of a new opioid while minimising side effects.

- **Opioid reduction or rotation should be considered as a useful strategy to manage opioid side-effects. (recommendation category B)**

- **Haloperidol may be recommended for those patients experiencing agitation, hallucinations and perceptual disturbances. Opioid reduction or rotation should be considered. (recommendation category D)**
- **Opioid rotation should be performed where pain is poorly controlled, or side-effects are intolerable. Opioid rotation should only be performed by those with relevant clinical expertise. (recommendation category B)**

Opioid rotation has become common practice in the management of cancer pain. It has been found to be necessary in approximately 20% - 44% of cancer patients.

Data has shown that opioid rotation leads to clinical improvement in more than 50% of patients with a poor response to one opioid.

Pharmacology of opioid rotation

The biological mechanisms for the observed beneficial effect of switching from one opioid to another are not fully understood.

- *A significant factor in explaining the rationale for opioid rotation is inter-individual variability in the pharmacokinetics, pharmacodynamics, and pharmacogenetics of strong opioids.*
- *Incomplete cross-tolerance describes the phenomenon of reduced tolerance to a new opioid compared to a previously used opioid. This allows for a lower equivalent dose of a new opioid to achieve similar pain control as the higher dose of the initial opioid, thus potentially reducing side-effects.*
- *The role of genetic polymorphisms in inter-individual variation in response to opioid has yet to be fully elucidated. Further research may allow prospective prediction of inter-individual response to different opioids, and strategic opioid prescribing.*
- *Opioids differ in their binding to mu, delta and kappa receptors, although all opioids in common clinical use appear to produce the majority of their analgesic effect through mu-opioid receptor agonism. Variations in receptor types, receptor interactions, density and binding may lead to inter-individual variation in response to opioids.*

Dose conversion ratios used for opioid rotation

When converting from an 'initial' opioid to a new opioid, the dose of the new opioid should depend on the relative potency ratio of the two drugs. However, limitations in the evidence mean that relative potency ratios, and descriptions of equianalgesic doses of opioids, can only represent an approximate guide. Clinicians must remember that opioid dose conversion ratios are not fixed but are affected by the clinical context of the switch and the setting of care. Careful monitoring during opioid rotation is required to avoid either under-dosing, leading to uncontrolled symptoms, or over-dosing, leading to undesirable side-effects. Indeed, Webster and Fine (2012) caution that increases in morbidity and mortality attributable to errors in opioid rotation have been observed in the last decade. They cite inadequate prescriber's competence, proliferation of inconsistent guidelines for opioid rotation, conflation of equianalgesic tables as conversion tables, and limitations inherent in the equianalgesic dose tables as contributory causes.

Indications for opioid rotation

Predictable side-effects such as nausea and drowsiness on initiation of a strong opioid are expected to resolve within days, and are not an indication to opioid rotate. Prior to opioid rotation, it should be ensured that measures to manage side-effects have been attempted, e.g. optimising laxatives and anti-emetics. Where opioid rotation is being considered due to poorly controlled pain, the use of adjuvant agents or non-pharmacological interventions should be considered in addition to opioid analgesia.

If side-effects are experienced while taking a stable dose of an opioid that has previously been well tolerated, other factors contributing to opioid toxicity should be considered, such as infection, dehydration, renal impairment or hypercalcaemia.

Opioid rotation may be indicated in many clinical scenarios, including:

- *In order to improve adherence to analgesia e.g. by using a more convenient route of administration such as transdermal patch*
- *In order to improve unacceptable opioid side-effects, including symptoms of neurotoxicity or opioid-induced hyperalgesia*
- *Where there has been rapid development of tolerance to an opioid*
- *In order to rationalise the choice of opioid, where there has been a significant change in condition e.g. development of renal failure.*

Dose reduction post-opioid rotation

To take into account the phenomenon of incomplete cross-tolerance, a dose reduction for the first 12 to 24 hours of alternative opioid should be considered, especially when rotating between high doses. There is no definite evidence currently for the optimal percentage dose reduction, but a range from 25-50% has been suggested in the literature.

Opioid potency ratios

Key finding

There is evidence for the usefulness of opioid rotation as a clinical strategy to optimise analgesia and limit side effects. There is less robust evidence to support the relative drug potency ratios commonly used in practice.

- **Evidence-based relative potency ratios should be applied, taking into account individual patient factors. Pain control should be assessed regularly and doses titrated as required. (recommendation category D)**

When converting from one strong opioid to another, the initial dose of the new opioid should depend on the relative potency of the two drugs, as well as other clinical factors.

... Therefore, the relative drug potency ratio used should not be a simple mathematical calculation, but should take in to account the underlying clinical situation.

Attention to monitoring and dose titration is required, especially when:

- *Rotating between opioids at high doses,*
- *When there has been a rapid recent up-titration in the dose of the primary opioid,*
- *When rotating to or from methadone.*

Dose reduction post-opioid rotation

To take into account the phenomenon of incomplete cross-tolerance, a dose reduction for the first 12 to 24 hours of alternative opioid should be considered, especially when rotating between high doses. There is no definite evidence currently for the optimal percentage dose reduction, but a range from 25-50% has been suggested in the literature.

Relative potencies of individual opioids

Note – most relative potencies relate to the relative potency of a strong opioid in relation to morphine sulphate. When switching from a strong opioid other than morphine sulphate, it may be necessary to convert the dose of the initial opioid to the oral morphine sulphate equivalent dose, and then use this to determine the dose of the new opioid.

Key finding

Despite limitations, there is evidence from randomised controlled trials to support the use of a conversion ratio of oral morphine sulphate to oral oxycodone of between 1.5 : 1 and 2 : 1.

- **A relative potency ratio of oral morphine sulphate to oral oxycodone of between 1.5 : 1 and 2 : 1 is recommended. (recommendation category B)**
- **A relative potency ratio of oral morphine sulphate to oral hydromorphone of 5 : 1 is recommended. (recommendation category C)**

Key finding

Buprenorphine is a partial mu-receptor agonist and a partial kappa-receptor antagonist and has slow receptor dissociation that may impede the full effectiveness of other opioids used. Evidence is limited regarding the equipotency of transdermal buprenorphine and other opioids.

- **A relative potency ratio of oral morphine sulphate to transdermal buprenorphine of 75 : 1 is recommended. (recommendation category C)**
- **A relative potency ratio of oral morphine sulphate to transdermal fentanyl of 100 : 1 is recommended. (recommendation category B)**

More details about switching to or from transdermal opioids can be found in the DOH_Ireland 2015 guideline.

Key finding

The relative potency ratio from morphine sulphate : methadone increases as the dose of morphine sulphate increases.

When switching back from methadone to morphine sulphate, a conservative ratio of 1:1 should be used initially, and the dose of morphine sulphate uptitrated as required.

With regard to methods for switching to methadone from another strong opioid over another, there is not enough evidence to determine the superiority of one method over another. The 'ad libitum' stop and go (SAG) method and the 3 day switch (3DS) methods both appear safe and efficacious in small, non-randomised studies. The 'rapid conversion' SAG method appears to risk excess toxicity at high opioid doses.

- **Consensus-based relative potency ratios should be utilised when switching from a strong opioid to methadone, and doses should be titrated up or down following the switch. (recommendation category C)**
- **Methadone is a complex strong analgesic agent and should be used under specialist supervision only. (recommendation category D)**

Table 8 Oral morphine sulphate dose conversion to oral methadone
(adapted from NCCN Guidelines (52))

Oral morphine sulphate	Dose conversion ratio to oral methadone (oral morphine sulphate : oral methadone)
30 – 90mg	4 : 1
91 – 300mg	8 : 1
> 300mg	12 : 1

Table 8 of the DOH_Ireland 2015 guideline

It is important to note that the above conversion ratios do NOT apply when converting from methadone to an alternative strong opioid. This is due to the highly lipophilic nature of methadone and the long elimination half-life which results. On discontinuation of methadone, a conservative ratio for oral morphine sulphate : oral methadone of 1 : 1 may be used, and supplemented with additional short acting morphine sulphate as needed. The dose of morphine sulphate or other strong opioid will require frequent dose adjustment and uptitration in the following days as methadone clears.

The use of methadone is challenging due to its unique pharmacological properties in comparison to most other opioids used for cancer pain. Methadone use outside of the specialist setting is not recommended.

More details on the methods of rotating from morphine sulphate or other strong opioids to methadone can be found in the DOH_Ireland 2015 guideline.

Opioid rotation: conclusions

Opioid switching is a useful therapeutic tool, used in order to maximise analgesia and limit side-effects. The relative potency ratios used to convert doses should take into account the clinical context and the needs of the individual patient.

It is difficult to reproduce complex clinical situations in randomised controlled blinded trials, but prospective studies provide good evidence for predictable conversion ratios between oral hydromorphone, oral morphine sulphate, oral oxycodone and transdermal fentanyl.

Opioid switching to methadone requires expertise, and requires frequent reevaluation to adjust opioid doses. Randomised controlled studies are required to provide definitive recommendations based on more solid evidence.

Practical Guidance

- 1. Most relative potencies relate to the relative potency of a strong opioid in relation to morphine sulphate. When switching from a strong opioid other than morphine sulphate, it may be necessary to convert the dose of the initial opioid to the oral morphine sulphate equivalent dose, and then use this to determine the dose of the new opioid.*
- 2. Buprenorphine is a partial mu-receptor agonist and a partial kappa-receptor antagonist and has slow receptor dissociation that may impede the full effectiveness of other opioids used.*
- 3. Fentanyl and buprenorphine are most commonly used via a transdermal patch and in patients with stable pain where the oral route is not possible or not convenient. When using patches, it is recommended that an interval of at least three days should be used between dose changes. This is to allow time for steady state of the drug to be achieved. When converting from a patch to an oral or parenteral opioid, this also needs to be considered: please see full guideline for further guidance, or seek specialist advice.*

Table 9 Weak opioids – Equivalence to oral morphine sulphate

Codeine	Morphine sulphate	Tramadol
24 hr total oral dose (mg)	24 hr total oral dose (mg)	24 hr total oral dose (mg)
60mg	6	50
-	10	100
240mg	20	200
-	30	
-	40	400
-	50	
-	60	
-	70	
-	80	

Table 9 of the DOH_Ireland 2015 guideline

Table 11 Processes for converting opioids

Converting From	Converting To	Process
Oral (mg)	Oral (mg)	
Codeine	Morphine sulphate	Divide by 10
Tramadol	Morphine sulphate	Divide by 5 – 10
Morphine sulphate	Oxycodone	Divide by 1.5 – 2
Morphine sulphate	Hydromorphone	Divide by 5
Oral (mg) / 24 hours	Subcutaneous / 24 hours	
Morphine sulphate	Fentanyl (mcg)	Divide by 100 to obtain equivalent fentanyl dose in mg. Multiply by 1000 to obtain dose in mcg / 24 hrs.
Morphine sulphate	Alfentanil (mg)	Divide by 32
Oral (mg) / 24h hours	Transdermal (mcg / hour)	
Morphine sulphate	Buprenorphine	Divide by 75 to obtain equivalent buprenorphine dose in mg. Multiply by 1000 to obtain dose in mcg / 24 hrs. Divide this by 24 to obtain equivalent transdermal dose in mcg / hour, and use closest available patch strength.
Morphine sulphate	Fentanyl	Divide by 100 to obtain equivalent fentanyl dose in mg. Multiply by 1000 to obtain dose in mcg / 24hrs. Divide this by 24 to obtain equivalent transdermal dose in mcg / hour, and use closest available patch strength.
	Alternatively, use Table 10 to obtain closest appropriate patch strength	

Table 11 of the DOH_Ireland 2015 guideline

Opioid Equivalence Summary Table⁶

Guidelines for use:

- relative potency ratios should only be used as an approximate guide and individual and clinical factors should be taken into account*
- on opioid rotation, particularly at high doses, a dose reduction of 25 – 50% should be considered to account for incomplete cross-tolerance*
- pain control should be assessed regularly, and doses titrated as required.*

⁶ Tapentadol is a relatively new opioid. It was not included in this opioid equivalence table, probably due to lack of data.

Table 12 Opioid Equivalence Summary Table
(all recommendations Grade C)

Morphine		Codeine	Tramadol	Oxycodone		Hydromorphone		Buprenorphine		Fentanyl	Morphine	
(mg / 24 hrs)		(mg / 24 hrs)	(mg / 24 hrs)	(mg / 24 hrs)		(mg / 24 hrs)		(mcg / hour) Butrans®	(mcg / hour) Transtec®	(mcg / hour)	(mg / 24 hrs)	
Oral	S/C	Oral	Oral	Oral	S/C	Oral	S/C	Transdermal		Transdermal	Oral	S/C
5	2.5	60	50	-	-	-	-	-		-	5	2.5
10	5	120	100	-	-	-	-	5	See Butrans®		10	5
20	10	240	200	-	-	4	2	10		12	20	10
30	15	Titrate to strong opioid		20	10	6	3			20	18	30
40	20		8			4	40	20				
50	25		-	-	10	5	35	25	50	25		
60	30		40	20	12	6			See Transtec®	52.5	60	30
70	35				14	7		70			35	
80	40				16	8		37			80	40
90	45		60	30	18	9			90	45		
100	50				20	10			100	50		
110	55				-	-	50	110	55			
120	60				24	12		120	60			
130	65		80	40	-	-	70	62	130	65		
140	70				28	14			140	70		
150	75				-	-			150	75		
160	80				100	50			32	16	160	80
170	85		-	-			Consider the use of an alternative opioid	75	170	85		
180	90		36	18					180	90		
190	95		-	-					190	95		
200	100		-	-	-	200			100			
Converting From				Converting To						Process		
Oral				Oral								
Codeine				Morphine sulphate						Divide by 10		
Tramadol				Morphine sulphate						Divide by 5 – 10		
Morphine sulphate				Oxycodone						Divide by 1.5 – 2		
Morphine sulphate				Hydromorphone						Divide by 5		
Converting From				Converting To						Process		
Oral (mg / 24 hrs)				S/C (mg / 24 hrs)								
Morphine sulphate				Alfentanil						Divide by 32		

Table 12 of the DOH_Ireland 2015 guideline

5.5.9 KCE 2013

- The available evidence does not allow to conclude on the effectiveness of opioid rotation in patients with inadequate pain relief and intolerable opioid-related toxicity or adverse effects. However, opioid rotation can be a treatment option in some of these patients,

after a thorough reassessment of pain management has been performed (very low level of evidence; strong recommendation).

Opioid rotation or switching is the term given to the clinical practice of substituting one strong opioid with another, in an attempt to achieve a better balance between pain relief and side effects (Quigley 2010). When opioids are switched, analgesia is often achieved at doses lower than equianalgesic dose conversions would suggest necessary. Opioid rotation or switching is an established clinical practice for patients with cancer pain (Quigley 2010).

The SRs dealing with this topic concluded as follows:

Dale 2011 concluded that firm evidence for the efficacy of opioid switching is lacking. However, the authors stated that opioid switching may well be a useful clinical manoeuvre in some patients.

Quigley 2010 concluded that switching to an alternative opioid may be an option in patients with inadequate pain relief and intolerable opioid-related toxicity or adverse effects. However, evidence supporting this practice is anecdotal and RCTs are needed.

According to the expert panel (see colophon), there is a lot of clinical evidence that points to the usefulness of opioid rotation in patients with inadequate pain relief and intolerable opioid-related adverse effects. Drug dosing is considered to be out of scope of the present review, however it is an important issue when switching from one opioid to another. For principles underpinning a rational choice of the new opioid during rotation, see Vissers et al. (2010).

5.6 Tapering/Deprescribing

For which situations or indications is deprescribing of opioids recommended?

Which methods of deprescribing are available?

5.6.1 Summary

All patients on long-term opioids at all doses should be regularly evaluated and counselled about the benefits and harms of ongoing therapy and the potential benefits of tapering.

Reasons for tapering include lack of improvement in pain and/or function, high-risk regimens (e.g., dosages ≥ 50 MME/day or opioids combined with benzodiazepines), nonadherence to the treatment plan, signs of substance misuse, serious opioid-related adverse events, and patient request.

There are no high-quality studies that compare the effectiveness of different tapering protocols (CDC 2016). The NPC_Canada 2017 and the CDC_2016 guideline provide more detailed information on how to taper opioids than the other selected guidelines. The tapering plan should be individualized for each patient.

5.6.2 NPC_Canada 2017

- **The guideline suggests tapering opioids to the lowest effective dose, potentially including discontinuation, rather than making no change in opioid therapy for patients with chronic noncancer pain who are currently using 90mg morphine equivalents of opioids per day or more. (Weak recommendation)**

Some patients are likely to experience significant increase in pain or decrease in function that persists for more than one month after a small dose reduction; tapering may be paused and potentially abandoned in such patients.

Practical Info

There are a number of specific reasons to consider opioid tapering:

- *Lack of improvement in pain and/or function*
- *Nonadherence to the treatment plan*
- *Signs of substance misuse*
- *Serious opioid-related adverse event*
- *Patient request*

Otherwise, all patients on long-term opioids at all doses should be regularly evaluated and counselled about the benefits and harms of ongoing therapy and the potential benefits of tapering.

Opioid benefits may attenuate with time (owing to tolerance and/or hyperalgesia) and for some patients may come to be defined, in whole or in part, by the relief of interdose withdrawal symptoms. The potential harms of opioids generally increase with dose, and some may not be attributed to the drugs (particularly depression, hormonal disturbance, sleep disturbance and opioid-induced hyperalgesia).

Patients on high doses (≥ 90 mg MED/day) should be prioritized for gradual opioid tapering. The balance of benefits and harms often becomes unfavourable at doses above 90mg MED/day. For these patients the potential harms of therapy often outweigh the benefits the patient can achieve in terms of pain and function.

Patients should be actively engaged in a discussion about the merits of gradual dose reduction, including the potential for better pain control and quality of life. Prepare the patient for tapering by optimizing non-opioid strategies for pain management, setting realistic functional goals, optimizing psychosocial support, creating a schedule of dose reductions and follow-up visits and having a plan in place to manage withdrawal symptoms and emerging pain. Establishing a plan with patients takes the uncertainty out of the process and helps engage them in the process (see nationalpaincentre.mcmaster.ca/guidelines for a Patient Information Sheet for Tapering).

A gradual dose reduction of 5-10% of the morphine equivalent dose every 2-4 weeks with frequent follow up is a reasonable rate of opioid tapering. Switching the patient from immediate release to controlled release opioids on a fixed dosing schedule may assist some patients in adhering to the

withdrawal plan. Patients and physicians may wish to consult a pharmacist to assist with scheduling dose reductions.

Alternative methods of tapering include:

- *Reducing the dose rapidly over a few days/weeks or immediately: This method may result in severe withdrawal symptoms and is best carried out in a medically supervised withdrawal centre*
- *Tapering with methadone or buprenorphine-naloxone preparations: patients may be rotated to methadone or buprenorphine-naloxone and then gradually tapered. In Canada, all physicians prescribing methadone require a Federal exemption for pain or addiction. The requirement for supplementary training for the use of buprenorphine-naloxone varies from province to province. If unfamiliar, clinicians should consult with someone knowledgeable with buprenorphine-naloxone use.*

In patients struggling with the tapering plan (distressing or intolerable pain/withdrawal symptoms/decreased function which persists longer than 4 weeks), pausing the taper and re-evaluating the patient's pain/clinical status/coping mechanisms and the approach to tapering can help formulate a go-forward plan. (See the following recommendation)

In patients with the emergence of significant mental health symptoms and/or ambiguous drug-related behaviours, consultation with local experts is advised.

Patients should be encouraged to taper to the lowest opioid dose achievable without a loss of previously achieved function. Some patients may not eliminate use of opioids, but any reduction in dose may be beneficial.

- **The guideline recommends a formal multidisciplinary program for patients with chronic noncancer pain who are using opioids and experiencing serious challenges in tapering. (Strong recommendation)**

Recognizing the cost of formal multidisciplinary opioid reduction programs and their current limited availability/capacity, an alternative is a coordinated multidisciplinary collaboration that includes several health professionals whom physicians can access according to their availability (possibilities include, but are not limited to, a primary care physician, a nurse, a pharmacist, a physical therapist, a chiropractor, a kinesiologist, an occupational therapist, an addiction specialist, a psychiatrist, and a psychologist).

Practical Info

Serious challenges in tapering could include re-emergence of or new functional or psychological impairment, aberrant behaviors around opioid use, or behaviors indicative of an emerging or overt substance use disorder.

5.6.3 WOREL 2017

No specific recommendations were provided.

5.6.4 CDC 2016

- **Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids (recommendation category: A, evidence type: 4).**

Established patients already taking high dosages of opioids, as well as patients transferring from other clinicians, might consider the possibility of opioid dosage reduction to be anxiety-provoking, and tapering opioids can be especially challenging after years on high dosages because of physical and psychological dependence. However, these patients should be offered the opportunity to re-evaluate their continued use of opioids at high dosages in light of recent evidence regarding the association of opioid dosage and overdose risk. Clinicians should explain in a nonjudgmental manner to patients already taking high opioid dosages (≥ 90 MME/day) that there is now an established body of scientific evidence showing that overdose risk is increased at higher opioid dosages. Clinicians should empathically review benefits and risks of continued high-dosage opioid therapy and should offer to work with the patient to taper opioids to safer dosages. For patients who agree to taper opioids to lower dosages, clinicians should collaborate with the patient on a tapering plan. Experts noted that patients tapering opioids after taking them for years might require very slow opioid tapers as well as pauses in the taper to allow gradual accommodation to lower opioid dosages. Clinicians should remain alert to signs of anxiety, depression, and opioid use disorder that might be unmasked by an opioid taper and arrange for management of these co-morbidities. For patients agreeing to taper to lower opioid dosages as well as for those remaining on high opioid dosages, clinicians should establish goals with the patient for continued opioid therapy, maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate, and consider consulting a pain specialist as needed to assist with pain management.

If clinically meaningful improvements in pain and function are not sustained, if patients are taking high-risk regimens (e.g., dosages ≥ 50 MME/day or opioids combined with benzodiazepines) without evidence of benefit, if patients believe benefits no longer outweigh risks or if they request dosage reduction or discontinuation, or if patients experience overdose or other serious adverse events (e.g., an event leading to hospitalization or disability) or warning signs of serious adverse events, clinicians should work with patients to reduce opioid dosage or to discontinue opioids when possible.

For patients with problematic opioid use that does not meet criteria for opioid use disorder, experts noted that clinicians can offer to taper and discontinue opioids.

Although the clinical evidence review did not find high-quality studies comparing the effectiveness of different tapering protocols for use when opioid dosage is reduced or opioids are discontinued, tapers reducing weekly dosage by 10%–50% of the original dosage have been recommended by other clinical guidelines, and a rapid taper over 2–3 weeks has been recommended in the case of a severe adverse event such as overdose. Experts noted that tapers slower than 10% per week (e.g., 10% per month) also might be appropriate and better tolerated than more rapid tapers, particularly when patients have been taking opioids for longer durations (e.g., for years). Opioid withdrawal during pregnancy has been associated with spontaneous abortion and premature labor.

When opioids are reduced or discontinued, a taper slow enough to minimize symptoms and signs of opioid withdrawal (e.g., drug craving, anxiety, insomnia, abdominal pain, vomiting, diarrhea, diaphoresis, mydriasis, tremor, tachycardia, or piloerection) should be used. A decrease of 10% of the original dose per week is a reasonable starting point; experts agreed that tapering plans may be individualized based on patient goals and concerns. Experts noted that at times, tapers might have to be paused and restarted again when the patient is ready and might have to be slowed once patients reach low dosages. Tapers may be considered successful as long as the patient is making progress. Once the smallest available dose is reached, the interval between doses can be extended. Opioids may be stopped when taken less frequently than once a day. More rapid tapers might be needed for patient safety under certain circumstances (e.g., for patients who have experienced overdose on their current dosage). Ultrarapid detoxification under anesthesia is associated with substantial risks, including death, and should not be used. Clinicians should access appropriate expertise if considering tapering opioids during pregnancy because of possible risk to the pregnant patient and to the fetus if the patient goes into withdrawal. Patients who are not taking opioids (including patients who are diverting all opioids they obtain) do not require tapers. Clinicians should discuss with patients undergoing tapering the increased risk for overdose on abrupt return to a previously prescribed higher dose. Primary care clinicians should collaborate with mental health providers and with other specialists as needed to optimize nonopioid pain management, as well as psychosocial support for anxiety related to the taper. More detailed guidance on tapering, including management of withdrawal symptoms has been published previously. If a patient exhibits signs of opioid use disorder, clinicians should offer or arrange for treatment of opioid use disorder and consider offering naloxone for overdose prevention.

5.6.5 NHG 2018

The following was mentioned in step 4 in the section “Management of chronic pain with opioids”.

- *Indien door afname van de pijn de dosering verlaagd kan worden, doe dit dan geleidelijk om lichamelijke onthoudingsverschijnselen te voorkomen. Halveer de dosering elke twee tot zeven dagen.*

5.6.6 NICE 2017

No specific recommendations were provided.

5.6.7 ASCO 2016

- **If opioids are no longer warranted, clinicians should taper the dose to avoid abstinence syndrome. The rate of tapering and the use of cotherapies to reduce adverse effects should be individualized for each patient. (Evidencebased and informal consensus; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)**

For clinicians aiming to discontinue long-term opioid therapy, the ASCO 2016 guideline refers to other guidelines and systematic reviews.

5.6.8 DOH_Ireland 2015

Patients recovering from addiction

- For patients recovering from addiction, opioids should be tapered when their pain allows.

For all patients with a history of substance abuse, the use of adjuvant agents and non-pharmacological interventions should be maximised. (recommendation category D)

Best Practice Point: Management of opioid toxicity

Mild opioid toxicity: In mild opioid toxicity; reduce the dose of opioid. Ensure adequate hydration and treat any underlying cause. If agitation/confusion are problematic, consider a neuroleptic such as haloperidol.

If diversion is occurring or risks now exceed benefit, taper and discontinue.

5.6.9 KCE 2013

No specific recommendations were provided.

5.7 Opioids and substance use disorder

5.7.1 Summary

Opioid use in patients with substance use disorder

In non-cancer patients with an **active substance use disorder**, the NPC_Canada 2017 guideline recommends against the use of opioids (Strong recommendation).

In non-cancer patients with a **history of substance use disorder**, whose nonopioid therapy has been optimized, and who have persistent problematic pain, the guideline suggests continuing nonopioid therapy rather than a trial of opioids (Weak recommendation).

In patients with a history of addiction, short acting formulations such as transmucosal fentanyl preparations should be avoided due to their greater abuse potential (ASCO 2016, DOH_Ireland 2015).

Risk mitigation/prevention of abuse/misuse

Screening and risk-assessment instruments are available to identify patients at higher risk for misuse or abuse of opioids (NPC_Canada, CDC 2016, ASCO 2016).

Risk factors for opioid-related harms should be evaluated before starting and periodically during continuation of opioid therapy.

The guidelines describe a universal approach or provide recommendations to mitigate the risk for abuse, addiction, overdose, and other adverse events. Recommended interventions include urine drug testing, treatment agreements, review of prescription drug monitoring data, pill counts, and education (NPC_Canada 2017, CDC 2016, ASCO 2016, DOH_Ireland 2015). However, the implementation of some of the mentioned interventions are not common practice in Belgium. The NPC_Canada 2017 guideline and the CDC 2016 found no or low to very low evidence for for these interventions. However, the guidelines provide arguments for this approach that could augment patient safety. The ASCO 2016 guideline refers to evidence in favour of these interventions.

Some guidelines mention the use of tamper-resistant or abuse deterrent formulations to avoid or deter abuse. Tamper-resistant formulations, designed to impede normal crushing or dissolving of the product are currently not available in Belgium. Some formulations that ‘may’ deter abuse by adding naloxone to the opioid are available on the Belgian market (e.g. tilidine + naloxone).

Multiple guidelines recommend the use of methadone under specialist supervision because of the risks of accumulation and toxicity. In Belgium, primary care physicians need to fulfill certain conditions to prescribe substitution therapy. They need to be registered and work closely with addiction services⁷. An exception is made for physicians who do not treat more than 2 patients simultaneously with substitution therapy.

5.7.2 NPC_Canada 2017

- **The guideline recommends against the use of opioids for patients with chronic noncancer pain with an active substance use disorder. (Strong recommendation)**

Clinicians should facilitate treatment of the underlying substance use disorders, if not yet addressed. The studies that identified substance use disorder as a risk factor for adverse outcomes characterized the conditions as alcohol abuse and dependence, narcotic abuse and dependence, and sometimes referred to ICD-9 diagnoses.

Practical Info

Patients with chronic pain and probable substance use should be screened with the CAGE substance abuse screening tool or similar validated questionnaire for alcohol use, and validated substance abuse/misuse tools such as the Current Opioid Misuse Measure (COMM). Although not evidence-based, urine drug testing and review of prescription drug monitoring data is suggested initially and periodically.

- **The guideline suggests continuing nonopioid therapy rather than a trial of opioids for patients with chronic noncancer pain with a history of substance use disorder, whose**

⁷ “professionele drughulpverleningscentra/-netwerken” or “les centres/réseaux professionnels d’aide aux toxicomanes”. <https://www.ordomedic.be/nl/adviezen/advies/behandeling-met-methadon-en-andere-substitutie medicatie-door-huisartsen>

nonopioid therapy has been optimized, and who have persistent problematic pain. (Weak recommendation)

The studies that identified a history of substance use disorder as a risk factor for adverse outcomes characterized the conditions as alcohol abuse and dependence, and narcotic abuse and dependence, and sometimes referred to ICD-9 diagnoses.

5.7.3 WOREL 2017

De combinatie van codeïne, cafeïne of andere psychotrope middelen met paracetamol kan chronisch gebruik en misbruik in de hand werken.

L'association de codéine, de caféine ou d'autres psychotropes au paracétamol, pourrait favoriser une prise chronique et un abus.

Als men beslist om sterke opioïden te starten, moeten er strategieën worden voorzien om de behandeling, indien ze niet succesvol is of onaanvaardbare bijwerkingen veroorzaakt, geleidelijk te stoppen. Men kan ook overwegen om bij onvoldoende effect of onaanvaardbare bijwerkingen een ander morfineanalgeticum in te zetten (opioïdrotatie). In dat geval baseert men zich best op de dosisconversietabel. Bij chronisch gebruik van een morfineanalgeticum kan een laxativum obstipatie wellicht voorkomen. Het risico op opioïdafhankelijkheid moet met de patiënt worden besproken.

Si un traitement par opioïdes forts est décidé, il y a lieu de prévoir des stratégies pour interrompre progressivement le traitement si celui-ci s'avère inefficace ou est à l'origine d'effets indésirables inacceptables. On peut également envisager de modifier l'analgésique morphinique (rotation des opioïdes), en cas d'effet insuffisant ou d'effets indésirables inacceptables. Dans ce cas, il vaut mieux se référer au tableau de conversion des doses. En cas d'utilisation chronique d'un analgésique morphinique, il convient probablement de prévenir la constipation au moyen d'un laxatif. Le risque de dépendance aux opiacés doit être évoqué avec le patient.

5.7.4 CDC 2016

- **Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥ 50 MME/day), or concurrent benzodiazepine use, are present (recommendation category: A, evidence type: 4).**

Illicit drugs and alcohol are listed as contributory factors on a substantial proportion of death certificates for opioid-related overdose deaths (contextual evidence review). Previous guidelines have recommended screening or risk assessment tools to identify patients at higher risk for misuse or abuse of opioids. However, the clinical evidence review found that currently available risk-

stratification tools (e.g., Opioid Risk Tool, Screener and Opioid Assessment for Patients with Pain Version 1, SOAPP-R, and Brief Risk Interview) show insufficient accuracy for classification of patients as at low or high risk for abuse or misuse.

Clinicians should ask patients about their drug and alcohol use. Single screening questions can be used. “How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?”...

Validated screening tools such as the Drug Abuse Screening Test (DAST) and the Alcohol Use Disorders Identification Test (AUDIT) can also be used. Clinicians should use prescription drug monitoring program (PDMP) data and drug testing as appropriate to assess for concurrent substance use that might place patients at higher risk for opioid use disorder and overdose. Clinicians should also provide specific counseling on increased risks for overdose when opioids are combined with other drugs or alcohol and ensure that patients receive effective treatment for substance use disorders when needed.

If clinicians consider opioid therapy for chronic pain outside of active cancer, palliative, and end-of-life care for patients with drug or alcohol use disorders, they should discuss increased risks for opioid use disorder and overdose with patients, carefully consider whether benefits of opioids outweigh increased risks, and incorporate strategies to mitigate risk into the management plan, such as considering offering naloxone (see *Offering Naloxone to Patients When Factors That Increase Risk for Opioid-Related Harms Are Present*) and increasing frequency of monitoring when opioids are prescribed. Because pain management in patients with substance use disorder can be complex, clinicians should consider consulting substance use disorder specialists and pain specialists regarding pain management for persons with active or recent past history of substance abuse. Experts also noted that clinicians should communicate with patients’ substance use disorder treatment providers if opioids are prescribed.

- **Clinicians should review the patient’s history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months (recommendation category: A, evidence type: 4).**

Similar prescription drug monitoring programs (PDMP) are not available in Belgium.

The clinical evidence review did not find studies evaluating the effectiveness of PDMPs on outcomes related to overdose, addiction, abuse, or misuse. However, even though evidence is limited on the effectiveness of PDMP implementation at the state level on prescribing and mortality outcomes (28), the contextual evidence review found that most fatal overdoses were associated with patients receiving opioids from multiple prescribers and/or with patients receiving high total daily opioid dosages; information on both of these risk factors for overdose are available to prescribers in the PDMP. PDMP data also can be helpful when patient medication history is not otherwise available (e.g., for patients from other locales) and when patients transition care to a new clinician. The contextual evidence review also found that PDMP information could be used in a way that is harmful

to patients. For example, it has been used to dismiss patients from clinician practices (211), which might adversely affect patient safety.

If patients are found to have high opioid dosages, dangerous combinations of medications, or multiple controlled substance prescriptions written by different clinicians, several actions can be taken to augment clinicians' abilities to improve patient safety which are further discussed in the CDC 2016 guideline.

- **When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs (recommendation category: B, evidence type: 4).**

Concurrent use of opioid pain medications with other opioid pain medications, benzodiazepines, or heroin can increase patients' risk for overdose. Urine drug tests can provide information about drug use that is not reported by the patient. In addition, urine drug tests can assist clinicians in identifying when patients are not taking opioids prescribed for them, which might in some cases indicate diversion or other clinically important issues such as difficulties with adverse effects. Urine drug tests do not provide accurate information about how much or what dose of opioids or other drugs a patient took. The clinical evidence review did not find studies evaluating the effectiveness of urine drug screening for risk mitigation during opioid prescribing for pain. The contextual evidence review found that urine drug testing can provide useful information about patients assumed not to be using unreported drugs. Urine drug testing results can be subject to misinterpretation and might sometimes be associated with practices that might harm patients (e.g., stigmatization, inappropriate termination from care). Routine use of urine drug tests with standardized policies at the practice or clinic level might destigmatize their use. Although random drug testing also might destigmatize urine drug testing, experts thought that truly random testing was not feasible in clinical practice. Some clinics obtain a urine specimen at every visit, but only send it for testing on a random schedule. Experts noted that in addition to direct costs of urine drug testing, which often are not covered fully by insurance and can be a burden for patients, clinician time is needed to interpret, confirm, and communicate results.

Experts agreed that prior to starting opioids for chronic pain and periodically during opioid therapy, clinicians should use urine drug testing to assess for prescribed opioids as well as other controlled substances and illicit drugs that increase risk for overdose when combined with opioids, including nonprescribed opioids, benzodiazepines, and heroin. There was some difference of opinion among experts as to whether this recommendation should apply to all patients, or whether this recommendation should entail individual decision making with different choices for different patients based on values, preferences, and clinical situations. While experts agreed that clinicians should use urine drug testing before initiating opioid therapy for chronic pain, they disagreed on how frequently urine drug testing should be conducted during long-term opioid therapy. ...However, experts thought that predicting risk prior to urine drug testing is challenging and that currently available tools do not allow clinicians to reliably identify patients who are at low risk for substance use disorder.

... Clinicians should not test for substances for which results would not affect patient management or for which implications for patient management are unclear. For example, experts noted that there might be uncertainty about the clinical implications of a positive urine drug test for tetrahydrocannabinol (THC). In addition, restricting confirmatory testing to situations and substances for which results can reasonably be expected to affect patient management can reduce costs of urine drug testing, given the substantial costs associated with confirmatory testing methods. Before ordering urine drug testing, clinicians should have a plan for responding to unexpected results. Clinicians should explain to patients that urine drug testing is intended to improve their safety and should also explain expected results (e.g., presence of prescribed medication and absence of drugs, including illicit drugs, not reported by the patient). Clinicians should ask patients about use of prescribed and other drugs and ask whether there might be unexpected results. This will provide an opportunity for patients to provide information about changes in their use of prescribed opioids or other drugs. Clinicians should discuss unexpected results with the local laboratory or toxicologist and with the patient. Discussion with patients prior to specific confirmatory testing can sometimes yield a candid explanation of why a particular substance is present or absent and obviate the need for expensive confirmatory testing on that visit. For example, a patient might explain that the test is negative for prescribed opioids because she felt opioids were no longer helping and discontinued them. If unexpected results are not explained, a confirmatory test using a method selective enough to differentiate specific opioids and metabolites (e.g., gas or liquid chromatography/mass spectrometry) might be warranted to clarify the situation.

Clinicians should use unexpected results to improve patient safety (e.g., change in pain management strategy [see Recommendation 1], tapering or discontinuation of opioids [see Recommendation 7], more frequent re-evaluation [see Recommendation 7], offering naloxone [see Recommendation 8], or referral for treatment for substance use disorder [see Recommendation 12], all as appropriate). If tests for prescribed opioids are repeatedly negative, confirming that the patient is not taking the prescribed opioid, clinicians can discontinue the prescription without a taper. Clinicians should not dismiss patients from care based on a urine drug test result because this could constitute patient abandonment and could have adverse consequences for patient safety, potentially including the patient obtaining opioids from alternative sources and the clinician missing opportunities to facilitate treatment for substance use disorder.

- Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder (recommendation category: A, evidence type: 2).

5.7.5 NHG 2018

In a footnote was mentioned:

Door de WHO-ladder zonder meer op chronische, niet aan kanker gerelateerde pijn toe te passen bestaat het risico dat het aantal patiënten dat opioïden als onderhoudsmedicatie gebruikt, stijgt. Gevaren van opioïdafhankelijkheid en overmatig gebruik moeten niet uit het oog worden verloren. Dat neemt niet weg dat er ook bij niet aan kanker gerelateerde ernstige pijn kortdurend een indicatie voor opioïden kan bestaan als niet-medicamenteuze therapie en andere pijnstilling faalt.

5.7.6 NICE 2017

No specific recommendations were provided

5.7.7 ASCO 2016

- **Clinicians should clearly understand terminology such as tolerance, dependence, abuse, and addiction as it relates to the use of opioids for pain control. (Informal consensus; benefits outweigh harms; evidence quality: insufficient; strength of recommendation: moderate)**
- **Clinicians should incorporate a universal precautions approach to minimize abuse, addiction, and adverse consequences of opioid use such as opioid-related deaths. Clinicians should be cautious in coprescribing other centrally acting drugs, particularly benzodiazepines (Table 7, see “management of chronic pain with opioids”). (Evidence-based and informal consensus; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)**

A number of validated risk-assessment instruments and screening questionnaires are available to help identify patients prone to misuse or those currently misusing prescribed opioids. Some of the tools include the Screener and Opioid Assessment for Patients in Pain and its revision, the Current Opioid Misuse Measure, the Opioid Risk Tool, and the Brief Risk Interview and Questionnaire. These tools vary in how they are conducted, but all offer clinicians resources for conducting risk stratification.

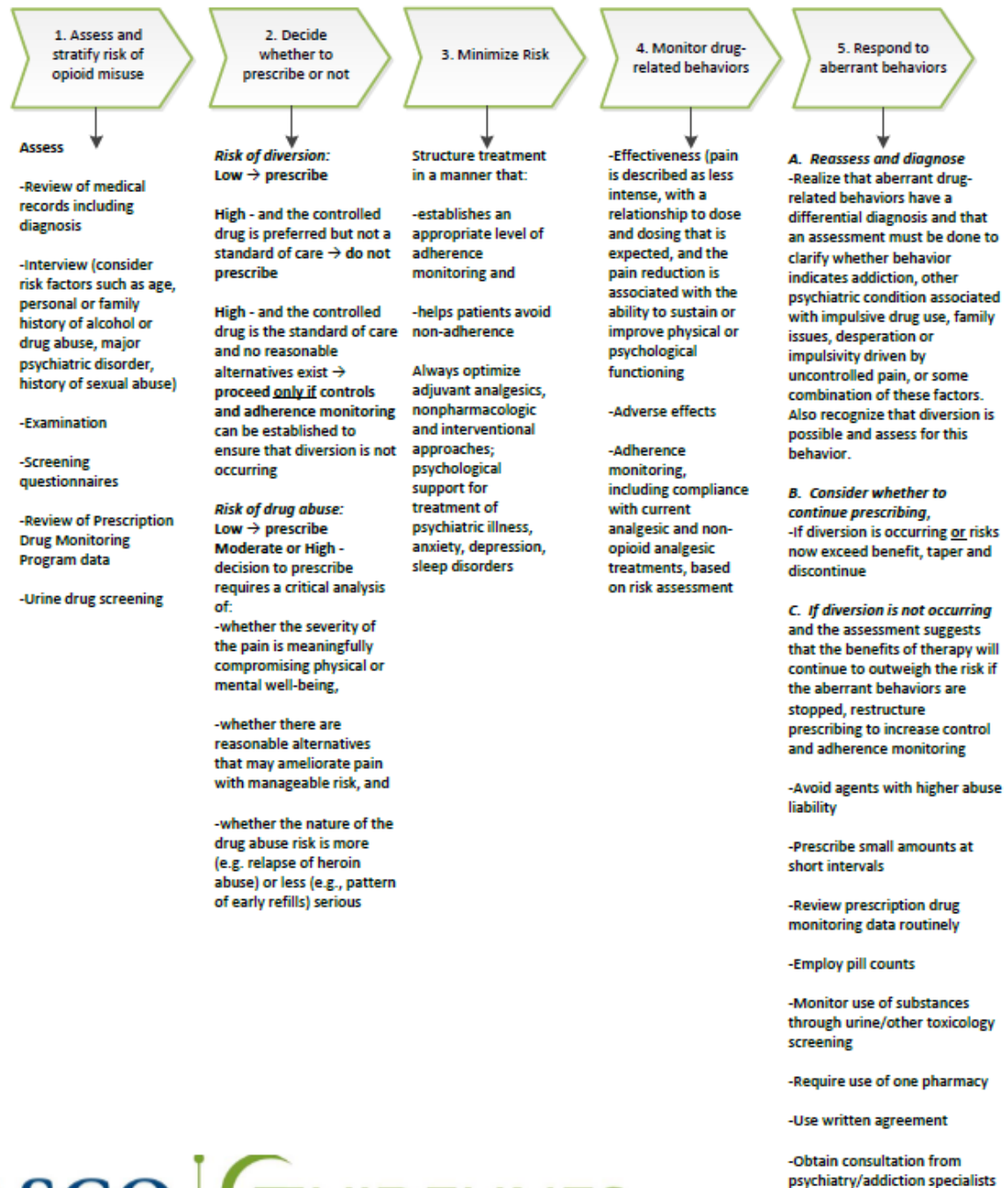
Prospective studies have shown that adherence monitoring with a controlled substance agreement, periodic monitoring, periodic drug testing, pill counts, and education when necessary served to reduce controlled substance abuse and increase compliance. A systematic review investigating the effectiveness of opioid treatment agreements and urine drug testing in reducing opioid misuse among patients with chronic noncancer pain found a decrease in opioid misuse with the use of treatment agreements as part of the opioid management strategy. Absolute risk reductions ranged from 6.5% (95% CI 1.3% to 11.7%) to 22.9% (95% CI, 17.3% to 28.7%) in four controlled studies.

Most of the studies evaluating risk factors associated with misuse have been conducted in people diagnosed with noncancer pain syndromes. There is no evidence to suggest that people surviving cancer, who might also have PTSD-like symptoms, would be at reduced risk. In fact, some populations may be at more risk of misuse in concert with lifestyle choices that may have contributed to the development of cancer (eg, smoking, excess alcohol intake, obesity). Tools such as agreements, urine drug testing, and use of drug monitoring programs that may mitigate risk are available, although more information is needed to determine which are most effective in the setting of cancer survivorship.

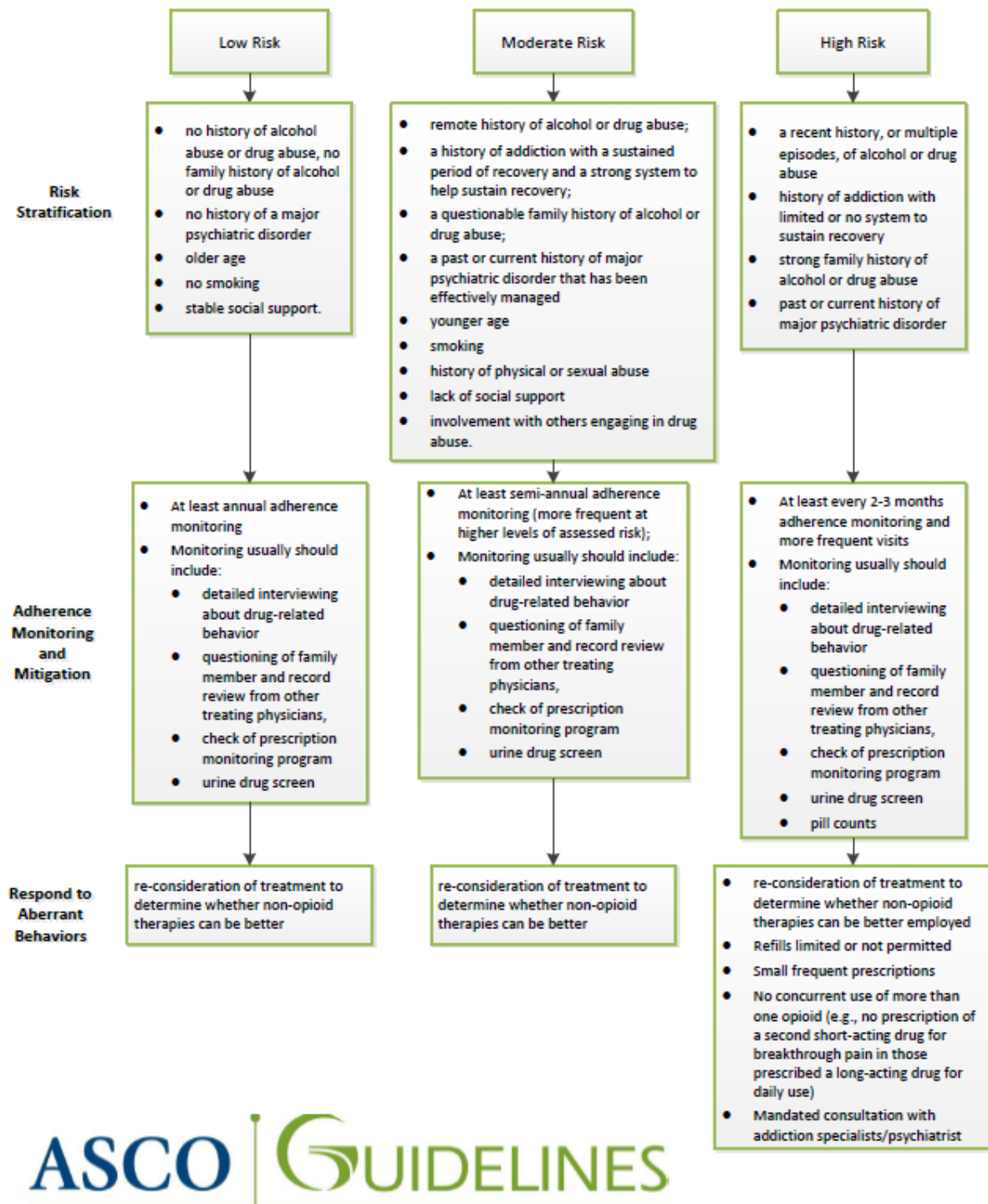
See also table 5 and table 6 under “Management of chronic pain” for universal precautions, risk stratification, and adherence monitoring.

Opioid-related harm may also result from misuse or abuse, the development of opioid addiction, or the occurrence of drug diversion within the community. The problem of prescription drug abuse is serious, leading to an increase in opioid-related deaths, but mitigation efforts designed to assess, stratify, and limit risk can enhance safety for patients, prescribers, and the community. These efforts must be coupled with the education of professionals, patients, and their family members. together with the public, about safe storage (eg, locked boxes for medications) and safe disposal (eg, take-back programs). Balance in policies and regulations regarding opioids is needed to ensure appropriate access to prescription opioids for those in pain.

Universal Precautions in Chronic Cancer Pain Management



Opioid Risk Stratification and Adherence Monitoring



www.asco.org/chronic-pain-guideline ©American Society of Clinical Oncology 2016. All rights reserved.

5.7.8 DOH_Ireland 2015

Risk of opioid dependence in cancer pain treatment

Clinicians should consider the use of opioids because of their proven effectiveness in treating pain and ameliorating quality of life of suffering patients—regardless of the fact that the published literature does not permit a conclusive statement about the risk of dependence. Clinical practice guidelines developed in the chronic noncancer pain setting recommend that: ‘Adherence monitoring is crucial to avoid abuse of the drugs and at the same time to encourage appropriate use, and involves the initiation of drug screening, pill counts, and patient care agreements, with the motto of “trust but verify”.

Managing cancer pain in patients with a history of addiction

Key finding

Physical, psychological, and social factors may compromise the management of cancer pain in patients with a history of substance misuse, in particular those with a history of opioid abuse or on methadone maintenance therapy.

- **In patients with a history of addiction, short acting formulations such as transmucosal fentanyl preparations should be avoided due to their greater abuse potential.**

Cancer pain assessment and management principles as outlined elsewhere in this document should be used to guide the management of cancer pain in individuals with a history of substance misuse. However, management should be modified if required and take into consideration the biological, social, and psychological features of the syndrome of addiction.

**A multidisciplinary approach that involves Addiction Services should be adopted.
(recommendation category D)**

Addiction is a syndrome and pattern of substance misuse, with biological, psychological and social aspects. A history of addiction to opioids, such as heroin, may compromise the effective control of cancer pain. In addition, patients may be receiving treatment for an addiction, such as methadone maintenance therapy (MMT), which may further complicate management.

Important points to note are as follows:

- *Long term opioid exposure, such as that from heroin or MMT, may induce neuroplastic changes such as tolerance, and hyperalgesia. Cross-tolerance occurs between different opioids. Hyperalgesia describes increased pain sensitivity resulting from up-regulation of pro-nociceptive systems such as excitatory NMDA receptors. Repeated episodes of under treatment of acute pain may lead to decreased responsiveness to opioid analgesic. Pain may also be exacerbated by subtle withdrawal symptoms, sleep disturbance, and affective changes characteristic of the syndrome of addiction.*
- *Psychological features of addiction include distress avoidance, learnt behaviour and chemical coping. The use of alcohol and benzodiazepines has been identified as a poor prognostic indicator for cancer pain control. Patients with a history of addiction may have co-morbidities such as depression and anxiety, further complicating management of their physical pain.*
- *Social aspects influencing care include a complex social milieu, social exclusion and reduced opportunities. The resonance of addiction through generations of families may have implications for bereavement follow up.*

- *Patients' relationships with healthcare professionals may be eroded by unrealistic expectations of the patient and concerns of the physician regarding the potential for side-effects, drug diversion, or iatrogenic worsening of addiction.*

Assessment of pain in patients with a history of substance misuse

Assessment of pain in patients with a history of substance misuse should include consideration of the following:

- *A full substance misuse and medication history should be taken, including over-the-counter preparations*
- *The presence of co-dependence on substances e.g. alcohol or benzodiazepines,*
- *The presence of psychiatric co-morbidities e.g. anxiety or depression*
- *An awareness of potential barriers to effective assessment such as a reluctance of the patient to disclose substance misuse due to anxiety that their pain may not be adequately treated*
- *An awareness of the potential for pseudo-addiction: the phenomenon of patients who seek alternate sources, or increased doses, of analgesia, as they fail to obtain adequate analgesic relief with doses prescribed. A defining characteristic of this syndrome is that sufficient pain relief eliminates the patient's need to self-medicate.*

Analgesic drug selection: general principles

Cancer pain in patients with a history of addiction should be managed according to the principles of cancer pain management outlined further in the text.

General principles apply in order to reduce the risk of drug diversion or precipitation of relapse of addiction:

- *Short acting drugs such as transmucosal fentanyl preparations and pethidine should be avoided, as in theory these have greater abuse potential than longer acting preparations*
- *Sustained release tablets can be less easily crushed and injected than nonsustained release tablets.*

Management: general principles

A treatment agreement should be agreed at the outset with the patient, either in writing or verbally.

A multidisciplinary team approach, including the involvement of addiction services should be employed. Optimally, the use of non-pharmacological interventions such as brief counseling should be used. Regular assessment of the 'Four A's' should occur: analgesia, activity, adverse effects, aberrant behavior.

Co-prescribed medications: issues to consider when prescribing opioids for analgesia

Buprenorphine is a partial agonist at mu-receptors and may be used either for its analgesic effect (usually in transdermal patch form) or as opioid substitution therapy in the management of opioid addiction. Buprenorphine should not be prescribed as an analgesic to patients receiving full mu-receptor agonists (e.g. methadone) as withdrawal may be precipitated. Similarly, patients taking high dose buprenorphine may be refractory to the analgesic effects of other co-administered opioids.

Naltrexone is a long-acting opioid antagonist used as a therapy for opioid addiction. Patients receiving naltrexone are likely to be refractory to opioid analgesia. If opioid analgesia is required, a continuous infusion is required to displace naltrexone from the opioid receptors. Close monitoring,

under specialist supervision, is required due to the high risk of opioid toxicity that results when the naltrexone is displaced from the receptors.

Methadone is a synthetic strong opioid, which acts at both mu- and NMDA receptors. Methadone is used as an analgesic in cancer pain management, but also as an opioid substitution therapy in the treatment of opioid addiction (methadone maintenance therapy, MMT). Chronic MMT leads to neuroplastic changes at opioid receptors, and increased tolerance and refractoriness to analgesia from opioids other than methadone. When opioids other than methadone are used for analgesia, MMT should be continued, as abrupt discontinuation may precipitate an acute pain crisis.

Methadone has itself been shown to be an effective analgesic agent in the management of cancer pain. However, while methadone has a long and variable half-life, its duration for analgesia is only 4 – 9 hours, therefore once daily dosed MMT will not provide sustained analgesia. As an analgesic agent, methadone's long and variable half-life, and the variable potency ratios between methadone and other strong opioids, may pose practical challenges. It should be used as an analgesic agent only with specialist palliative care or pain team supervision.

For any patient receiving opioid substitution therapy or naltrexone, consultation with the patient's addiction services and primary care team is necessary in order to ensure safe prescribing.

Opioid prescribing in patients with a history of addiction

Key finding

Methadone, buprenorphine and naltrexone are drugs used in the treatment of opioid addiction. Knowledge of their pharmacology and pharmacokinetics is important when managing cancer pain in patients with a history of substance misuse. Methadone may be used either as a treatment for addiction, or as an analgesic agent.

- **Communication with the patient's addiction services and primary care team should be maintained.**

For patients on methadone maintenance therapy (MMT), when using opioids other than methadone for analgesia, the MMT should be continued. When using methadone as an analgesic, once daily dosing will be ineffective. (recommendation category D)

- **Methadone should be used as an analgesic agent only under specialist supervision. (recommendation category D)**

Patients recovering from addiction

- **For patients recovering from addiction, opioids should be tapered when their pain allows.**

For all patients with a history of substance abuse, the use of adjuvant agents and non-pharmacological interventions should be maximised. (recommendation category D)

Prolonged substance misuse may lead to changes in the neural reward circuitry, giving rise to the potential for relapse if opioids are required for analgesia. This is often a source of anxiety to patients, who may under report their symptoms, and healthcare professionals, who may under-treat pain. Relapse prevention theories show that the stress associated with unrelieved pain is more likely to trigger relapse than adequate analgesia in these patients. A plan for pain management in such patients should include a clear plan to taper opioids, as pain allows.

Non-opioid interventions

Adjuvant agents such as anti-convulsants and anti-depressants should be used where appropriate. Similarly, non-pharmacologic strategies such as nerve blocks should be utilised where possible. Focusing on pain as entirely organic and nociceptive in origin may lead to overuse of pharmacological interventions, underuse of other interventions and an increased risk of opioid-related toxicity. The impact of co-morbid psychiatric conditions should be taken into account in the management of pain, and measures such as brief counselling should be considered.

Communication, goal setting and support

Effort should be made to set realistic goals of treatment, and response to treatment should be regularly reviewed. The role of a contract between the physician, the treating multidisciplinary team and the patient has had anecdotal success. Advice should be sought at an early stage from a pain specialist or addiction psychiatry services, where appropriate.

5.7.9 KCE 2013

In Belgium, there is only one commercial preparation available for oral methadone at a dose of 5 mg. This is a relatively low dosage which makes its use in monotherapy more difficult. Moreover, it is not reimbursed by the national health insurance system (however, the magisterial preparations are reimbursed for the treatment of opioid dependence where it is used to substitute the (illegal) opioid use). Further, the consulted expert panel (see colophon) advises to avoid high dosages, because of one of the specific although rare adverse effects of methadone, prolongation of the QT interval with cardiac dysrhythmias (Martindale 2009). It is possible that this adverse effect did not occur in the trials mentioned above, given their limited number of participants and their short duration. For these reasons, according to the expert panel, methadone for analgesic purposes should preferably be used as add-on to other opioids.

6 Summary and conclusions from the literature review. Chronic (non-cancer) pain, general

6.1 Long term opioids for chronic (non-cancer) pain

Several systematic reviews have been published about the use of long-term opioids in chronic (non-) cancer pain.

Chou 2015 (17, 18) and Dowell 2016(1) searched for RCTs and observational studies about long term opioids, taken for at least 3 months, for chronic pain (cancer and non-cancer, pain lasting > 3 months). To be included in the review, the studies were also required to report outcomes after at least 1 year. No studies evaluating these long-term outcomes were found by the authors. These systematic reviews also found no placebo-controlled trials that lasted at least 6 months. Another systematic review, by Noble 2010 (19) searched for RCTs with 6 months of opioid therapy in chronic non-cancer pain and found no RCTs comparing opioids with placebo or non-opioid treatment of this duration.

GRADE: insufficient evidence

6.2 High dose opioids for chronic non-cancer pain

Els 2017 (20) performed an overview of Cochrane reviews about high dose opioids for chronic non-cancer pain. High dose was defined as 200 mg morphine equivalent or more per day). No reviews met the inclusion criteria: most publications were about low dose or a titrated dose where all doses were analysed together. No information on high dose opioid use could be extracted.

GRADE: insufficient evidence

7 Summary and conclusions from the literature review. Opioids versus optimization of non-opioid therapy for chronic (non-cancer) pain

7.1 Opioids versus optimization of non-opioids for chronic non-cancer pain

A systematic review and meta-analysis by Busse 2017(9) searched for all RCTs that compare the initiation of opioids to the optimisation of non-opioid medication (NSAIDs) in chronic non-cancer pain. 13 RCTs were found, but only 1 met the inclusion criteria for our consensus conference literature review (the other RCTs had either a short duration, assessed opioids not on the Belgian market, were open label or not available in English). The RCT that met our inclusion criteria compared Tramadol ER to celecoxib and placebo (21), but did not provide any statistical testing for the comparison tramadol vs celecoxib.

This systematic review also found RCTs comparing opioids to initiation of tricyclic antidepressants (N=3) and to initiation of anticonvulsants (N=3). None of these RCTs met the inclusion criteria for our consensus conference literature review.

7.2 Opioid medication strategy versus non-opioid medication strategy for chronic back pain or chronic pain from knee or hip osteoarthritis

Opioid medication strategy versus mainly non-opioid medication strategy for chronic back pain or chronic pain from knee or hip osteoarthritis			
Bibliography: Krebs 2018 SPACE TRIAL (22)			
Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Pain intensity (4-item BPI severity scale) (range, 0-10 higher = worse) (main SO)	240 (1 study) 12 months	mean BPI severity opioid 4.0 (SD 2.0) non-opioid 3.5 (SD 1.9) difference 0.5 (95% CI, 0.0 to 1.0) ⁸ overall p*=0.03 ⁹ SS better with non-opioid	⊕⊕⊕⊖ MODERATE Study quality: -1 open label Consistency: NA Directness: OK Imprecision: ok
Pain intensity response (≥30% improvement in BPI severity scale) (SO)	240 (1 study) 12 months	opioid 41.0% non-opioid 53.9% risk difference -12.8% (95% CI, -25.6 to 0.0) ¹⁰ p= 0.05	⊕⊕⊕⊖ MODERATE ⊕⊕⊖⊖ LOW Study quality: -1 open label Consistency: NA Directness: OK Imprecision: ok
Global pain response ≥ moderately better (SO)	240 (1 study) 12 months	opioid 44.4% non-opioid 44.4% risk difference 0.0 (-12.8, 13.0) p=0.99 NS	⊕⊕⊕⊖ MODERATE Study quality: -1 open label Consistency: NA Directness: OK Imprecision: OK
Pain-related function (7-item BPI interference scale) (range 0-10, higher = worse) (PO)	240 (1 study) 12 months	mean BPI interference opioid 3.4 (SD 2.5) non-opioid 3.3 (SD 2.6) Difference 0.1 (95%CI, -0.5 to 0.7) ¹¹ overall p*=0.58 ¹² NS Note: RMDQ pain-related physical function: NS	⊕⊕⊕⊖ MODERATE Study quality:-1 open label Consistency: NA Directness: ok Imprecision: ok
Functional response	240 (1 study)	opioid 59.0% non-opioid 60.7%	⊕⊕⊕⊖ MODERATE Study quality:-1 open label

⁸ A 1-point improvement was considered clinically important.

⁹ P values are from mixed models for repeated measures comparing between-group difference during the 12-mo trial, controlling for baseline and including all available time points.

¹⁰ 30% reduction from baseline as MCID was considered moderate improvement.

¹¹ A 1-point improvement was considered clinically important.

¹² P values are from mixed models for repeated measures comparing between-group difference during the 12-mo trial, controlling for baseline and including all available time points.

(>= 30% improvement from baseline)	12 months	risk difference -1.7% (95%CI -14.4 to 11.0) ¹³ p=0.79	Consistency: NA Directness: ok Imprecision: OK
12-item Health Survey (VR-12) quality-of-life measure (range, 0-100; (higher = better))	240 (1 study) 12 months	physical health at 12 months ¹⁴ opioid 32.7 (SD 10.1) non-opioid 33.9 (SD 9.9) mean difference at 12 m -1.3 (-3.8 to 1.3) overall p value 0.23 ¹⁵ NS mental health at 12 months ¹⁶ opioid 51.2 (11.6) non-opioid 50.4 (12.6) mean difference at 12 m 0.7 (-2.4 to 3.8) overall p = 0.40 ¹⁷ NS	⊕⊕⊕⊖ MODERATE Study quality: -1 open label Consistency: NA Directness: ok Imprecision: ok
Medication-related symptoms (patient-reported checklist; range 0-19; higher = worse)	240 (1 study) 12 months	at 12 months opioid 1.8 (SD 2.6) non-opioid 0.9 (SD 1.8) difference at 12 months 0.9 [95% CI, 0.3 to 1.5] overall: P = 0.03 ¹⁸ SS more adverse events with opioid	⊕⊕⊕⊖ MODERATE Study quality: -1 open label Consistency: NA Directness: ok Imprecision: ok
Discontinuation due to adverse events	240 (1 study) 12 months	Opioid 7.5% non-opioid 0% NT	NA
Potential misuse measures	240 (1 study) 12 months	NS differences for - urine drug test/unexplained prescription drug - clinician-assessed behavior - patient-reported substance use	⊕⊕⊕⊖ LOW Study quality: -1 open label Consistency: NA Directness: ok Imprecision: -1 insufficient power

This was a pragmatic open label RCT in 240 patients from Veterans Affairs primary care clinics. Patients with **moderate to severe chronic back pain or hip or knee osteoarthritis pain** despite analgesic use were randomized to a stepwise opioid medication strategy or a stepwise non-opioid medication strategy. A **collaborative pain care model** was used for both treatment arms. Treatment

¹³ 30% reduction from baseline as MCID was considered moderate improvement.

¹⁴ Baseline score physical health +/- 27

¹⁵ P values are from mixed models for repeated measures comparing between-group difference during the 12-mo trial, controlling for baseline and including all available time points.

¹⁶ Baseline score mental health +/- 47.5

¹⁷ P values are from mixed models for repeated measures comparing between-group difference during the 12-mo trial, controlling for baseline and including all available time points.

¹⁸ P value for treatment by time interaction

was targeted to meet **individual functional goals** and adjusted during the course of the study to achieve individual goals.

In the opioid treatment strategy, the first step consisted of immediate release opioids (morphine, oxycodone or hydrocodone/acetaminophen. Step 2 consisted of morphine sustained-action (SA) or oxycodone SA and step 3 was transdermal fentanyl. In the non-opioid treatment strategy, step 1 consisted of acetaminophen (paracetamol) or NSAID, step 2 consisted of adjuvant oral (nortriptyline, amitriptyline, gabapentin) and/or topical (capsaicin, lidocaine) medication and step 3 were drugs requiring prior authorization from the VA clinic (i.e. pregabalin, duloxetine) and also the opioid tramadol.

Patients were instructed to receive medications for back, hip, or knee pain only from the study.

Nonpharmacological therapies were allowed outside of the study.

Contrary to most studies with opioids, patients with psychiatric problems such as severe depression or posttraumatic stress disorder symptoms were not excluded.

Prior to treatment allocation, 21 % of patients in the opioid group had expressed a preference for opioids, whereas in the non-opioid group 37% preferred opioids.

The study duration was 12 months.

At the end of the 12 months period, 20.2% (24 patients) in the opioid treatment arm was not using any opioids and 10.9% (12 patients) in the non-opioid treatment arm was using opioids (tramadol). At the end of the 12 months period, most patients who used opioids were on a dose of < 50 mg morphine-equivalent/day.

The primary endpoint in this trial was pain-related function.

To calculate the difference in symptom scores between treatment strategies, this trial used a statistical model using all available time-points, which must be taken into account when interpreting the results.

This trial has quite a unique design within the available body of evidence: it aims to be maximally applicable to primary care by using a collaborative pain care model and a pragmatic approach with a flexible treatment strategy, individual treatment targets and allowing non pharmacological treatments (however, the non-pharmacological treatments were not managed by the study).

The fact that patients and care givers were **not blinded** to treatment may cause a certain bias, especially since the endpoints are mostly of a subjective nature (patient reported outcomes).

On the other hand, this trial tries to mimic clinical practice as much as possible and does provide us with valuable information that would be very difficult to obtain otherwise.

Taking into account the fact that there was a higher number of patients in the non-opioid group with a **preference for opioids** than in the opioid group, the results could be biased to favour opioids.

The fact that **tramadol** could be used in step 3 of the non-opioid arm is unfortunate when researching the comparison between opioids and non-opioids. We can however learn a lot from comparing the swift initiation of opioids to a stepped approach in which opioids are only used if all other treatment options are insufficient.

This was quite a selective **patient population**, recruiting U.S. Veterans (predominantly male).

Extrapolating the results to the general population should be done with caution.

In patients with chronic low back pain or chronic pain from osteoarthritis of the hip or knee, a statistically significantly better **pain intensity score** (Brief Pain Inventory, BPI) is achieved with a non-

opioid treatment than with an opioid treatment strategy, used for 12 months. However, the difference is small and the clinical significance is unclear.

The difference in the number of **patients reporting a $\geq 30\%$ improvement** (Brief Pain Inventory, BPI) at 12 months is of borderline statistical significance, favouring the non-opioid treatment.

However, no significant difference was observed for the number of patients who reported a **global pain response that was 'moderately' or 'much' better** at 12 months.

GRADE: HIGH MODERATE LOW VERY LOW quality of evidence

In patients with chronic low back pain or chronic pain from osteoarthritis of the hip or knee, there is no significant difference in improvement of **pain-related physical function** (Brief pain inventory – BPI) between the use of an opioid treatment strategy and a non-opioid treatment strategy for 12 months.

There is also no statistically significant difference between the two treatment strategies when considering the **number of patients who report a $\geq 30\%$ improvement** at 12 months.

GRADE: MODERATE quality of evidence

In this population, there was a higher number of **medication-related symptoms** with the opioid treatment strategy compared to the non-opioid strategy.

GRADE: MODERATE evidence

Frequent adverse events were not reported separately.

Discontinuation due to adverse events seemed also to occur more frequently with the opioid treatment strategy (7.5% vs 0%) but no statistical tests were performed.

GRADE: NA evidence

No statistically significant difference was found in a range of **measures for potential misuse**.

However, numbers were low; this trial was not powered to detect differences in these outcomes.

GRADE: LOW quality of evidence

8 Summary and conclusions from the literature review. Opioids versus placebo for chronic (non-cancer) pain

8.1 Opioids versus placebo for chronic non-cancer pain in patients optimized non-opioid treatment but persistent pain

Opioids vs placebo for chronic non-cancer pain			
Bibliography: Busse 2017(9)			
Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Pain 10 cm VAS Scale: 0-10 (Lower better)	13876 (27 studies) 3-6 months	Mean difference: -0.64 (95%CI -0.76 to -0.53) SS in favour of opioids	⊕⊕⊕⊕ LOW Study quality:-1 high drop out Consistency: unclear Directness: -1 variable previous treatment Imprecision: ok
Pain (difference in patients who achieve the MID¹⁹ or greater)	13876 (27 studies) 3-6 months	RR 1.25 (95%CI 1.21 - 1.29) absolute effect estimate no opioids 488 per 1000 opioids 560 per 1000 Difference: 112 more per 1000 (95%CI 94 more - 130 more) SS in favour of opioids	⊕⊕⊕⊕ LOW Study quality:-1 high drop out Consistency: unclear Directness: -1 variable previous treatment Imprecision: ok
Physical function SF-36 physical component summary 0-100 (High better)	12058 (33 studies) 1-6 months	Mean difference: +2.16 (95%CI 1.56 - 2.76) SS in favour of opioids	⊕⊕⊕⊕ LOW Study quality:-1 high drop out Consistency: unclear Directness: -1 variable previous treatment, study duration Imprecision: ok
Physical function (difference in patients who achieve the MID²⁰ or greater) 1-6 months	12058 (33 studies) 1-6 months	RR 1.24 (95%CI 1.17 - 1.30) absolute effect estimate no opioids 424 per 1000 opioids 526 per 1000 Difference: 102 more per 1000 (95%CI 72 more - 127 more) SS in favour of opioids	⊕⊕⊕⊕ LOW Study quality:-1 high drop out Consistency: unclear Directness: -1 variable previous treatment, study duration Imprecision: ok
Gastrointestinal side effects	14449 (36 studies) 4-26 weeks	RR 3.08 (95%CI 2.53 - 3.75) absolute effect estimate	⊕⊕⊕⊕ LOW Study quality:-1 high drop out Consistency: unclear Directness: -1 variable previous

¹⁹ MID=minimally important difference. This author defined the minimally important difference on the 10 cm VAS scale as a reduction of 1 cm

²⁰ This author defined the minimally important difference on a 100-point short form-36 (SF-36) physical component summary score as an increase of 5-points

	no opioids 28 per 1000 opioids 86 per 1000 Difference: 58 more per 1000 (95%CI 43 more - 77 more) SS in favour of placebo	treatment, study duration Imprecision: ok
--	--	--

This SR and meta-analysis by Busse 2017 found and included 36 RCTs in chronic non-cancer pain. Any type of chronic pain could be included. Most RCTs included patients with osteoarthritis or chronic low back pain, some included patients with neuropathic pain. A few included specific pain syndromes such as fibromyalgia or pain due to Parkinson's disease. Most RCTs examined an opioid that is available on the Belgian Market.

This SR aimed to examine the effect of opioids in patients with chronic non-cancer pain, whose therapy is optimized with non-opioids (but who still have problematic pain) and compare them to a continuation of the established therapy without opioids. Studies in patients with current or past substance use disorder and current serious psychiatric disorders were excluded.

However, it is questionable whether the patients in the included trials did in fact have an 'optimised' therapy prior to enrollment. Inclusion criteria in these trials usually describe the patients as having persistent pain despite their current pain treatment, but their current treatment varies within and between studies and is usually described in terms of analgesics used (of example: insufficient pain relief despite NSAID treatment), but hardly ever mentions any non-pharmacological treatment, or the use of co-analgesics (e.g. antidepressants, anti-convulsants). Some trial explicitly exclude patients on drugs that can be used as a co-analgesic.

Moreover, in a lot of trials, the previous analgesic medication is stopped (washed out) before entering the trial. As a result, these trials do not examine the effect of opioids added to the current pain treatment versus the continuation of current pain treatment.

Drop-out rates were high to very high in most studies.

For the outcome 'pain', 27 RCTs were included, with a duration from 3 to 6 months.

In patients who have inadequate pain control with their current (optimized?) pain treatment, starting opioids results in a lower **pain score** on a VAS scale than starting placebo.

GRADE: LOW quality of evidence

In patients who have inadequate pain control with their current (optimized?) pain treatment, starting opioids will increase the likelihood of having an **improvement on the VAS score of 1 cm or more**, compared to placebo.

GRADE: LOW quality of evidence

For the outcome 'function' 33 RCTs were included, with a duration from 1 to 6 months. More than 1/3 of the RCTs were under 12 weeks.

In patients who have inadequate pain control with their current (optimized?) pain treatment, starting opioids results in a better score on the **SF-36 physical component summary** than starting placebo. The mean difference with placebo is smaller than the minimally important difference of 5 points.

GRADE: LOW quality of evidence

In patients who have inadequate pain control with their current (optimized?) pain treatment, starting opioids will increase the likelihood of **having an improvement on the SF-36 physical component summary of 5 points or more**, compared to placebo.

GRADE: LOW quality of evidence

For the outcome 'gastro-intestinal side effects' 36 RCTs were included. More than 1/3 of the RCTs were under 12 weeks.

In patients who have inadequate pain control with their current (optimized?) pain treatment, starting opioids will result in a higher risk of **gastro-intestinal adverse events** compared to starting placebo.

GRADE: LOW quality of evidence

8.2 Opioids versus placebo for chronic non-cancer pain: adverse events

Opioids versus placebo for chronic non-cancer pain			
Bibliography: Cochrane Els 2017 (23)			
Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Withdrawal due to adverse events	11511 (studies from 10 reviews) 4 to 52 weeks?	Crude absolute event rate opioid 25.1% (24.1 to 26.1) placebo 7.1% (6.3 to 7.9) RR 3.40 (95%CI 3.02 to 3.82) SS More withdrawal with opioids	Assessed by Els 2017, based on only 4 reviews ⊕⊕⊕⊖ MODERATE Study quality: serious risk Consistency: ok Directness: ok Imprecision: ok
Constipation	4255 (studies from 4 reviews) 4 to 36 weeks??	Crude absolute event rate opioids 11.3% (10.1 to 12.6) placebo 5.4% (4.3 to 6.5) RR 2.23 (95%CI 1.39 – 3.59) SS More constipation with opioids	assessed by Els 2017 ⊕⊕⊕⊖ MODERATE Study quality: serious risk Consistency: ok Directness: serious risk Imprecision: ok
Nausea	4346 (studies from 3 reviews) 4 to 36 weeks?	Crude absolute event rate opioids 20.9% (20.9 to 20.9) placebo 8.4% (8.4 to 8.4) RR 2.46 (95%CI 2.08-2.92) SS More nausea with opioids	assessed by Els 2017 ⊕⊕⊕⊖ MODERATE Study quality: serious risk Consistency: ok Directness: serious risk Imprecision: ok
Vomiting	3368 (studies from 2 reviews) 4 to 16 weeks?	Crude absolute event rate opioids 8.9% (8.9 to 8.9) placebo 2.1% (2.1 to 2.1) RR 4.29 (95%CI 2.90 – 6.34) SS More vomiting with opioids	assessed by Els 2017 ⊕⊕⊖⊖ LOW Study quality: serious risk Consistency: ok Directness: very serious Imprecision: ok
Drowsiness	3856 (studies from 3 reviews) 4 to 36 weeks?	Crude absolute event rate opioids 10.3% (9 to 11.5) placebo 3.7% (2.8 to 4.6) RR 2.89 (95%CI 2.19 to 3.83) SS more drowsiness with opioids	assessed by Els 2017 ⊕⊕⊕⊖ MODERATE Study quality: serious risk Consistency: ok Directness: serious risk Imprecision: ok
Cognitive function Addiction Endocrine dysfunction		No data	insufficient evidence

This overview of Cochrane reviews by Els 2017(23) searched for all Cochrane reviews about opioid use (2 weeks or more) for chronic non-cancer pain in adults. Using the data from the trials that were included in these Cochrane reviews, a meta-analysis was performed to report on the adverse events associated with opioid use.

The included Cochrane reviews study opioid use for a variety of conditions, such as osteoarthritis, chronic low back pain, neuropathic pain, ... The duration of the included studies range from 4 weeks to 52 weeks.

There are some methodological problems that limits our interpretation of these results.

Els 2017 did not report which individual trials were included in the meta-analysis. Therefore, we are unsure of the actual duration of follow up for the reported endpoints and of the included population.

Els 2017 calculated the crude absolute event rates (as an average of the event rates in the included trials). A number needed to harm was also calculated for each outcome, based on this crude event rate. Because this method is not recommended by the GRADE approach and because the duration of treatment for these NNHs is unclear, we decided not to report these here. This information can be found in the appendices of the full consensus conference document (English).

Els also performed a GRADE assessment for the different outcomes. **We cannot reproduce these results because we have no information about the individual trials that were used for this assessment.**

In chronic non-cancer pain, the use of opioids leads to more withdrawal due to adverse events than the use of placebo.

GRADE assessed by Els 2017 (23): MODERATE quality of evidence

In chronic non-cancer pain, the risk of constipation and the risk of nausea is increased with opioids compared to placebo.

GRADE assessed by Els 2017 (23): MODERATE quality of evidence

In chronic non-cancer pain, there is a higher risk of vomiting with opioids compared to placebo.

GRADE assessed by Els 2017 (23): LOW quality of evidence

In chronic non-cancer pain, the risk of drowsiness is higher with opioids compared to placebo.

GRADE assessed by Els 2017 (23): MODERATE quality of evidence

This overview of Cochrane reviews found no data on the risk of cognitive dysfunction, addiction and endocrine disorders.

GRADE: insufficient evidence

8.3 Opioids versus placebo for chronic non-cancer pain: quality of life

Opioids versus placebo for chronic non-cancer pain			
Bibliography: Thornton 2017 (24)			
Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
SF-36 Physical component summary	4040 (5 studies, 8 comparisons) 12-15 weeks	Hedge's g Effect size ²¹ 0.18 (95%CI 0.08 to 0.28) SS in favor of opioids NNT = 10 (for 1 patient to have a larger improvement than the placebo group(25))	⊕⊕⊕⊕ VERY LOW Study quality: high risk of bias due large drop out and handling of missing values Consistency: ok Directness: -2 high risk of bias due to only 3 opioids included, various previous treatment, washout of previous analgesics Imprecision: ok
SF-36 Mental component summary	4040 (5 studies, 8 comparisons) 12-15 weeks	Hedge's g Effect Size ¹ -0.05 (9%CI -0.18 to 0.08) NS	⊕⊕⊕⊕ VERY LOW Study quality: high risk of bias due large drop out and handling of missing values Consistency: ok Directness:-2 high risk of bias due to only 3 opioids included, various previous treatment, washout of previous analgesics Imprecision: ok

This systematic review and meta-analysis by Thornton 2017 tries to evaluate the effect of opioids used for chronic non-cancer pain on quality of life, as defined by 2 sub-parameters of the SF-36 (short form (36) health survey) questionnaire. The authors searched for all RCTs that reported the SF-36 questionnaire **physical component summary** and **mental component summary**.

For opioids compared to placebo, the authors only found studies with **oxycodone, tapentadol and tramadol + paracetamol in chronic osteoarthritis or chronic low back pain**. The population consisted of patients with either chronic low back pain or chronic osteoarthritis pain. Duration of treatment was between 12 and 15 weeks.

The authors chose to report the results of the SF-36 questionnaire as a Hedge's g effect size, which is difficult to interpret in a clinical setting.

Our interpretation of the results is severely limited by the high drop-out rates, the handling of missing values and the fact that only 3 different opioids could be included in the meta-analysis. Previous analgesic use varied within and between studies. All trials required a washout of previous analgesics.

²¹ Hedge's g effect size is calculated by dividing the difference in means by the pooled and weighted standard deviation. According to the authors, the magnitude of effect sizes were interpreted as very small (0.01), small (0.2), medium (0.5), large (0.8), very large (1.2), and huge (2.0)

In chronic non-cancer pain, opioid use results in a better score on the physical component summary of the SF-36 survey compared to placebo. The size of the effect is considered small.

GRADE: VERY LOW quality of evidence

In chronic non-cancer pain, there is no statistically significant difference in the mental component summary score of the SF-36 survey between opioids and placebo.

GRADE: VERY LOW quality of evidence

9 Summary and conclusions from the literature review. Opioids versus placebo for specific musculoskeletal pain conditions

9.1 Opioids versus placebo for chronic pain in osteoarthritis

Non-tramadol opioids versus placebo for chronic pain in knee or hip osteoarthritis			
Bibliography: Cochrane da Costa Bruno 2014 (26)			
Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Pain intensity Various pain scales example in VAS scale (range 0-10)	8275 (22 studies) median 4 weeks 2w – 30 w	SMD -0.28 (-0.35 to -0.20) Assumed risk placebo -1.8 cm change on 10 cm VAS corresponding risk (opioids) -2.5 cm change on 10 cm VAS estimated difference ²² : -0.7 cm (-0.9 to -0.5) NNT 10 (95% CI 8 to 14) for treatment response (50% improvement)	⊕⊕⊕⊕ VERY LOW Study quality:-1 large drop outs Consistency: ok Directness:-2 short study duration, tramadol excluded, various previous treatments Imprecision: ok
	(10 studies) 8w – 30 w	Result for trials > 1 month SMD -0.15 (-0.22 to -0.08) SS	⊕⊕⊕⊕ LOW Study quality:-1 large drop outs Consistency: ok Directness: -1 tramadol excluded, various previous treatments Imprecision: ok
Function Various validated function scales example in WOMAC scale (range 0-10)	3553 (12 studies) median 5 weeks 2w – 15 w	SMD -0.26 (-0.35 to -0.17) Assumed risk placebo -1.2 units on WOMAC Corresponding risk opioids -1.8 units on WOMAC estimated difference: -0.6 (-0.8 to -0.4) ²³ NNT 12 (95% CI 10 to 18) for treatment response (50% improvement)	⊕⊕⊕⊕ VERY LOW Study quality:-1 large drop outs, selective reporting Consistency: ok Directness:-2 short study duration, tramadol excluded, various previous treatments Imprecision: ok
	(6 studies) 8w – 15w	Result for trials > 1 month SMD -0.25 (-0.41 to - 0.09)	⊕⊕⊕⊕ LOW Study quality:-1 large drop outs, selective reporting Consistency: ok Directness: -1 tramadol excluded, various previous treatments Imprecision: ok

²² The Cochrane authors defined the clinically meaningful difference for pain as an SMD of 0.37, which corresponds to 0.9 cm on a 10 cm VAS scale.

²³ The authors do not define a clinically meaningful difference for function

Number of participants who withdrew because of adverse events	7712 (19 studies) median 6 weeks	RR 3.76 (2.93 to 4.82) Assumed risk placebo 17 per 1000 participant-years Corresponding risk opioids 64 per 1000 participant-years (50 to 82) NNH 21 (95% CI 15 to 30)	⊕⊕⊕⊕ LOW Study quality: -1 large drop outs Consistency: ok Directness: -1 short duration Imprecision: ok
--	--	--	---

This Cochrane systematic review and meta-analysis includes all RCTs that compare opioids to placebo in chronic osteoarthritis pain of the knee or hip. Studies with tramadol were excluded, because these trials are discussed in another Cochrane review (Cepeda 2006 (27)).

The trials varied in duration, about half of the included trials were shorter than 12 weeks.

In all trials, patients were eligible if they had insufficient pain relief with their current analgesic treatment. This current treatment varied between studies (paracetamol, NSAID, weak opioids, stronger opioids, unspecified). There were also differences between the trials about allowing other analgesics than the study medication.

Our confidence in the estimate of the treatment effect is limited by the large drop-outs in the studies, the apparent underreporting of functional outcomes and the short duration of treatment in a lot of the trials.

In patients with chronic osteoarthritis pain of the knee or hip, the use of (non-tramadol) opioids results in a lower **pain score** than the use of placebo. The difference is small and of questionable clinical significance. In trials with a duration longer than 1 month, the difference is even smaller.
GRADE: VERY LOW quality of evidence (LOW when considering durations of >4 w)

In patients with chronic osteoarthritis pain of the knee or hip, the use of (non-tramadol) opioids results in a better **function score** than the use of placebo. The difference is small and of questionable clinical significance.
GRADE: VERY LOW quality of evidence (LOW when considering durations of >4 w)

In patients with chronic osteoarthritis pain of the knee or hip, the use of (non-tramadol) opioids results in a higher **withdrawal rate due to adverse events** than the use of placebo.
GRADE: LOW quality of evidence

9.2 Opioids versus placebo for chronic low back pain

We found several systematic reviews and meta-analysis about opioids for chronic low back pain (7, 28-30). Details can be found in the appendices of the full consensus conference document (English).

9.2.1 Opioids versus placebo for chronic low back pain

Opioids versus placebo for chronic low back pain			
Bibliography: Abdel Shaheed 2016 (7)			
Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Pain outcome (0 to 100 scale) (lower is better)	2605 (6 studies) 12 weeks	MD -8.1 (-10.2 to -6.0) SS in favour of opioids	⊕⊕⊕⊕ LOW Study quality: -1 high drop out, enrichment and non-enrichment Consistency: ok Directness: -1 various previous treatments Imprecision: ok
Disability (0 to 100 scale??)	322 (1 studies) 91 d	MD -3.7 [-11.8, 4.4] NS	⊕⊕⊕⊕ VERY LOW Study quality: -2 high drop out, reporting bias (only 1 trial for this outcome) Consistency: NA Directness: -1 only tramadol Imprecision: ok

Abdel Shaheed 2016 performed a systematic review and meta-analysis about opioids for chronic low back pain and made separate analyses for trials durations ≥ 12 weeks. The author also performed analyses according to trial design (enriched enrollment versus normal enrollment). Details can be found in the appendices of the Full consensus conference document (English).

We will report the results for the meta-analysis of all trials of ≥ 12 weeks duration.

The opioids that could be included in the meta-analysis were tapentadol, oxycodone, hydromorphone, buprenorphine and tramadol.

Our interpretation of the results is limited by the large drop-outs in most of the included trials, the use of various scales to measure disability, and by the different ways of dealing with the previous (opioid or non-opioid) pain medication throughout the different trials.

In patients with chronic low back pain, opioids result in a larger pain reduction than placebo.

GRADE: LOW quality of evidence

In patients with chronic low back pain, the use of opioids does not lead to a statistically significant change in disability.

GRADE: VERY LOW quality of evidence

9.2.2 Strong opioids versus placebo for chronic low back pain

Strong opioids versus placebo for chronic low back pain			
Bibliography: Chaparro 2013 (28)			
Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Pain outcome various scales (lower is better)	1886 (6 studies) 4w to 15 w	Std MD -0.43 [-0.52, -0.33] SS in favour of strong opioids	⊕⊕⊕⊕ LOW Study quality: attrition bias Consistency:ok Directness: various previous treatments Imprecision:ok
Disability various scales (lower is better)	1375 (4 studies) 4w-15w	Std MD -0.26 [-0.37, -0.15] SS in favour of strong opioids	⊕⊕⊕⊕ LOW Study quality: -1 attrition bias Consistency: Directness: -1 various previous treatments Imprecision: ok
Nausea	2346 (6 studies) 9w-15w	RD 12% (5% to 19%) illustrative comparative risks placebo 102 per 1000 opioids 223 per 1000 (151 to 291)	⊕⊕⊕⊕ LOW Study quality: -2 attrition bias, some performance bias, unclear rando in 1 trials Consistency: ok Directness: various previous treatments Imprecision: ok
Constipation	2346 (6 studies) 9w-15w	RD 11% (4% to 19%) illustrative comparative risks placebo 36 per 1000 opioids 148 per 1000 (76 to 226)	⊕⊕⊕⊕ LOW Study quality: attrition bias, some performance bias, unclear rando in 1 trial Consistency: heterogeneity Directness: various previous treatments Imprecision: ok
Somnolence	2346 (6 studies) 9w-15w	RD 6% (2% to 10%) illustrative comparative risks placebo 25 per 1000 opioids 86 per 1000 (45 to 125)	⊕⊕⊕⊕ LOW Study quality: -2 attrition bias, some performance bias, unclear rando in 1 trials Consistency: ok Directness: various previous treatments Imprecision:ok

Chaparro 2013 also performed a Cochrane systematic review and meta-analysis about opioids use in chronic low back pain. The author did a separate analysis for strong opioids versus placebo. RCTs with a shorter study duration were also included. This author managed to include more trials in the analysis for disability than Abdel Shaheed 2016, but not all of these trials met our inclusion criteria.

Our interpretation of the results is mainly limited by the large drop-outs in most of the included trials, the short duration of some of the trials and by the different ways of dealing with the previous (non-opioid) pain medication throughout the different trials.

In patients with chronic low back pain, strong opioids result in a larger pain reduction than placebo. The effect is small.

GRADE: LOW quality of evidence

In patients with chronic low back pain, strong opioids result less disability than placebo. The effect is very small.

GRADE: LOW quality of evidence

In patients with chronic low back pain, the use of strong opioids results in more nausea than the use of placebo.

GRADE: LOW quality of evidence

In patients with chronic low back pain, the use of strong opioids results in more constipation than the use of placebo.

GRADE: LOW quality of evidence

In patients with chronic low back pain, the use of strong opioids results in more somnolence than the use of placebo.

GRADE: LOW quality of evidence

10 Summary and conclusions from the literature review. Individual opioids versus placebo for chronic musculoskeletal pain

10.1 Tramadol +/- paracetamol versus placebo for chronic pain from osteoarthritis

Tramadol or tramadol/paracetamol versus placebo in chronic osteoarthritis pain			
Bibliography: Cochrane Cepeda 2006(27), Gana 2006 (31), DeLemos 2011 (21), Burch 2007 (32)			
Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Pain intensity	553 (2 studies) (27) 84-91 d	tramadol +/- paracetamol 0-100 scale (long study durations) MD -9.06 (95%CI -13.68, -4.44) SS	⊕⊕⊕⊕ VERY LOW Study quality:-2 for study quality and drop outs Consistency: unclear Directness: -1 variable previous analgesics, tramadol and tramadol/pctm Imprecision: difficult to assess
	2031 (2 studies) (31), (21) 12w	tramadol WOMAC pain subscale SS across 5 treatment arms (different doses) vs placebo in 2 trials ²⁴ SS for individual dose vs placebo in 1 of 2 trials	
	646 (1 study) (32) 12 w	tramadol PI-NRS (0-10) MD -0.70 (95%CI -1.02 to -0.38) SS	
Proportion of subjects with at least moderate (>=50%*) improvement	436 (2 studies) (27) 91 d	tramadol +/- paracetamol (long study durations) RR 1.36 (1.05, 1.75) SS	⊕⊕⊕⊕ VERY LOW Study quality:-2 for study quality and drop outs, selective reporting Consistency: unclear Directness: -1 various previous treatment, tramadol and tramadol/pctm Imprecision: ok
WOMAC	990 (4 studies) (27) 10– 91 d	tramadol +/- paracetamol WOMAC total score (0-10) MD -0.34 (95%CI -0.49 to -0.19) SS	⊕⊕⊕⊕ LOW Study quality:- 1 for study quality and drop outs Consistency: -1 unclear Directness: various previous treatment Imprecision: unable to assess
	2031 (2 studies) (31), (21) 12w	tramadol WOMAC function subscale SS across 5 treatment arms (different doses) vs placebo in 2 trials ²⁵	

²⁴ However, celecoxib was included as a treatment arm in 1 of these studies.

	SS for individual dose vs placebo in 1 of 2 trials		
Discontinuation due to adverse events	1338 (7 studies) (27) 10-91 d	RR 2.67 (95%CI 1.96 to 3.63) SS NNH= 8 (95% CI 7 to 12)	⊕⊕⊕⊕ LOW Study quality: - 2 for study quality and drop out Consistency: ok Directness: - various previous treatments Imprecision: unable to assess
	2031 (2 studies) (31), (21) 12w	Tramadol 400 29.7% Tramadol 300 26.9% to 30.7% Tramadol 200 19.9 to 23.1% Tramadol 100 12.4% to 14.3% placebo 7.5% to 10.2%	
	646 (1 study) (32) 12 w	Tramadol 200 or 300 10% placebo 5%	

- A Cochrane **systematic review**, published in 2006 by Cepeda 2006, searched for all RCTs comparing tramadol with or without paracetamol to placebo, in patients with chronic pain from osteoarthritis in the hip or knee.

The duration of the included trials ranged from 10 days to 91 days.

Results for tramadol only and for tramadol + paracetamol were analysed together.

Subanalyses for studies with longer duration were performed for pain outcomes. We report results for the long duration trials only wherever possible.

We found 3 more RCTs that were published after the search date of this Cochrane review, in patients with chronic pain due to osteoarthritis (See appendix Full Consensus conference document (English) under Busse 2017.

- Gana 2006 (31) was a 12 week **5-arm double blind RCT** with 1020 adults with chronic pain due to osteoarthritis of the hip or knee. Patients were randomized to once daily tramadol ER 100 mg, 200 mg, 300 mg, 400 mg or placebo. 558 of the randomized patients completed the 12 weeks of treatment.

Statistical testing for the 3 co-primary efficacy endpoints (the WOMAC pain subscale, the WOMAC physical function subscale and the patient global assessment of disease activity) was performed first for the overall treatment effect (comparing 5 treatment arms) and showed a **statistically significant difference** between the 5 treatment arms **for pain and for physical function**. This test does not inform us which groups differ. For this we need pairwise comparisons. Pairwise comparisons for the different tramadol doses versus placebo also showed statistically significant differences for each dose for both endpoints. **No statistically significant difference** was found when testing the overall treatment effect for the **global assessment of disease activity**.

- DeLemos 2011(21) was a 12 week **5-arm double blind RCT** with 1011 adults with chronic pain due to osteoarthritis of the hip or knee. Patients were randomized to once-daily tramadol ER 100 mg, 200 mg, 300 mg, celecoxib 200 mg or placebo. 555 of the participants completed the 12 weeks of treatment.

²⁵ However, celecoxib was included as a treatment arm in 1 of these studies.

Statistical testing for the 3 co-primary efficacy endpoints (the WOMAC pain subscale, the WOMAC physical function subscale and the patient global assessment of disease activity) was performed for the overall treatment effect and showed statistically significant difference between the 5 treatment arms on all 3 endpoints. These tests do not inform us which groups differ. For this we need pairwise comparisons. However, pairwise comparisons between the different tramadol doses and placebo, were **not statistically significant** for the WOMAC pain subscale and the WOMAC physical function subscale. A statistically significant difference was only found for tramadol 300 vs placebo in the patient global assessment of disease activity. It is possible that the celecoxib treatment arm influenced the overall statistical significance of the results for these 3 efficacy endpoints.

- Burch 2007 (32) was an **enriched-enrollment double blind RCT**. Of the 1028 patients with osteoarthritis of the knee who entered the open-label tramadol run-in, 62.8% (646) were subsequently randomized to tramadol once daily controlled release or placebo. Tramadol was titrated to 200 mg or 300 mg according to pain response and tolerability. 76% of the randomized patients completed the 12 weeks.

A different pain scale was used in this trial (PI-NRS).

Our confidence in the estimate of the results is limited by the fact that studies with tramadol and tramadol + paracetamol were analysed together in Cochrane Cepeda 2006(27), as well as different doses of tramadol (both IR and ER). Furthermore, there was a large drop-out in many studies (26% in a large tramadol + paracetamol trial, around 50% in 3 other 12 week trials, up to 74% in 1 other 12 week trial). Randomisation process and allocation concealment was also inconsistently reported.

In patients with chronic pain from osteoarthritis in the hip or knee, the use of tramadol with or without paracetamol for about 12 weeks results in a lower **pain score** compared to the use of placebo in one systematic review. In 3 subsequent RCTs, 2 trials found a statistically significant difference with placebo for different doses of tramadol whilst the other did not.

The difference is small and the clinical relevance is uncertain.

GRADE: VERY LOW quality of evidence

In patients with chronic pain from osteoarthritis in the hip or knee, the use of tramadol with or without paracetamol for about 12 weeks results in a higher number of patients **achieving moderate (>=50%) improvement in pain** scores compared to the use of placebo in 1 systematic review.

other

GRADE: VERY LOW quality of evidence

In patients with chronic pain from osteoarthritis in the hip or knee, the use of tramadol with or without paracetamol results in a lower (= better) total **WOMAC score** (pain, stiffness and physical function) compared to the use of placebo in 1 systematic review.

The difference is small. The clinical relevance of the difference is questionable.

In 2 subsequent RCTs the WOMAC pain subscale score for different tramadol doses was significantly different from placebo in 1 RCT, but not in the other RCT.

GRADE: LOW quality of evidence

In patients with chronic pain from osteoarthritis in the hip or knee, the use of tramadol with or without paracetamol results in higher rates of **discontinuation because of adverse events** compared to the use of placebo in 1 systematic review.

3 subsequent RCTs also found higher rates of discontinuation due to adverse events, with some indication of a dose-response effect (in 1 trial, discontinuation rates with tramadol 200 or 300 MG ER were only 10% but this was an enriched enrollment design).

GRADE: LOW quality of evidence

Constipation, nausea, vomiting and somnolence were more frequent with tramadol compared to placebo in 2 RCTs(31), (21), with indications of a dose-response effect.

Details can be found in the appendix of the Full Consensus Conference document (English) under the results for Busse 2016 (opioids vs placebo).

10.2 Tramadol +/- paracetamol versus placebo for chronic low back pain

tramadol or tramadol + paracetamol for chronic low back pain			
Bibliography: Cochrane Chaparro 2013 (28)			
Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Pain intensity (higher = worse)	1378 (5 studies) 4w – 12 w	Standardised mean difference -0.55 (95%CI -0.66, -0.44) SS in favour of tramadol	⊕⊕⊕⊕ LOW Study quality: -1 high drop out, unclear allocation concealment and assessor blinding Consistency: heterogeneity Directness: -1 study duration, various previous treatments, tramadol +/- pctlm Imprecision: ok
Disability (higher = worse)	1348 (5 studies) 4w – 12 w	Standardised mean difference -0.18 (95%CI -0.29, -0.07) SS	⊕⊕⊕⊕ LOW Study quality: -1 high drop out, unclear allocation concealment and assessor blinding Consistency: ok Directness: -1 study duration, various previous treatments, tramadol +/- pctlm Imprecision: ok
Nausea	1401 (5 studies) 4w-12w	Risk difference 0.09 (95%CI 0.05, 0.13) SS	⊕⊕⊕⊕ LOW Study quality: -1 high drop out, unclear allocation concealment and assessor blinding, 2 enrichment designs Consistency:OK Directness: -1 study duration, various previous treatments, tramadol +/- pctlm Imprecision: ok
Constipation	1102 (5 studies) 4w-12w	Risk difference 0.05 (95%CI 0.02, 0.09) SS	⊕⊕⊕⊕ LOW Study quality: -1 high drop out, unclear allocation concealment and assessor blinding, 2 enrichment designs Consistency:ok Directness: -1 study duration, various previous treatments, tramadol +/- pctlm Imprecision: ok
Somnolence	911 (3 studies) 12 w	Risk difference 0.06 (95%CI -0.01, 0.13) NS	⊕⊕⊕⊕ LOW Study quality: -1 high drop out, unclear allocation concealment and assessor blinding, 1 enrichment design Consistency: -1 heterogeneity Directness: various previous treatments, tramadol +/- pctlm Imprecision: ok

This Cochrane systematic review included all RCTs that compared tramadol or tramadol + paracetamol to placebo in patients with chronic low back pain who had insufficient pain relief with their current treatment. 5 trials were included, 2 of these were only 4 weeks in duration, the

remaining 3 were 12 weeks. 2 trials had an enriched enrollment design. The average daily dose of tramadol ranged from 150 mg to 300 mg.

Our confidence in the estimate of the treatment effect is limited by the large drop out in the included trials, uncertainties about allocation concealment and assessor blinding, the pooling of trials with tramadol and tramadol + paracetamol and the fact that 2 included trials were only 4 weeks long.

In patients with chronic low back pain, the use of tramadol or tramadol + paracetamol results in a lower **pain intensity score** compared to the use of placebo.

GRADE: LOW quality of evidence

In patients with chronic low back pain, the use of tramadol or tramadol + paracetamol results in a lower disability score compared to the use of placebo. The difference is small.

GRADE: LOW quality of evidence

In patients with chronic low back pain, the use of tramadol or tramadol + paracetamol results in higher rates of nausea compared to the use of placebo.

GRADE: LOW quality of evidence

In patients with chronic low back pain, the use of tramadol or tramadol + paracetamol results in a higher rate of constipation compared to the use of placebo

GRADE: LOW quality of evidence

In patients with chronic low back pain, the use of tramadol or tramadol + paracetamol does not result in a statistically significant difference in **somnolence** when compared to the use of placebo.

GRADE: LOW quality of evidence

10.3 Transdermal buprenorphine versus placebo for chronic pain in knee or hip osteoarthritis

Transdermal buprenorphine versus placebo for chronic pain in knee or hip osteoarthritis			
Bibliography: Cochrane da Costa Bruno 2014 (26)			
Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Pain intensity Various pain scales	1401 (4 studies) 4w - 30w	SMD - 0.19 (95%CI -0.30, -0.09) ²⁶ SS	⊕⊕⊕⊖ LOW Study quality: -1 large drop outs in at least 1 trial, unclear randomization, allocation concealment and blinding in ¾ trials Consistency: ok Directness: -1 duration, various previous treatment Imprecision: ok
Function Various validated function scales	501 (2 studies) 4w - 28w	SMD -0.23 (95%CI -0.40, -0.05) ²⁷ SS	⊕⊕⊖⊖ LOW Study quality: -1 large drop outs in at least 1 trial, selective reporting Consistency: ok Directness: -1 duration Imprecision: ok
Number of participants who withdrew because of adverse events	1407 (4 studies) 4w - 30w	RR 3.10 (95%CI 1.38, 6.94) SS	⊕⊖⊖⊖ LOW Study quality: -1 drop out, unclear randomization, allocation concealment and blinding in ¾ trials Consistency: heterogeneity Directness: -1 duration, various previous treatments Imprecision: ok

This Cochrane systematic review and meta-analysis includes all RCTs that compare opioids to placebo in chronic osteoarthritis pain of the knee or hip. We present here the results for the comparison of transdermal buprenorphine versus placebo.

The trials varied in duration, 1 of the 4 included trials were shorter than 12 weeks. 1 of the included trials was unpublished. 1 had an open label extension phase.

In all trials, patients were eligible if they had insufficient pain relief with their current analgesic treatment. This current treatment varied between studies (NSAID in 2 trials, opioid in 1 trial, mixed in 1 trial).

In patients with chronic osteoarthritis pain of the knee or hip, the use of transdermal buprenorphine results in a lower **pain score** than the use of placebo. The difference is small and of questionable clinical significance.

GRADE: LOW quality of evidence

²⁶ The Cochrane authors defined the clinically meaningful difference for pain as an SMD of 0.37, which corresponds to 0.9 cm on a 10 cm VAS scale.

²⁷ The authors do not define a clinically meaningful difference for function

In patients with chronic osteoarthritis pain of the knee or hip, the use of transdermal buprenorphine results in a better **function score** than the use of placebo. The confidence interval is too wide to reliably assess the clinical relevance of this result.

GRADE: LOW quality of evidence

In patients with chronic osteoarthritis pain of the knee or hip, the use of transdermal buprenorphine results in a higher **withdrawal rate due to adverse events** than the use of placebo.

GRADE: LOW quality of evidence

10.4 Buprenorphine versus placebo for chronic low back pain

Transdermal buprenorphine vs placebo for chronic low back pain			
Bibliography: Steiner 2011 (3)			
Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Average pain over the last 24 hours (11 point scale) (lower=worse)	541 (1 study) 12 w	BTDS: LSM 3.81+/- 0.166 Placebo: LSM 4.39 +/-0.152 LSMD = -0.58 (-1.02 to -0.14) (P = 0.0104) SS in favour of BTDS	⊕⊕⊕⊖ LOW Study quality: -2 enriched design, large drop out, insufficient information about randomization, allocation concealment and blinding Consistency: previous analgesics stopped at screening Directness: general comment Imprecision: ok
Responder analysis: improvement in pain scores of >=30%	541 (1 study) 12 w	BTDS 64% placebo 53% P = 0.0157 (hybrid imputation) (NS if BOCF imputation)	⊕⊕⊕⊖ LOW Study quality: -2 enriched design, large drop out, insufficient information about randomization, allocation concealment and blinding Consistency: previous analgesics stopped at screening Directness: general comment Imprecision: ok
Drop out due to adverse events	541 (1 study) 12 w	run in period BTDS 23% randomised period BTDS 16% placebo 7% NT	
Gastro-intestinal adverse events	541 (1 study) 12 w	run in period BTDS 31% randomised period BTDS 21% Placebo 16% NT	
Somnolence	541 (1 study) 12 w	run in period BTDS 8% randomised period BTDS 2% Placebo 2% NT	

This 12-week double blind RCT compared buprenorphine 7-day transdermal system 10µg/h or 20µg/h to placebo in patients with chronic low back pain who had insufficient pain relief with their previous (non-opioid) treatment. This was an enriched enrollment design: in an open label run-in, 1024 patients were treated with buprenorphine for 27 days. Those who tolerated and responded to buprenorphine (54%) were then randomized to either buprenorphine or placebo.

Of the 541 patients who were randomized, 66% completed the 12 weeks of buprenorphine and 70% completed the placebo treatment.

Our confidence in the estimate of the results is limited by the enrichment design and by the still large drop out during the randomized stage. Allocation concealment, randomisation process and blinding of assessors was not specified.

Functional outcomes were measured as exploratory outcomes only, and not statistically tested. This study had 2 main secondary outcomes: sleep disturbance and number of non-opioid analgesics used. More information can be found in the appendix of the Full Consensus Conference literature review document (English).

In patients with chronic low back pain, the use of a 7 day buprenorphine transdermal system 10µg or 20µg results in a **lower average pain score** compared to the use of placebo. The difference is small. The clinical relevance of the effect is uncertain.

GRADE: LOW quality of evidence

In patients with chronic low back pain, the use of a 7 day buprenorphine transdermal system 10µg or 20µg results in a higher number of patients achieving $\geq 30\%$ improvement in pain scores.

GRADE: LOW quality of evidence

Adverse events were recorded and reported, but not statistically tested.

GRADE: Not applicable

10.5 Methadone versus placebo for chronic non-cancer pain

A Cochrane systematic review by Haroutounian 2012 (33) searched for all trials with methadone for chronic non-cancer pain in adults. None of the included trials met the inclusion criteria for our literature review. See also chapter neuropathic pain.

10.6 Hydromorphone versus placebo for chronic pain

A Cochrane systematic review by Quigley 2013 (34) about hydromorphone for acute and chronic pain has been withdrawn due to failure to update. The last search date was 2006. It only found studies in chronic cancer pain. For information on hydromorphone in neuropathic pain or cancer pain: see other chapters.

We found 3 RCTs in other systematic reviews.

2 RCTs studied hydromorphone in chronic pain due to osteoarthritis of the hip or knee. They are reported below.

The third RCT, by Hale 2010 (35) was a 12 week double blind enriched enrollment RCT that compared hydromorphone to placebo in patients with **chronic moderate-to-severe low back pain** that were on daily opioids (opioid tolerant; ≥ 60 mg/d morphine equivalent). As such, this study does not meet the inclusion criteria for our literature review. Details about this study can be found in the appendix of the Full consensus conference document (English), in the systematic reviews by Busse 2017 and Abdel Shaheed 2016.

10.6.1 Hydromorphone versus placebo for chronic pain in osteoarthritis of the hip or knee

hydromorphone vs placebo for chronic pain in osteoarthritis of the hip or knee			
Bibliography: Vojtassak 2011 (36), Rauck 2013 (37)			
Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Pain	1278 (2 studies) 16 w	<p><u>BPI average pain</u> (36) (0-10) hydromorphone -2.4 (SD 2.1) placebo -2.6 (SD 2.3) P = .1212 NS</p> <hr/> <p><u>Pain intensity Likert</u> (37) (0-10) Primary outcome using BOCF: NS for all comparisons</p> <p>Outcomes using LOCF: hydromorphone 8 -2.0 (SEM 0.16) hydromorphone 16 -2.5 (SEM 0.16) placebo -1.9 (SEM 0.16) NS for hydromorphone 8mg SS for hydromorphone 16 mg (p 0.007)</p>	<p>⊕⊕⊕⊖ LOW Study quality: -1 drop out, unclear allocation concealment, randomization, blinding Consistency: ok Directness: -1 previous treatment Imprecision: unable to assess</p>
Function	1278 (2 studies) 16 w	<p><u>WOMAC physical function</u> (36) (range 0-68) hydromorphone -11.93 (SD 13.17) placebo -11.90 (SD 14.35) NS</p> <hr/> <p><u>WOMAC physical function</u> (37) (range 0-10) hydromorphone 8: -1.6 (SEM 0.11) hydromorphone 16: -1.7 (SEM 0.11) placebo: -1.3 (SEM 0.11) hydromorphone 8 vs pla p=0.056 NS hydromorphone 16 vs pla p=0.006 SS</p>	<p>⊕⊕⊕⊖ LOW Study quality: -1 drop out, unclear allocation concealment, randomization, blinding Consistency: ok Directness: -1 previous treatment Imprecision: unable to assess</p>
Discontinuation due to adverse events	1278 (2 studies) 16 w	<p>(36) hydromorphone 25.9% placebo 4.7% SS</p> <hr/> <p>(37) hydromorphone 8: 25.7% hydromorphone 16: 38.5% placebo: 6.3% NT</p>	<p>⊕⊕⊕⊖ LOW Study quality: -1 drop out, unclear allocation concealment, randomization, blinding Consistency: ok Directness: -1 previous treatment Imprecision: unable to assess</p>

- Vojtassak 2011 (36) was a 16 week double blind RCT comparing hydromorphone OROS once daily vs placebo (4 mg, titrated up to max 32 mg) in 288 patients with chronic pain due to **osteoarthritis of the hip or knee**, who had insufficient pain relief from their current analgesic treatment (paracetamol or NSAID). Early discontinuation occurred in 39.6% of patients in the hydromorphone treatment arm and in 23.6% of placebo-treated patients.

- Rauck 2013 (37) was a 16 week double blind RCT comparing hydromorphone OROS 8 mg or 16 mg to placebo in 990 patients with chronic pain due to **osteoarthritis of the hip or knee**, who had insufficient pain relief from their current (opioid or non-opioid) analgesic. Early discontinuation occurred in 50.8% of patients taking hydromorphone 8 mg, 61.2% of patients taking hydromorphone 16 mg and 43.7% of patients on placebo.

In patients with chronic pain due to **osteoarthritis of the hip or knee**, inadequately controlled by (opioid or non-opioid) analgesic treatment, the use of hydromorphone does not result in a statistically different change in **pain score** compared to placebo. (A statistically significant difference is observed when considering less conservative imputation methods for missing values.)

GRADE: LOW quality of evidence

In patients with chronic pain due to **osteoarthritis of the hip or knee**, inadequately controlled by (opioid or non-opioid) analgesic treatment, the use of hydromorphone does not result in a statistically different change in **physical function** compared to placebo. A statistically significant difference is observed for hydromorphone 16 mg when considering less conservative imputation methods for missing values.

GRADE: LOW quality of evidence

In patients with chronic pain due to **osteoarthritis of the hip or knee**, inadequately controlled by (opioid or non-opioid) analgesic treatment, the use of hydromorphone results in higher rates of discontinuation due to adverse events compared to placebo.

GRADE: LOW quality of evidence

10.7 Oxycodone versus placebo for chronic pain due to osteoarthritis

Oxycodone versus placebo for chronic pain in knee or hip osteoarthritis			
Bibliography: Cochrane da Costa Bruno 2014 (26)			
Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Pain intensity Various pain scales	2943 (10 studies) 2w – 15w	SMD -0.31 [-0.47, -0.15] ²⁸	⊕⊕⊕⊕ VERY LOW Study quality:-1 large drop outs Consistency: ok Directness:-2 short study duration in half of the studies, mixed previous treatment/handling Imprecision: ok
Function Various validated function scales	680 (4 studies) 4w-15w	SMD -0.30 [-0.58, -0.01] ²⁹	⊕⊕⊕⊕ VERY LOW Study quality:-2 large drop outs, selective reporting Consistency: ok Directness: -1 various previous treatments./handling Imprecision:-ok
Number of participants who withdrew because of adverse events	2653 (9 studies) 2w – 15w	RR 5.55 [3.47, 8.87]	⊕⊕⊕⊕ VERY LOW Study quality:- :1 large drop outs Consistency: ok Directness: -1 many short duration trials, various previous treatment Imprecision: ok

This Cochrane systematic review and meta-analysis includes all RCTs that compare opioids to placebo in chronic osteoarthritis pain of the knee or hip. We present here the results for the comparison of oxycodone versus placebo.

The trials varied in duration, half of the included trials were shorter than 12 weeks.

In all trials, patients were eligible if they had insufficient pain relief with their previous analgesic treatment. This previous treatment varied within and between studies (non-opioid, opioid, unspecified); in all studies, the previous use of opioids was allowed.

Our confidence in the estimates of the results is limited by several factors: A large drop-out in the included trials, short durations in about half the trials, the variability in previously used analgesic treatment, the lack of reporting functional outcomes in a lot of the trials.

For result of the individual trials that have adequate study duration: see the appendix Full Consensus Conference document (English) under Busse 2017 and Da Costa Bruno 2014.

²⁸ The Cochrane authors defined the clinically meaningful difference for pain as an SMD of 0.37, which corresponds to 0.9 cm on a 10 cm VAS scale.

²⁹ The authors do not define a clinically meaningful difference for function

In patients with chronic osteoarthritis pain of the knee or hip, the use of oxycodone results in a **lower pain score** than the use of placebo. The Clinical relevance this result is unclear.

GRADE: VERY LOW quality of evidence

In patients with chronic osteoarthritis pain of the knee or hip, the use of oxycodone results in a **better function score** than the use of placebo. The Clinical relevance this result is unclear.

GRADE: VERY LOW quality of evidence

In patients with chronic osteoarthritis pain of the knee or hip, the use of oxycodone results in a higher withdrawal rate due to adverse events than the use of placebo.

GRADE: VERY LOW quality of evidence

10.8 Oxycodone versus placebo for chronic low back pain

Oxycodone versus placebo for chronic low back pain			
Bibliography:			
Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Pain ³⁰ (converted to 0-100 scale, lower=better)	660 (2 studies) 12-15w	(38) MD -12.0 (95%- 18.9 to -5.1) SS in favour of oxycodone (39) MD -8.9 (95%CI-12.8 to - 5.0) SS in favour of oxycodone	⊕⊕⊕⊕ LOW Study quality:-1 high dropout, LOCF Consistency: ok Directness:-1 previous opioid use in half of the patients, washout Imprecision: ok
>= 50% improvement in pain intensity	981 (1 study) 15 w	(39) oxycodone 23.3% placebo 18.9% p = 0.174 NS	⊕⊕⊕⊕ VERY LOW Study quality: -2 high dropout, LOCF, selective reporting Consistency: only 1 study Directness: -1 previous opioid use Imprecision: unable to assess
Function - physical	967 (2 studies) 12-15w	(38) SF-12 physical component reported as significant (p<0.01) but no results provided (39) SF-36 physical component LSMD -2.3 (SE 0.65) <0.001 SS	⊕⊕⊕⊕ VERY LOW Study quality:-1 dropout, LOCF, Consistency: ok Directness: -1 previous opioid use Imprecision: -1 unable to assess, incomplete reporting
Function - mental	967 (2 studies) 12-15w	SF-12 mental component (38) reported as NS, no results provided (39) SF-36 mental component LSMD vs pla -0.7 (SE 0.69); p=0.285 NS	⊕⊕⊕⊕ VERY LOW Study quality:-1 dropout, LOCF Consistency: ok Directness: -1 previous opioid use Imprecision: -1 unable to assess, incomplete reporting
Discontinuation due to adverse events	967 (2 studies) 12-15w	(38) oxycodone 23.8% placebo 5% (39) oxycodone 32.0% placebo 4.6%	

³⁰ Result as reported by Abdel Shaheed 2016, because original trials used different ways of presenting data.

3 RCTs with oxycodone in chronic **low back pain** were included in the SRs that are reported in this document.

The first, a 12 week RCT by Webster 2006 (38) included 719 patients with chronic low back pain despite daily analgesic use. Patients were randomized to oxycodone 4x/day (up to 80 mg/day) or oxycodone + naltrexone (not on the Belgian market) or placebo. Almost half of the patients had used opioids in the previous month, 5% were on high dose opioids. Discontinuation of study medication was high (>50%).

The second RCT by Buynak 2010 (39) was 15 weeks, included 918 patients with chronic low back pain, dissatisfied with their current analgesic therapy. Patients were randomized to oxycodone 20-50 mg twice daily or tapentadol (not reported here) or placebo. Half of the included patients had had previous opioid use. Discontinuation of study medication was high (>50%).

In the third RCT by Vondrackova 2008 (40), oxycodone + naloxone was compared to oxycodone and placebo in patients with low back pain that was 'adequately managed' with ≥ 2 weeks of opioids. This population, already on high dose opioids, does not really match our research questions, therefore we do not report it here. Details about this study can be found in the appendix of the Full Consensus Conference document (English), under Busse 2017.

Our confidence in the estimate of the treatment effect is limited by the large drop-out (>50%), handling of missing values, previous opioid use and lack of reporting of some outcomes.

In patients with chronic low back pain, the use of oxycodone results in a lower **pain score** compared to the use of placebo. The clinical relevance of the effect is uncertain.

GRADE: LOW quality of evidence

In patient with chronic low back pain, the use of oxycodone does not result in a statistically significant difference in the number of patients achieving ≥ 50 reduction in pain score compared to the use of placebo.

GRADE: LOW VERY LOW quality of evidence

In patients with chronic low back pain, the use of oxycodone results in a lower **physical component summary score on the SF-12 or SF-36** compared to the use of placebo. The clinical relevance of the effect is uncertain.

GRADE: LOW VERY LOW quality of evidence

In patients with chronic low back pain, the use of oxycodone does not result in a statistically significant difference on the **mental component summary score on the SF-12 or SF-36** compared to the use of placebo.

GRADE: LOW VERY LOW quality of evidence

In patients with chronic low back pain, the use of oxycodone results in numerically higher rates of discontinuation due to adverse events compared to placebo. The difference was not statistically tested.

Information on individual adverse events was reported in different ways in both trials. More information can be found in the appendix of the Full Consensus Conference document under Abdel Shaheed 2016.

10.9 Tapentadol versus placebo for chronic musculoskeletal pain

Tapentadol versus placebo for chronic musculoskeletal pain			
Bibliography: Cochrane Santos 2015 (41)			
Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Change in pain intensity from baseline at week 12 (11-point numerical rating scale; lower=better)	3001 (3 studies) 15w	MD -0.56 (-0.92, -0.20] SS less pain with tapentadol	⊕⊕⊕⊕ VERY LOW Study quality: -1 high drop out, LOCF, Consistency: -1 some heterogeneity Directness: -1 previous opioid use in some patients, washout Imprecision: ok
Responder rate (at least 50% pain reduction)	2011 (2 studies) 15w	RR 1.36 (1.13, 1.64) SS more responders with tapentadol NNT 16 (95% CI 9 to 57)	⊕⊕⊕⊕ VERY LOW Study quality: -1 high drop out, LOCF, Consistency: -1 information from 2 studies Directness: -1 previous opioid use in some patients, washout Imprecision: ok, but range includes no clinically relevant effect
SF-36 physical component summary score (scale 0-100?) (lower=better)	2011 (2 studies) 15w	MD 2.57 (1.69 to 3.44) SS better score with tapentadol	⊕⊕⊕⊕ VERY LOW Study quality: -1 high drop out, LOCF, Consistency: -1 information from 2 studies, other functional outcomes NS Directness: -1 previous opioid use in some patients, washout Imprecision: ok
discontinuation due to adverse events	3001 (3 studies) 15w	RR 2.68 (2.05, 3.52) SS more discontinuations with tapentadol NNH 10; 95% CI 7 to 12, for 12 weeks	⊕⊕⊕⊕ LOW Study quality: -1 high drop-out Consistency: ok Directness: -1 previous opioid use in some patients, washout Imprecision: ok
Constipation	3001 (3 studies) 15w	RR 2.43, 95% CI 1.86 to 3.17;	⊕⊕⊕⊕ LOW Study quality: -1 high drop-out Consistency: ok Directness: -1 previous opioid use in some patients, washout Imprecision: ok
Nausea	3001 (3 studies) 15w	RR 2.81, 95% CI 2.18 to 3.62;	⊕⊕⊕⊕ LOW Study quality: -1 high drop-out Consistency: ok Directness: -1 previous opioid use in some patients, washout Imprecision: ok
Vomiting	3001 (3 studies) 15w	RR 2.77, 95% CI 1.83 to 4.21	⊕⊕⊕⊕ LOW Study quality: -1 high drop-out Consistency: ok Directness: -1 previous opioid use in some patients, washout Imprecision: ok
Somnolence	3001	RR 3.27, 95% CI 2.26 to 4.73	⊕⊕⊕⊕ LOW

	(3 studies) 15w	Study quality: -1 outcome, high Consistency: ok Directness: -1previous opioid use in some patients Imprecision: ok
--	--------------------	--

This Cochrane systematic review includes all RCTs that compare tapentadol to placebo in chronic musculoskeletal pain in adults. 3 15-week RCTs, with a total of 3001 patients were included. 2 RCTs included patients with osteoarthritis, 1 RCT included patients with low back pain. Patients had to have inadequate pain relief with their current analgesic treatment. In all 3 trials, previous use of opioids was allowed but the number of patients who had used opioids before was only reported in 2 of the trials. Discontinuation was high in all 3 trials and reached >50%.

Our confidence in the estimate of the results is limited by the large drop-out rates in the 3 trials, the handling of missing values, heterogeneity in some of the outcomes, some incomplete reporting and the previous opioid use in some of the included patients.

In patients with chronic musculoskeletal pain, the use of tapentadol results in a lower **pain score** compared to the use of placebo. The difference is small and of unclear clinical significance.

GRADE: VERY LOW quality of evidence

In patients with chronic musculoskeletal pain, the use of tapentadol results in a higher rate of patients achieving at least **50% pain reduction** compared to placebo.

GRADE: VERY LOW quality of evidence

In patients with chronic musculoskeletal pain, the use of tapentadol results in a better **SF-36 physical component summary score** compared to the use of placebo. The clinical significance of the difference is unclear. Other scores for **functional health status and well-being** were not statistically significantly different from placebo.

GRADE: VERY LOW quality of evidence

In patients with chronic musculoskeletal pain, the use of tapentadol results in a higher rate of **discontinuation due to adverse events** compared to the use of placebo.

GRADE: LOW quality of evidence

Tapentadol was associated with a higher risk of **constipation, nausea, vomiting and somnolence** compared to placebo.

GRADE: LOW quality of evidence

10.10 Codeine for chronic non-cancer pain

We found no studies that met our inclusion criteria.

10.11 Tilidine for chronic non-cancer pain

We found no studies that met our inclusion criteria.

10.12 Morphine for chronic non-cancer pain

We found no studies that met our inclusion criteria.

11 Summary and conclusions from the literature review. Opioids for neuropathic pain

11.1 Opioids in general for neuropathic pain

McNicol 2013 (42) searched for RCT's that compared opioid agonists with placebo or an active comparator for central or peripheral neuropathic pain of any aetiology. The authors of this Cochrane review divided the included studies in "short-term" studies and "intermediate-term" studies. From the 14 included intermediate-term studies, only 1 met our inclusion criterion for study duration (≥ 12 weeks). This study (43) has already been discussed elsewhere in this document.

Chaparro 2012 (44) searched for various drug combinations, including combinations without an opioid, for neuropathic pain. The authors of this Cochrane review included 21 studies. From these 21 studies, 5 studies met our inclusion criterion in terms of intervention. From these 5 studies, only 1 study (43) met our inclusion criterion for study duration (≥ 12 weeks) and has already been discussed elsewhere in this document.

GRADE: insufficient evidence

11.2 Codeine for neuropathic pain

Wiffen 2016 (45) searched for RCT's comparing paracetamol with or without codeine or dihydrocodeine for neuropathic pain in adults. Patients had to have at least 2 weeks of treatment. No study satisfied the inclusion criteria of this Cochrane review.

GRADE: insufficient evidence

11.3 Tramadol for neuropathic pain

Dy 2017 (46) performed a meta-analysis on RCT's comparing "atypical" opioids (i.e. tramadol and tapentadol) with placebo for neuropathic pain. Patients had to have at least 2 weeks of treatment. The authors identified two studies with tramadol. Both studies did not meet our inclusion criterion for study duration (≥ 12 weeks).

Duehmke 2017 (47) searched for RCT's comparing tramadol with placebo or an active comparator for neuropathic pain. Patients had to have at least 2 weeks of treatment. The authors of this Cochrane review included 6 studies with a study duration between 4 and 6 weeks. None of these studies met our inclusion criterion for study duration (≥ 12 weeks).

GRADE: insufficient evidence

11.4 Tilidine for neuropathic pain

Our literature search did not find any study meeting our inclusion criteria comparing tilidine with placebo or an active comparator for neuropathic pain.

GRADE: insufficient evidence

11.5 Buprenorphine for neuropathic pain

Buprenorphine vs placebo for neuropathic pain			
Bibliography: (48)			
Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
30% reduction in pain at week 12 (PO) (score range: 0-10)	168 (1 study) 12 weeks	ITT analysis: 51.7% (46/89) vs 41.3% (38/92) OR: 1.56 (95%: 0.82-2.97) NS; p= 0.175 Note: buprenorphine was superior in the per protocol analysis	⊕⊕⊕⊕ LOW Study quality:-1 attrition bias Consistency: NA Directness: acceptable Imprecision: -1 sparse data
At least 50% reduction in pain intensity from baseline at week 12 (proportion)	168 (1 study) 12 weeks	34.8% vs 20.7% SS, p<0.05 in favour of buprenorphine	⊕⊕⊕⊕ LOW Study quality:-1 attrition bias Consistency: NA Directness: acceptable Imprecision: -1 sparse data
Neuropathic Pain Symptom Inventory(NPSI): change from baseline	168 (1 study) 12 weeks	Total pain intensity score: -22.50 (17.70) vs -20.10 (21.68) SS, <0.05, in favour of buprenorphine Paroxymal pain: SS, p<0.05, in favour of buprenorphine No SS difference for burning spontaneous pain, pressing spontaneous pain, evoked pain, and parathesia/dysthesia pain	⊕⊕⊕⊕ LOW Study quality:-1 attrition bias Consistency: NA Directness: acceptable Imprecision: -1 sparse data
Brief Pain Inventory interference scale	168 (1 study) 12 weeks	Sleep: SS, p<0.05, in favour of buprenorphine No SS differences for general activity, mood, walking ability, normal work, relationships, enjoyment of life.	⊕⊕⊕⊕ LOW Study quality:-1 attrition bias Consistency: NA Directness: acceptable Imprecision: -1 sparse data
HRQoL (MOS 36-item SF): change from baseline	168 (1 study) 12 weeks	Bodily pain: 17.26 (19.43) vs 10.00 (20.56) SS, p<0.05, in favour of buprenorphine No SS differences for physical functioning, physical role, general health, vitality, social functioning, emotional role, and mental health	⊕⊕⊕⊕ LOW Study quality:-1 attrition bias Consistency: NA Directness: acceptable Imprecision: -1 sparse data
Participant Global Impression of Change(PGIC)	168 (1 study) 12 weeks	2.37 (1.09) vs 3.03 (1.35) SS, p<0.05, in favour of buprenorphine	⊕⊕⊕⊕ LOW Study quality:-1 attrition bias Consistency: NA Directness: acceptable Imprecision: -1 sparse data

Clinician Global Impression of Change(CGIC)	168 (1 study) 12 weeks	2.39 (1.19) vs 2.91 (1.21) NS, p=0.25	⊕⊕⊕⊕ LOW Study quality:-1 attrition bias Consistency: NA Directness: acceptable Imprecision: -1 sparse data
At least 1 adverse event (AE) (mostly mild and moderate)	168 (1 study) 12 weeks	93.6% (87/93) vs 81.7% (76/93) NT	⊕⊕⊕⊕ LOW Study quality:-1 attrition bias Consistency: NA Directness: acceptable Imprecision: -1 sparse data

Wiffen 2015 (49) searched for RCT's comparing buprenorphine with placebo or an active comparator for neuropathic pain. Patients had to have at least 2 weeks of treatment. None of the studies satisfied the inclusion criteria of the authors and so no studies were included in this cochrane review.

Simpson 2016 et al. (48) conducted a double-blind, parallel-group RCT comparing transdermal buprenorphine with placebo in patients with **diabetic peripheral neuropathic pain**. Patients were included with moderate to severe pain for at least 6 months on maximal tolerated conventional therapy. Patients who were currently or previously treated with strong opioids were excluded from the study. The use of weak opioids, NSAID, and topical therapies were discontinued at the screening visit. A total of 61.3% and 68.8% were on concomitant pain treatment with anticonvulsants in the buprenorphine and the placebo arm, respectively.

168 patients were enrolled, with 93 randomized to either buprenorphine or placebo. 37/93 (39.8%) and 24/93 (25.8%) did not complete the study, respectively. Interaction analyses were done to assess the effect of antidepressant or anti-epileptic use on the effectiveness of buprenorphine. According to the authors evaluation, there was no meaningful effect. More information can be found in the appendix of the Full Consensus Conference literature review document (English).

Our confidence in the estimate of the results is limited by the high dropout rate and the inadequate study power.

In patients with diabetic peripheral neuropathic pain, the use of buprenorphine results in **no difference for a 30% pain reduction** compared to placebo.

GRADE: low quality of evidence

In patients with diabetic peripheral neuropathic pain, the use of buprenorphine results in **more patients with a 50% pain reduction** compared to placebo.

GRADE: low quality of evidence

In patients with diabetic peripheral neuropathic pain, the use of buprenorphine results in a reduction of the total pain intensity score according to the **Neuropathic Pain Symptom Inventory(NPSI)**. A small difference was observed for paroxysmal pain in favour of buprenorphine, no differences were observed for all other subscales (burning spontaneous pain, pressing spontaneous pain, evoked pain, and parathesia/dysthesis pain).

GRADE: low quality of evidence

In patients with diabetic peripheral neuropathic pain, the use of buprenorphine results in improved sleep compared to placebo according to the **Brief Pain Inventory interference scale**. However, no differences were observed for all other subscales (general activity, mood, walking ability, normal work, relationships, enjoyment of life).

GRADE: low quality of evidence

In patients with diabetic peripheral neuropathic pain, the use of buprenorphine results in a reduction of bodily pain compared to placebo according to **the SF 36 questionnaire**. However, no differences were observed for all other subscales (physical functioning, physical role, general health, vitality, social functioning, emotional role, and mental health).

GRADE: low quality of evidence

In patients with diabetic peripheral neuropathic pain, the use of buprenorphine results in an **improved global impression of change according to the patient** compared to placebo.

GRADE: low quality of evidence

In patients with diabetic peripheral neuropathic pain, the use of buprenorphine results in **no difference in the global impression of change according to the clinician** compared to placebo.

GRADE: low quality of evidence

In patients with diabetic peripheral neuropathic pain, the use of buprenorphine results in **more adverse events** compared to placebo. No statistical tests were performed to compare the groups.

GRADE: low quality of evidence

11.6 Fentanyl for neuropathic pain

Derry 2016 (50) searched for RCT's comparing fentanyl with placebo or an active comparator for neuropathic pain. Patients had to have at least 2 weeks of treatment. One study satisfied the inclusion criteria of the authors of this Cochrane review. We did not include this study in our analysis since the studied formulation (one-day patch) is currently not available in Belgium.

GRADE: insufficient evidence

11.7 Hydromorphone for neuropathic pain

Stannard 2016 (51) searched for RCT's comparing hydromorphone with placebo or an active comparator for neuropathic pain. Patients had to have at least 2 weeks of treatment. One study satisfied the inclusion criteria of the authors of this Cochrane review. We did not include this study in our analysis since it did not meet our inclusion criterion for study design (no post-hoc analyses). However, the original study (35) on which the post-hoc analysis was based on is included elsewhere in this document.

GRADE: insufficient evidence

11.8 Methadone for neuropathic pain

McNicol 2017 (2) searched for RCT's comparing methadone with placebo or an active comparator for neuropathic pain. Patients had to have at least 2 weeks of treatment. Three cross-over studies satisfied the inclusion criteria of the authors of this Cochrane review. There were too few data to perform a pooled analysis. We did not include these 3 studies in our analysis since they did not meet our inclusion criteria for several reasons.

GRADE: insufficient evidence

11.9 Morphine for neuropathic pain

Cooper 2017 (52) searched for RCT's comparing morphine with placebo or an active comparator for neuropathic pain. Patients had to have at least 2 weeks of treatment. The authors of this Cochrane review included 5 cross-over studies with treatment periods of 4 to 7 weeks. We did not include these studies in our analysis since they did not meet our inclusion criteria for study duration (≥ 12 weeks) or sample size (>40 patients per study-arm).

GRADE: insufficient evidence

11.10 Oxycodone for neuropathic pain

Oxycodone vs placebo/active comparator for diabetic neuropathic pain			
Bibliography: (43) discussed in (53)			
Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
At least moderate pain relief (>30% pain reduction)	338 (1 study) 12 weeks	72/163 (44.2%) vs 51/165 (30.9%) RR 1.43 (95%CI: 1.07-1.90) SS, in favour of oxycodone	⊕⊕⊕⊖ LOW Study quality:-1 attrition bias, unclear blinding Consistency: NA Directness: ok Imprecision: -1 sparse data
Adverse event withdrawals	338 (1 study) 12 weeks	27/163 (16.6%) vs 9/165 (5.5%) RR 3.04 (95%CI: 1.47,6.26) SS, in favour of placebo	⊕⊕⊕⊖ LOW Study quality:-1 attrition bias, unclear blinding Consistency: NA Directness: ok Imprecision: -1 sparse data
Lack of efficacy withdrawals	338 (1 study) 12 weeks	6/163 (3.7%) vs 20/165 (12.1%) RR 0.30 (95%CI: 0.13-0.74) SS, in favour of oxycodone	⊕⊕⊕⊖ LOW Study quality:- 1 attrition bias, unclear blinding Consistency: NA Directness: ok Imprecision: -1 sparse data
Any adverse event	338 (1 study) 12 weeks	147/168 (87.5%) vs 119/167 (71.3%) RR 1.23 (95%CI: 1.10-1.37) SS, in favour of placebo	⊕⊕⊕⊖ LOW Study quality:-1 attrition bias, unclear blinding Consistency: NA Directness: ok Imprecision: -1 sparse data

Gaskell (53) searched for RCT's comparing oxycodone with placebo or an active comparator for neuropathic pain. Patients had to have at least 2 weeks of treatment.

The authors of this Cochrane review included 5 studies. Three studies did not meet our inclusion criteria due to study duration (≥ 12 weeks) and sample size (>40 patients per study arm). Therefore, we only report on the 2 studies that met our inclusion criteria and do not report any pooled results presented in the Cochrane review. Both studies had a study duration of 12 weeks and included patients with painful diabetic neuropathy (pain intensity $\geq 5/10$) stable on gabapentin ((43) or pregabalin (NCT00944697 study). We only include Hanna et al. 2008 in our summary and refer for the NCT00944697 study comparing oxycodone/naloxone with placebo to the appendix of the Full consensus conference document (English) since it concerned unpublished data.

Hanna et al. 2008 excluded patients who received long-acting opioids in the previous month; treatment (stable frequency and dose) started >3 weeks prior to screening with NSAIDS and tricyclic antidepressants was allowed.

In patients with painful diabetic neuropathy stable on gabapentin, the use of oxycodone results in **more patients with at least moderate pain relief (30% reduction)** than the use of placebo.

GRADE: low quality of evidence

In patients with painful diabetic neuropathy stable on gabapentin, the use of oxycodone results in **more withdrawals due to adverse events** than the use of placebo.

GRADE: low quality of evidence

In patients with painful diabetic neuropathy stable on gabapentin, the use of oxycodone results in **fewer withdrawals due to a lack of efficacy** than the use of placebo.

GRADE: low quality of evidence

In patients with painful diabetic neuropathy stable on gabapentin, the use of oxycodone results in **more adverse events** than the use of placebo.

GRADE: low quality of evidence

11.11 Tapentadol for neuropathic pain

Tapentadol vs placebo for diabetic neuropathic pain			
Bibliography: (54) discussed in (46)			
Outcomes	N° of participants (studies) Follow up	Results	Quality of the evidence (GRADE)
Change in average pain intensity	395 (randomized) (1 study) 12 weeks	Least-squares mean difference of -1.3 (95%CI: -1.70, -0.92); p<0.001 SS, in favour of tapentadol	⊕⊕⊕⊕ VERY LOW Study quality:-2 enriched design, attrition bias, LOCF Consistency: NA Directness: -1, washout and various previous treatments Imprecision: sparse data
'very much' or 'much' improved patient's global impression of change (PGIC) at week 12:	395 (randomized) (1 study) 12 weeks	116/180 (64.4%) vs 68/177 (38.4%); SS p<0.001 in favour of tapentadol ER	⊕⊕⊕⊕ VERY LOW Study quality:-2 enriched design, attrition bias, LOCF Consistency: NA Directness: -1, washout and various previous treatments Imprecision: sparse data
Any adverse event (double-blind phase)	395 (randomized) (1 study) 12 weeks	139/196 (70.9%) vs 100/193 (51.8%) No statistical tests were performed.	⊕⊕⊕⊕ VERY LOW Study quality:-1 enriched design, attrition bias, LOCF Consistency: NA Directness: -1, washout and various previous treatments Imprecision: sparse data

Dy 2017 (46) performed a meta-analysis on RCT's comparing "atypical" opioids (i.e. tramadol and tapentadol) with placebo for diabetic peripheral neuropathy symptoms. Patients had to have at least 2 weeks of treatment. The authors identified 3 studies with tapentadol. We excluded one study for not meeting our inclusion criteria for study duration (≥ 12 weeks) and sample size (>40 patients per study arm). We excluded Vinik et al. 2014 (55) because a new formulation was studied that is currently not available in Belgium leaving one study (54) for our analysis.

Schwartz et al. (54) conducted a double blind RCT with an enriched enrollment randomized-withdrawal design, comparing tapentadol with placebo in patients with painful diabetic peripheral neuropathy who were dissatisfied with their current treatment (opioid or non-opioid). After a washout period, 588 patients (pain intensity $\geq 5/10$) entered the 3-week open-label phase receiving tapentadol. A total of 33.3% discontinued the open-label phase early, 51.0% due to adverse events. The responders were subsequently randomized in the 12-week maintenance phase to tapentadol (n=199) or placebo (n=196). Of the randomized patients, 31.7% and 31.6% discontinued the study early, respectively. More information can be found in the appendix of the Full Consensus Conference literature review document (English).

Our confidence in the estimate of the results is limited by the enrichment design and by the high dropout rate. Nonstandard pain outcomes were used in this study. Furthermore, the impact of pain on function or quality of life was not measured or reported.

In patients with painful diabetic neuropathic pain, the use of tapentadol results in **a reduction of the average pain intensity** compared to placebo.

GRADE: very low quality of evidence

In patients with painful diabetic neuropathic pain, the use of tapentadol results in **an improvement of the patient's global impression of change** compared to placebo.

GRADE: very low quality of evidence

In patients with painful diabetic neuropathic pain, the use of tapentadol results in **more adverse events** compared to placebo. However, no statistical tests were performed.

GRADE: very low quality of evidence

12 Summary and conclusions from the literature review. Opioids for cancer pain

An overview of systematic reviews (56) identified nine Cochrane systematic reviews evaluating the use of opioids in chronic cancer pain. We have reported the last updated version of each of these systematic reviews.

The nine reviews searched for RCTs comparing an opioid drug (**tramadol** (57), **codeine** (58), **hydromorphone**(59), **transdermal fentanyl** (60), **methadone** (61), **oxycodone** (62), **buprenorphine** (63), **oral tapentadol** (64), and **oral morphine** (65)) to placebo or an active comparator in patients suffering from chronic cancer pain.

An additional review (66) specifically searched for RCTs evaluating morphine, fentanyl, oxycodone or codeine preparations that reported adverse events of level of consciousness or inability to eat or drink.

We also found a systematic review (14) that searched for both pharmacologic and non-pharmacologic interventions for pain management in adult cancer survivors.

None of the RCTs that were found by these systematic reviews met our inclusion criteria.

GRADE: *insufficient evidence*

13 Summary and conclusions from the literature review. Opioid rotation

We found four systematic reviews that searched for RCTs on rotation of opioids compared to maintenance of current opioid therapy in adults with chronic pain.
Two reviews (1), (9) found no RCTs comparing opioid rotation to maintenance of current therapy.
One review (67) has been retracted.
Schuster 2018 (68) found 5 very small RCTs, but none met our inclusion criteria.

GRADE: *insufficient evidence*

14 Summary and conclusions from the literature review. Tapering of Opioids

We found four systematic reviews that searched for RCTs on tapering compared to continuation of opioid therapy in adults with chronic pain.
Three reviews (1), (9), (69) found no RCTs comparing tapering to continuation of opioid therapy.
One review (70) found 5 small RCTs, but none met our inclusion criteria.

GRADE: *insufficient evidence*

15 Rare adverse events. Information from observational studies

15.1 Endocrinological dysfunction

Our source document, the systematic review by Chou 2015(17) and Dowell 2016 (1) did not identify any cohort studies about sexual dysfunction.

An overview of Cochrane reviews by Els 2017(23) found no information in the available RCTs.

We performed a search for systematic review, meta-analyses of cohort studies and of individual cohort studies of > 1000 participants. We focused on long-term use of opioids in a chronic pain population. We considered only the populations that were selected in our methods section. We excluded studies about opioid dependence disorder, and short term use of opioids.

15.1.1 Opioids and hypogonadism

A systematic review by Ali 2016 (71) about the effect of opioids on the **endocrine system and the development of hypogonadism** identified only very small observational studies (<100 participants). No studies met the inclusion criteria for our literature review.

15.1.2 Opioids and reproductive dysfunction in women

A systematic review by Wersocki 2017 (72) about the association of long-term opioids in women with chronic non-cancer pain and **reproductive dysfunction (hypothalamic-pituitary-gonadal axis disruption)** found only 1 cohort study of 8 subjects. No studies met the inclusion criteria for our literature review.

We identified 1 cohort study of a later date. Richardson 2018(73) reported a matched cohort study about the association of long-term prescribed opioids for musculoskeletal pain and the risk of **reproductive dysfunction** in women. Long-term opioid use was associated with a greater risk of abnormal menstruation and menopause compared to short-term (<90 days) opioid use.

Reproductive dysfunction: Long-term opioid use versus short-term opioid use Richardson 2018(73)					
Design	N/n	Population	Risk factor	Outcome	Results*
matched cohort	n = 44260	-UK women (18-55 y) - with musculoskeletal pain and starting an opioid prescription - in primary care database	long-term opioid use (≥90 days) versus short-term opioid use (<90 days)	Abnormal menstruation	HR 1.13 (95% CI 1.05 to 1.21)
	Low libido			HR 1.19 (95% CI 0.96 to 1.48)	
	Infertility			HR 0.82 (95% CI 0.64 to 1.06)	
	Menopause			HR 1.16 (95% CI 1.10 to 1.23)	
*Adjusted for the outcome of interest (if pre-existing), thyroid conditions, structural gynaecological conditions, illegal opioid use, NSAID use, BMI (<25 kg/m2, ≥25 kg/m2 or missing), smoking status, alcohol use and age.					

Table: results of Richardson 2018

15.1.3 Opioids and erectile dysfunction in men

A systematic review by Zhao 2017 (74) examined the association between opioid use and the risk of **erectile dysfunction**. Only 1 very small cohort study was found. The other includes studies had a cross-sectional design. No studies met the inclusion criteria for our literature review.

15.1.4 Opioids and testosterone suppression in men

A systematic review by Bawor 2015 (75) examined the association between opioid use and the risk of **testosterone suppression** in men. 7 very small cohort studies were found (<200), as well as 10 cross-sectional studies. No studies met the inclusion criteria for our literature review.

15.2 Immunological dysfunction

Our source document, the systematic review by Chou 2015 (17) and Dowell 2016 (1) did not identify any cohort studies about immunity disorders.

An overview of Cochrane reviews by Els 2017 (23) found no information in the available RCTs.

We performed a search for systematic review, meta-analyses of cohort studies and for individual cohort studies of > 1000 participants. We focused on long-term use of opioids in a chronic pain population. We considered only the populations that were selected in our methods section. We excluded studies about opioid dependence disorder, and short term use of opioids.

15.2.1 Opioid use and breast cancer recurrence

A Danish population-based cohort study by Cronin-Fenton 2015 (76) examined the association between the postdiagnosis use of opioids in women with breast cancer and the risk of **breast cancer recurrence**. A subanalysis for chronic use (≥ 6 months) was also performed. No association was found between opioid use and breast cancer recurrence.

Breast cancer recurrence: opioid use versus no opioid use Cronin-Fenton 2015 (76)					
Design	N/n	Population	Risk factor	Outcome	Results*
cohort	n = 34188	-Denmark -patients with incident, early stage breast cancer	opioid prescription use versus no opioid prescription	Breast cancer recurrence	HR 1.0 (95% CI 0.92 to 1.1)
	Subanalysis: chronic long-term opioid use (>=6 months) versus nonuse		Breast cancer recurrence	HR 1.1 (95% CI 0.93 to 1.4)	
	10 y follow-up				
	283666 person-years				

** Adjusted for age, menopausal status, histologic grade,ER/ET status, disease stage, primary surgery type, chemotherapy, time-varying exposures to simvastatin and aspirin, baseline HRT, and comorbid diseases.*

Table: results of Cronin-Fenton 2015

16 Additional safety information from other sources

16.1 Adverse effects

16.1.1 Opioids in general

- **All cause mortality:** a retrospective cohort study shows that the risk of all cause mortality is 1.64 times higher with a long-acting opioid (morphine or extended-release oxycodone, fentanyl patches) than with an anti-epileptic or a tricyclic antidepressant used for the same indication.(77)
- Constipation; no tolerance develops for this adverse effect.(78)
- Nausea and vomiting, mainly during the first weeks of treatment or when the dose is increased too quickly. (78)
- Sedation that is mainly present in the first days (with possible impact on traffic or work safety). (78)
- Euphoria. (78)
- Pylorus spasm, contraction of the bile duct and the sphincter of Oddi. (78)
- Dry mouth, dizziness, sweating, facial flushing, headache, vertigo, bradycardia, tachycardia, palpitations, orthostatic hypotension, hypothermia, restlessness, changes of mood, decreased libido or potency, hallucinations, and miosis also occur. These effects tend to occur more commonly in ambulant patients than in those at rest in bed and in those without severe pain.(79)
- Hyponatraemia; the incidence is likely to be low.(80)
- Higher doses of opioids: respiratory depression and hypotension, convulsions, rhabdomyolysis, death as a consequence of respiratory depression. (79)
- Opioid-induced hyperalgesia: well demonstrated when using opioids for acute postoperative pain; also possible when used for chronic pain. (78)
- Psychological dependence. (78)
- Physical dependence with prolonged use, with withdrawal symptoms when the treatment is suddenly interrupted. This risk exists for all opioids. When stopping treatment, the dose should be progressively reduced. (78)
- The undesirable effects of opioids increase with increasing dose. (77)
- Tolerance for therapeutic and unwanted effects, depending on dose and duration of administration; Dose increase is required to compensate for the tolerance. (78)

16.1.2 Additional adverse effects of specific opioids

- **Morphine:** Increase in intracranial pressure.(78) Hyperglycaemia. Morphine is associated with a dose-related histamine-releasing effect which may be responsible in part for reactions such as urticaria and pruritus as well as hypotension and flushing. (79)
- **Methadon:** QT prolongation. (78) Hypoadrenalism, hyperprolactinaemia and galactorrhoea. (79)
- **Tapentadol:** dizziness, headache, tremor, aggressive behavior; convulsions have also been seen, particularly in patients with epilepsy or who take other epileptogenic drugs. (78)

- **Tramadol:** anaphylactic reactions, dry mouth, vertigo, tremor, hypoglycaemia; convulsions, especially in patients with epilepsy or other epileptogenic medication. (78) Tramadol may have lower potential for producing dependence than morphine.(79)
- **Buprenorphine:** Local reactions such as rash, erythema, and itching have been reported with the transdermal patches. Respiratory depression, if it occurs, is relatively slow in onset and of prolonged duration; it may be only partially reversed by naloxone.(79)

16.2 Contraindications

16.2.1 Opioids in general

- Acute respiratory depression, acute asthma attack, severe COPD; coma; increased intracranial pressure; patients with risk of paralytic ileus. (78)
- Opioid analgesics should be given with caution or in reduced doses to patients with hypothyroidism, adrenocortical insufficiency, asthma or decreased respiratory reserve, renal or hepatic impairment, prostatic hyperplasia, hypotension, shock, inflammatory or obstructive bowel disorders, or myasthenia gravis. (79)
- It is usually recommended that opioids such as morphine should either be avoided in patients with biliary disorders or that they should be given with an antispasmodic. (79)

16.2.2 Additional contraindications for specific opioids

- **Codeine:** known ultrarapid metabolizers for CYP2D6 (See “Interactions”). (78)
- **Methadone:** risk factors for QT prolongation (genetic, pharmacologic). (78)
- **Tapentadol:** hepatic insufficiency and severe renal insufficiency. (78)
- **Tramadol:** uncontrolled epilepsy. (78) Severe renal impairment.(79)

16.3 Interactions

- Reduced analgesic effect of **pure agonists** (eg morphine, methadone) when adding a **partial agonist** such as buprenorphine or an opioid **antagonist**. (78)
- Exaggerated sedation when associating with other **drugs with sedative effect** or with **alcohol**. (78) An additive sedative effect is to be expected between opioid analgesics and benzodiazepines and has been reported with morphine and midazolam.(79)
- Fentanyl, hydromorphone, oxycodone, pethidine, tapentadol and tramadol: serotonin syndrome when associated with other substances with **serotonergic action** (especially MAO inhibitors or SSRIs). (78)
- Methadone: increased risk of torsades de pointes when associated with other **agents that increase the risk of QT prolongation**.(78)
- Tramadol and tapentadol: increased risk of convulsions when associated with other **drugs that lower the seizure threshold**. (78)
- **Rapid release or dose-dumping** of hydromorphone from a modified-release preparation (Palladone; Purdue Frederick, USA) has been associated with the ingestion of **alcohol**. Health Canada has warned that this interaction may occur with all modified-release formulations of opioid analgesics. Licensed product information for some modified-release preparations of morphine sulfate also warns against such use.(79)
- **Methadone** is substrate of CYP2B6 and an inhibitor of CYP2D6. (78)

- **Codeine, oxycodone, and tramadol** are substrates of CYP2D6. (78)
- **Buprenorphine and fentanyl** are substrates of CYP3A4. (78)

	Substrates	Inhibitors (↑ plasma concentration of substrate)	Inductors (↓ plasma concentration of substrate)
CYP2B6	methadone	Clopidogrel, ticlopidine, thiotepa	Carbamazepine, efavirenz, phenobarbital, phenytoin, rifampicin, ritonavir
CYP2D6	codeine, oxycodone, tramadol	Abiraterone, amiodarone, bupropion , celecoxib, chlorophenamine, cinacalcet , citalopram, cobicistat, diphenhydramine, duloxetine, escitalopram, fluoxetine , fluvoxamine, haloperidol, methadone, mirabegron , moclobemide, panobinostat, paroxetine , pitolisant, propafenone , ritonavir , sertraline, stiripentol, terbinafine , tetrabenazine, venlafaxine	
CYP3A4	buprenorphine, fentanyl	Amiodarone, aprepitant, atazanavir, ceritinib, clarithromycin , cobicistat , crizotinib, darunavir, diltiazem, erythromycin , fluconazole, fluoxetine, fluvoxamine, fosamprenavir, fosaprepitant, idelalisib , imatinib, itraconazole , ketoconazole , lapatinib, lopinavir, netupitant, nilotinib, olaparid, pazopanib, piperazine, grapefruit / pomelo , posaconazole , ritonavir , roxithromycin, saquinavir , simeprevir, stiripentol, telaprevir , telithromycin , tipranavir, verapamil, voriconazole	Bosentan, carbamazepine , dabrafenib , efavirenz, enzalutamide , phenobarbital , phenytoin , modafinil, nevirapine, pitolisant, primidone , rifabutin, rifampicin , rufinamide, St. John's wort , vandetanib

Table: CYP-isoenzymes, with their substrates, inhibitors and inductors. **In bold:** the substrates, inductors and inhibitors thought to lead to clinically important interactions. (78)

16.4 Use of opioids in specific patient categories

16.4.1 Hepatic dysfunction

- Caution should be exercised in patients hepatic insufficiency, due to a more pronounced effect.(78) Doses should generally be reduced.(79)
- Morphine and hydromorphone seem to be relatively safe compared to opioids metabolized by cytochrome P450 isoenzymes.(79) (see “Interactions” table)
- Oral immediate release or parenteral, short-acting opioids are preferable to long-acting preparations such as transdermal or modified-release formulations in hepatic insufficiency.(79)

16.4.2 Renal dysfunction

- Caution should be exercised in patients with renal dysfunction, due to a more pronounced effect. (78) Doses should generally be reduced.(79)
- Codeine and morphine: best avoided in patients with renal failure and/or on dialysis.
- Hydromorphone: may be used with caution and monitoring. (79)
- Fentanyl and methadone: probably safe to use in patients with renal dysfunction. (79)

16.4.3 The elderly

- Ageing can affect the pharmacokinetics and pharmacodynamics of opioids, although the clinical importance of these changes is unclear. (79)
- Practical recommendations include careful review of indication for opioid use both initially and at regular intervals thereafter, starting opioids cautiously at lower doses and with longer dosing intervals, and regular consideration given to dose reduction and drug substitution or discontinuation. If possible, further drugs should not be prescribed to manage the adverse effects of opioids. (79)

16.4.4 Other

- Codeine is a prodrug from which morphine is formed via CYP2D6. An exaggerated effect was seen with ultrarapid metabolizers of codeine(78), with an increased risk of unwanted effects such as respiratory depression. Young age and disorders associated with breathing problems, in particular sleep apnea, appear to be an important risk factor for severe respiratory problems when taking codeine.(81) In the case of poor metabolisers (5 to 10% of the white population), codeine may not provide an adequate analgesic effect. (78)

16.5 Precautions and monitoring

- Use of potent opioids for chronic pain in non-cancer patients is controversial. A thorough bio-psychosocial balance must be made in advance, and medical follow-up and periodic re-evaluations are necessary. (78)
- Associating codeine, caffeine or other psychotropic medicines with paracetamol or with ibuprofen is thought to promote chronic use and abuse. Such associations should be reserved for short-term treatment in acute pain. (78)
- **Buprenorphine:** Licensed product information states that baseline liver function levels should be established before starting buprenorphine therapy, and periodic monitoring of liver function should be performed throughout therapy in patients being treated for opioid dependence. It should be used with caution in all patients with pre-existing hepatic impairment. (79)
- In chronic use, long-acting preparations are preferable and systematic use of short-acting preparations can be avoided, except in case of breakthrough pains. (78)
- In case of chronic use of opioids, the constipation must be preventatively prevented by using a laxative. (78)
- For transdermal patches, it is very important to follow the practical modalities as described in the Summary of Product Characteristics (SPC): incorrect use has led to serious adverse effects. (78) Absorption from transdermal patches may be increased with rising temperatures (external heat, fever, vigorous exercise(79)). The patches should not be cut unless explicitly stated in the SPC that this is permitted. It is possible that the fentanyl patch should be replaced after 48 hours (instead of 72 hours) in thin patients. Great caution is advised in cachectic patients. (78)
- The sodium content in effervescent preparations (tablets, powders, granules) can cause problems for patients on a strictly low-sodium diet. (78)

17 Appendix. Evidence tables. Chronic (non-cancer) pain, general

17.1 Long term opioids (12 m) for chronic pain. Systematic review Chou 2015

Methods
<p>Systematic review: The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain (17). Evidence report/Technology assessment AHRQ (18)</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> - Long-term (>3 months) opioid therapy for chronic pain (>3 m) in adults - Randomized trials and observational studies that involved adults with chronic pain who were prescribed longterm (>3 m)opioid therapy and that evaluated opioid therapy versus placebo, no opioid, or nonopioid therapy; different opioid dosing strategies; or risk mitigation strategies. - outcomes reported after at least 1 year of opioid therapy - tramadol excluded, parenteral opioids excluded - cancer pain included, if not at end of life <p><u>Search strategy:</u></p> <p>MEDLINE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, PsycINFO, and CINAHL (January 2008 through August 2014); relevant studies from a prior review; reference lists; and ClinicalTrials.gov up to august 2014</p> <p><u>Assessment of quality of included trials:</u> yes, GRADE</p> <p><u>Other methodological remarks:</u></p> <p>No meta-analysis performed</p> <p>This review also examined tapering, switching</p> <p>This review also examined observational studies</p> <p>Author's remarks: "Non-English-language articles were excluded, meta-analysis could not be done, and publication bias could not be assessed. No placebo-controlled trials met inclusion criteria, evidence was lacking for many comparisons and outcomes, and observational studies were limited in their ability to address potential confounding.</p>

Results				
Ref	Comparison	N/n	Outcomes	Result
ref* (17, 18) Design: SR Search date: august 2014	Opioids versus placebo/no opioid	N=0	Pain Function Quality of life	No study of opioid therapy versus no opioid therapy evaluated long-term (>1 year) outcomes related to pain, function, quality of life, opioid abuse, or addiction

Remarks
<p>This systematic review found no study of opioid therapy versus no opioid therapy that evaluated long-term (>1 year) outcomes related to pain, function, quality of life, opioid abuse, or addiction.</p> <p>This systematic review also found no placebo-controlled trials that lasted at least 6 months.</p> <p>This systematic review found only observational studies about long-term harms.</p> <p>This systematic review found no cohort studies about sexual dysfunction/hypogonadism or about immunity disorders.</p> <p>This systematic review found 1 RCT of 10 patients that compared tapering versus continuation of opioid therapy. This sample size is smaller than the inclusion criteria for our consensus conference literature review.</p> <p>This systematic review found no RCTs comparing opioid rotation versus maintenance of current therapy.</p>

Author's conclusions
<p>"Evidence is insufficient to determine the effectiveness of long-term opioid therapy for improving chronic pain and function. Evidence supports a dose-dependent risk for serious harms."(17)</p>

17.2 Long term opioids (12 m) for chronic pain. Systematic review Dowell 2016

Methods
<p>Systematic review: CDC Guideline for Prescribing Opioids for Chronic Pain (1). Long term opioids for chronic pain.</p> <p><u>Inclusion criteria:</u> randomized trials and observational studies (cohort studies, case control studies, crosssectional studies) that controlled for potential confounders of adults (age >18 years) with chronic (>3 months) pain prescribed long-term opioid therapy (defined as opioid use on most days for >3 months) that evaluated opioid therapy versus placebo, no opioid, or non-opioid therapy, different opioid dosing strategies; or risk mitigation strategies.</p> <p><u>Search strategy:</u> MEDLINE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, PsychINFO, and CINAHL for English-language articles published January 2008 through August 2014, using search terms for opioid therapy, specific opioids, chronic pain, and comparative study designs. Also included were relevant studies from an earlier review in which searches were conducted without a start date restriction, reference lists were reviewed, and ClinicalTrials.gov was searched.</p> <p>Date april 2015</p> <p><u>Assessment of quality of included trials:</u> yes, GRADE</p> <p><u>Other methodological remarks:</u> This systematic review is an update of the SR by Chou 2015(17, 18)</p>

Results				
Ref	Comparison	N/n	Outcomes	Result
ref*(1) Design: SR Search date: april 2015		N= 0	Pain Function Quality of life	No study of opioid therapy versus placebo, no opioid therapy, or non-opioid therapy for chronic pain evaluated long-term (>1 year) outcomes related to pain, function, or quality of life.
		N= 0	Abuse Addiction	No randomized trial evaluated opioid abuse, addiction, or related outcomes with long-term opioid therapy versus placebo or no opioid therapy

Remarks
<p>This systematic review found no study of opioid therapy versus no opioid therapy that evaluated long-term (>1 year) outcomes related to pain, function, quality of life, opioid abuse, or addiction.</p>

This systematic review also found no placebo-controlled trials that lasted at least 6 months.

This systematic review found only observational studies about long-term harms. These are not included in our Consensus Conference literature review. The recommendations from the guideline that is based on this literature will be reported in the Consensus Conference literature review.

This systematic review found no cohort studies about sexual dysfunction/hypogonadism or about immunity disorders. Two cross-sectional studies on endocrinological harms were found, but this design does not meet the inclusion criteria for our literature review.

This systematic review found no actual studies on tapering versus continuation of opioid therapy. Three studies on tapering strategies were found, comparing abrupt cessation to continuation in a crossover design (10 patients), placebo-controlled reduction versus cocktail reduction (non-randomised, 108 patients) and detoxification followed by psychotherapeutic counseling versus detoxification followed by maintenance therapy if detoxification was unsuccessful (42 patients). None of these studies meet the inclusion criteria for our Consensus Conference literature review.

This systematic review found no RCTs comparing opioid rotation versus maintenance of current therapy.

17.3 Long term opioids (6m) for chronic non-cancer pain: Systematic review Noble 2010

Methods
Systematic review/Meta-analysis: Cochrane Review. Long-term opioid management for chronic noncancer pain (19) <u>Inclusion criteria:</u> studies that: collected efficacy data on participants after at least 6 months of treatment; were full-text articles; did not include redundant data; were prospective; enrolled at least 10 participants; reported data of participants who had CNCP. Randomized controlled trials (RCTs) and pre-post case-series studies were included <u>Search strategy:</u> The Cochrane Library, specifically: The Cochrane Central Register of Controlled Trials, The Cochrane Database of Systematic Reviews (Cochrane Reviews), Database of Abstracts of Reviews of Effects; • The ECRI Institute library, including: ECRI Institute Library Catalog, ECRI Institute Healthcare Standards, ECRI Institute International Health Technology Assessment from 1990; • MEDLINE from 1966; • EMBASE (Excerpta Medica) from 1980; • U.S. Food and Drug Administration (FDA) Web site from 1977; • U.S. National Guideline Clearinghouse (NGC) from 1998 search up to may 2009 <u>Assessment of quality of included trials:</u> yes
Remarks
This systematic review found only 1 RCT on long term opioid management for chronic noncancer pain, comparing 2 opioids. This comparison does not meet the inclusion criteria for our Consensus Conference literature review.

17.4 High-dose opioids for chronic non-cancer pain. Overview of Cochrane reviews Els 2017

Methods
Systematic review/Meta-analysis: High-dose opioids for chronic non-cancer pain: an overview of (20)Cochrane Reviews <u>Inclusion criteria:</u> Cochrane Reviews and Overviews regarding the efficacy and safety of high-dose opioids (here defined as 200 mg morphine equivalent or more per day) for chronic non-cancer pain <u>Search strategy:</u> a search of the Cochrane Database of Systematic Reviews (The Cochrane Library). The date of the last search was 18 April 2017
Remarks
This systematic review did not identify any reviews or overviews meeting the inclusion criteria. The excluded reviews largely reflected low doses or titrated doses where all doses were analysed as a single group; no data for high dose only could be extracted.
Author's conclusions
"There is a critical lack of high-quality evidence regarding how well high-dose opioids work for the management of chronic non-cancer pain in adults, and regarding the presence and severity of adverse events. No evidence-based argument can be made on the use of high dose opioids, i.e. 200 mg morphine equivalent or more daily, in clinical practice. Trials typically used doses below our cut-off; we need to know the efficacy and harm of higher doses, which are often used in clinical practice."(20)

18 Appendix. Evidence tables. Opioids versus optimization of non-opioid therapy for chronic (non-cancer) pain

18.1 Opioids vs optimisation of non-opioids in chronic non-cancer pain. Meta-analysis Busse 2017

Methods
<p>Systematic review/Meta-analysis: The effect of opioid add-on therapy vs. optimization of therapy with nonsteroidal anti-inflammatory drugs (NSAIDs), for adult patients with chronic non-cancer pain (9).</p> <p><u>Inclusion criteria:</u></p> <p>chronic pain (any painful condition that persists for ≥ 3 months that is not associated with a diagnosis of cancer), opioid therapy (not cancer, opioid use disorder, pain < 3 m, pain in end-of-life)</p> <ul style="list-style-type: none">• values and preferences• benefits and harms• dosing and risk mitigation• systematic reviews, RCTs, observational studies<ul style="list-style-type: none">○ opioids versus optimisation of non-opioids in chronic pain○ if optimal non-opioid therapy and persistent pain: opioids versus non-opioids (placebo)○ opioid rotation versus no opioid rotation○ tapering vs no tapering if persistent pain using opioids <p><u>Search strategy:</u></p> <p>AMED, CINAHL, Cochrane Library, Embase, MEDLINE, PsycINFO, and PubMed through October 2016, including randomized trials and observational studies (excluding case reports).Bibliographies of all retrieved articles, to april 2016</p> <p><u>Assessment of quality of included trials:</u> yes, GRADE</p> <p><u>Other methodological remarks:</u></p> <p>This is a systematic review that was performed as an evidence base for a Canadian Guideline on opioid therapy in chronic noncancer pain</p>
Remarks
<p>This systematic review (9) searched for studies comparing the starting of opioids to optimizing therapy with NSAID in chronic non-cancer pain.</p> <p>For the outcome pain, 13 studies were found, ranging between 1,5 to 6 months. For the outcome Function, 8 studies were found, ranging between 1 and 4 months. For gastro-intestinal adverse events, 7 studies were found.</p> <p>Some observational data were also found, reporting on opioid use disorder, fatal overdose, non-fatal overdose and diversion.</p> <p>Only 1 RCT out of these studies met the inclusion criteria for trial duration, sample size and blinded design (DeLemos 2011)(See table below). However, this RCT was not designed to compare tramadol to NSAID, and no statistical testing between tramadol and NSAID treatment was performed.</p> <p>This systematic review searched for studies comparing opioids to optimizing therapy with tricyclic antidepressants.</p>

3 RCTs were found, all < 8 weeks. Some observational data were also found, reporting on opioid use disorder, fatal overdose, non-fatal overdose and diversion.

This systematic review searched for studies comparing opioids to optimizing therapy with **anticonvulsants**

3 RCTs were found, all < 6 weeks. Some observational data were also found, reporting on opioid use disorder, fatal overdose, non-fatal overdose and diversion.

Characteristics of included studies					
Ref + design	n	Population	Duration	Comparison	Methodology
DeLemos 2011 (21) 5-arm double blind RCT	1001	<p>Adults with knee and/or hip osteoarthritis and baseline pain intensity of ≥ 40 on a 100-mm visual analog scale (0 = no pain, 100 = extreme pain)</p> <p>treatment with COX-2 inhibitors, NSAIDs, acetaminophen, or opioid analgesics for at least 75 of 90 days preceding the screening visit</p> <p>2-7 d washout of prior analgesics</p> <p>no rescue medication allowed (paracetamol allowed for pain other than osteoarthritis)</p> <p>patients were required to be able to discontinue acetaminophen, NSAIDs, COX-2 inhibitors, opioids, and other analgesics (except aspirin #325 mg once daily for cardiovascular prophylaxis) during the study.</p> <p>excluded if recent use of monoamine oxidase inhibitor, tricyclic antidepressant, other tricyclic compound, neuroleptic, selective serotonin reuptake inhibitor, serotonin/ norepinephrine reuptake inhibitor, anorectic, bupropion, carbamazepine, or quinidine</p>	12 w	<p>once-daily tramadol ER 100 mg (n = 201), 200 mg (n = 199), or 300 mg (n = 199), celecoxib 200 mg (n = 202; to test model sensitivity), or placebo (n = 200)</p> <p>For results: see information under Busse 2017 opioids vs placebo.</p> <p>Update: no statistical tests versus celecoxib were performed!</p>	<p>ALLOCATION CONC: unclear</p> <p>RANDO: unclear</p> <p>BLINDING : patient low risk personnel low risk assessors unclear</p> <p>ITT: no</p> <p>INDUSTRY FUNDING: yes</p> <p>555/1011 (54.9%) completed study</p> <p>reasons for discontinuation placebo</p> <ul style="list-style-type: none"> - lack of efficacy 32.5% - adverse events 7.5% <p>tramadol 100</p> <ul style="list-style-type: none"> - lack of efficacy 25.4% - adverse events 12.4% <p>tramadol 200</p> <ul style="list-style-type: none"> - lack of efficacy 16.6% - adverse events 23.1% <p>tramadol 300</p> <ul style="list-style-type: none"> - lack of efficacy 11.1% - adverse events 30.7% <p>celecoxib 200</p> <ul style="list-style-type: none"> - lack of efficacy 14.9% - adverse events 9.9% <p>handling missing values: LOCF</p>

18.2 Opioid medication strategy vs non-opioid medication strategy in chronic low back pain or chronic pain from knee or hip osteoarthritis. SPACE trial Krebs 2018

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Krebs 2018 SPACE TRIAL (22)	n= 240 Veterans Affairs primary care clinics	<u>Opioid medication strategy:</u> step 1 morphine IR, oxycodone IR or hydrocodone/acetaminophen Step 2 morphine sustained-action (SA) or oxycodone SA step 3 transdermal fentanyl	Efficacy		RANDO:
Design:	Mean age: 58.3 13% women		Pain-related function (Brief Pain Inventory [BPI] interference scale, 7- item) range, 0-10; higher scores = worse function) (PO)	mean BPI interference opioid 3.4 (SD 2.5) nonopioid 3.3 (SD 2.6) Difference 0.1 (95%CI, -0.5 to 0.7) overall p*=0.58 NS (a 1-point improvement was considered clinically important)	Adequate ALLOCATION CONC: adequate BLINDING : Participants: no Personnel: no Assessors: yes, but endpoints were questionnaires filled out by patients
RCT (PG) masked outcome assessment	<u>treatment preference</u> <u>at baseline:</u> opioid group, 60% no preference 21% preferred opioids nonopioid group, 43% no preference 37% preferred opioids	Vs <u>nonopioid medication strategy</u> step 1: acetaminophen (paracetamol) or NSAID step 2: adjuvant oral (nortriptyline, amitriptyline, gabapentin) and/or topical (capsaicin, lidocaine) step 3: drugs requiring prior authorization from the VA clinic (ie, pregabalin, duloxetine) and tramadol		Functional response (>= 30% improvement) opioid 59.0% nonopioid 60.7% risk difference -1.7% (95% CI -14.4 to 11.0) p=0.79 NS (30% reduction from baseline as MCID was considered moderate improvement)	FOLLOW-UP: 97.5% completed the trial Described: yes discontinued study medication opioid 19% (24 patients) (adverse events 7.5% improved pain 1.7%) nonopioid 8% (adverse events 0% (lack of benefit 4.2%)
Duration of follow-up: 12 m	<u>function and pain at baseline</u> BPI pain related function 5.4 vs 5.5 BPI pain intensity 5.4 vs 5.4 <u>Previous/current pain treatment:</u> not reported (see comment below table)	treat-to-target strategy aiming for improved pain and function.	Pain intensity (BPI severity scale, 4-item) range, 0-10; higher scores = worse pain)	mean BPI severity opioid 4.0 (SD 2.0) nonopioid 3.5 (SD 1.9) difference 0.5 (95% CI, 0.0 to 1.0) overall p*=0.03 SS better with nonopioid (a 1-point improvement was considered clinically important)	ITT:Yes SELECTIVE REPORTING: no Other important methodological remarks - pragmatic design, mimics clinical

<p><u>Inclusion</u></p> <ul style="list-style-type: none"> - moderate to severe chronic back pain or hip or knee osteoarthritis pain despite analgesic use - chronic pain = 6 m or more - randomization was stratified by primary pain diagnosis - severe depression or posttraumatic stress disorder symptoms were not excluded because these patients often receive opioids in practice <p><u>Exclusion</u></p> <ul style="list-style-type: none"> - long term opioid therapy (physiological opioid dependence) - conditions that could interfere with outcome assessment (psychotic disorder, moderate cognitive impairment, anticipated surgery, life expectancy <12 m) - contraindications to all drug classes 	<p>In both groups, patients received structured symptom monitoring and a treat-to-target approach to medication management. After randomization, the pharmacist reviewed past medications and identified individual functional goals. The initial medication regimen was determined by the assigned group and considerations such as patient preference and comorbidities</p> <p>Patients were instructed to receive medications for back, hip, or knee pain only from the study. Nonpharmacological therapies were allowed outside of the study</p> <ul style="list-style-type: none"> - Single-opioid therapy was preferred, but dual therapy with a scheduled SA opioid and as-needed IR opioid was considered based on patient needs and preferences - Max daily dose 100 morphine-equivalent mg - If use of 60 MEmg/d without a 		<p>Pain intensity response ($\geq 30\%$ improvement in BPI severity)</p> <p>opioid 41.0%</p> <p>nonopioid 53.9%</p> <p>risk difference -12.8% (95% CI, -25.6 to 0.0)</p> <p>p= 0.05</p> <p>(30% reduction from baseline as MCID was considered moderate improvement)</p>	<p>practice</p> <ul style="list-style-type: none"> - not blinded, reporting bias possible - imbalance in prerandomization treatment preference - VA population - previous pain treatment not reported (see notes below for some information) - actual drug regimen (e.g. how many patients on fentanyl, how many patients on co-analgesics) not reported. - study was underpowered for deaths, opioid use disorder or other serious harms. - most p values are from mixed models for repeated measures comparing between-group difference during the 12-mo trial, controlling for baseline and including all available time points. This is a different approach from many other trials, where difference from baseline in the two treatment groups is compared. - If patients desired discontinuation of all study medications, they were transitioned back to pre-enrollment pain medications <p>Sponsor: Merit Review Award from the US department of Veterans Affairs Health Services Research and Development Service</p>
		<p>Global pain response \geq moderately better (questionnaire; “How would you describe your pain now, compared to when you started in our study?” with response options of “much better, moderately better, a little better, no change, a little worse, moderately worse, much worse.” Clinically important improvement was defined as response of “moderately better” or “much better”.)</p>	<p>opioid 44.4%</p> <p>nonopioid 44.4%</p> <p>risk difference 0.0 (-12.8, 13.0)</p> <p>p=0.99</p> <p>NS</p> <p><i>This secondary endpoint was reported in the supplementary appendix</i></p>	
		<p>RMDQ-11 pain-related physical function</p>	<p>NS difference</p>	
		<p>Veterans RAND 12-item Health Survey (VR-12) quality-of-life measure (range, 0-100; higher score =</p>	<p>physical health at 12 months</p> <p>opioid 32.7 (SD 10.1)</p> <p>nonopioid 33.9 (SD 9.9)</p> <p>mean difference -1.3 (-3.8 to 1.3)</p>	

		<p>response, rotation to another opioid was considered before dosage escalation</p> <p><u>opioid daily dosage categories in morphine-equivalent mg/day at 12 months</u></p> <p>opioid: 0 mg 20.2% 1 to < 20 mg 42.9% 20 to < 50 mg 24.4% ≥50 mg: 12.6%</p> <p>nonopioid 0 mg 89.1% 1 to < 20 mg 10.1% 20 to < 50 mg 0.8% ≥50 mg: 0%</p>	<p>better quality of life, standardized to mean of 50)</p> <p>baseline score physical health +/- 27</p> <p>baseline score mental health +/- 47.5</p> <p>Other questionnaires</p> <p>Safety</p> <p>medication-related symptoms (patient-reported checklist; range, 0-19; higher score = worse) (modified from the original version by adding common analgesic adverse effects i.e. memory problems, dry mouth, trouble concentrating, sweating, and weight gain)</p>	<p>overall p value 0.23 NS</p> <p>mental health at 12 months opioid 51.2 (11.6) nonopioid 50.4 (12.6) mean difference 0.7 (-2.4 to 3.8) overall p value 0.40 NS</p> <p>NS difference on all other questionnaires (depression, sleep disturbance, headache, sexual function, fatigue, activity, motivation)</p> <p>generally SS less anxiety symptoms (GAD-7) with opioids (overall P=0.02), but difference was small</p> <p>The opioid group had significantly more medication-related symptoms over 12 months than the nonopioid group</p> <p>at 12 months opioid 1.8 (SD 2.6) nonopioid 0.9 (SD 1.8) difference at 12 months 0.9 [95% CI, 0.3 to 1.5] overall: P = .03 (P value for treatment by time interaction) SS</p>	
--	--	---	--	---	--

			other adverse events	no statistically significant difference in hospitalization, all-cause emergency department visit, number of falls no deaths Drug misuse measures: NS differences for - urine drug test/unexplained prescription drug - clinician-assessed behavior - patient-reported substance use	
			free serum testosterone	no significant difference in change in free serum testosterone between opioid and nonopioid group	

* P values are from mixed models for repeated measures comparing between-group difference during the 12-mo trial, controlling for baseline and including all available time points.

Information about pre-study treatments (author's correspondence, JAMA website)

"Prestudy treatments included spine injections (28%) or surgery (20%) and knee or hip injections (45%) or surgery (34%)"

Information about patients not on tramadol in the nonopioid group (author's correspondence, JAMA website)

"We reanalyzed data excluding tramadol-treated patients from the nonopioid group. At 12 months, nonopioid patients who never received tramadol (n = 99) had a mean Brief Pain Inventory (BPI) interference of 3.0 (SD, 2.5) and BPI severity of 3.3 (SD, 1.8). Main repeated-measures model results were unchanged: over 12 months, pain-related function did not differ between groups (P = .19) and the nonopioid group had better pain intensity (P = .01). Regardless, SPACE findings should be interpreted as applying to overall treatment strategies. "

Patient-reported non pharmacological co-interventions during the study year (from supplementary appendix)

Treatment, n (%) Opioid group (n=106), Non-opioid, group (n=105)

Acupuncture 7 (7) 9 (9)

Biofeedback 1 (1) 2 (2)

Chiropractic or osteopathic manipulation 24 (23) 15 (14)

Homeopathy or naturopathy 2 (2) 2 (2)

Hypnosis 0 0

Nutritional advice or counseling 11 (10) 13 (12)

Massage 20 (19) 25 (24)

Mental health counseling or therapy 15 (14) 14 (13)
Personal training or supervised exercise therapy 18 (17) 19 (18)
Physical therapy 39 (37) 25 (24)
Injections in spine, such as epidurals or facet blocks 9 (9) 8 (8)
Injections in the knee, hip, or other joints 29 (28) 23 (22)
Surgery for spine (neck or back) 1 (1) 1 (1)
Surgery for knee or hip, such as arthroscopy or joint replacement 3 (3) 8 (8)

Author's comments:

"To maximize applicability to primary care, the trial was designed to be pragmatic. Eligibility criteria facilitated enrollment of diverse patients from primary care.

Interventions were delivered with flexibility in medication selection and dosage.

Patients were allowed to participate in nonpharmacological pain therapies outside of the study and were encouraged to complete outcome assessments regardless of their participation in the active interventions."(22)

"Treatment with opioids was not superior to treatment with nonopioid medications for improving pain-related function over 12 months. Results do not support initiation of opioid therapy for moderate to severe chronic back pain or hip or knee osteoarthritis pain."(22)

19 Appendix. Evidence tables. Opioids versus placebo for chronic (non-cancer) pain

19.1 Opioids vs placebo for chronic non-cancer pain in patients with optimized non-opioid treatment but persistent pain Meta-analysis Busse 2017

Methods

Systematic review/Meta-analysis: The effect of opioid add-on therapy, vs. continued non-opioid therapy, for adult patients with chronic non-cancer pain, without current or past substance use disorder and without other current active psychiatric disorders, whose therapy is optimized with non-opioids with persistent problematic pain (9)
Inclusion criteria:

- chronic pain (any painful condition that persists for ≥ 3 months that is not associated with a diagnosis of cancer), opioid therapy (not cancer, opioid use disorder, pain < 3 m, pain in end-of-life) (9)
- any chronic pain: musculoskeletal, neuropathic, fibromyalgia, reumatoïd arthritis, migraine, complex regional pain syndrome, whiplash, temporomandibular joint,...
- studies evaluating:
 - values and preferences
 - benefits and harms
 - dosing and risk mitigation
 - systematic reviews, RCTs, observational studies
 - opioids versus optimisation of non-opioids in chronic pain
 - if optimal non-opioid therapy and persistent pain: opioids versus non-opioids (placebo)
 - opioid rotation versus no opioid rotation
 - tapering vs no tapering if persistent pain using opioids

Search strategy:

AMED, CINAHL, Cochrane Library, Embase, MEDLINE, PsycINFO, and PubMed through October 2016, including randomized trials and observational studies (excluding case reports).Bibliographies of all retrieved articles, to april 2016

Assessment of quality of included trials: yes, GRADE

Other methodological remarks:

This is a systematic review that was performed as an evidence base for a Canadian Guideline on opioid therapy in chronic noncancer pain.

Remarks
<p>This systematic review and meta-analysis found 27 RCTs that reported the outcome 'pain' in chronic noncancer pain (any type) that compared opioids to placebo in patients with insufficient pain control from their current treatment. All these trials were ≥ 3 months.</p> <p>This systematic review and meta-analysis found 33 RCTs in this population that reported the outcome 'function'. 13 of these trials were < 12 weeks.</p> <p>This systematic review and meta-analysis found 36 studies that reported the outcome 'gastro-intestinal side effects'. 14 of these trials were < 12 weeks.</p> <p>This SR aimed to examine the effect of opioids in patients with chronic non-cancer pain, without current or past substance use disorder and without other current serious psychiatric disorders, whose therapy is optimized with non-opioids with persistent problematic pain and compare them to a continuation of the established therapy without opioids.</p> <p>It is questionable whether the patients in the included trials did in fact have an 'optimised' therapy prior to enrollment. Inclusion criteria in these trials usually describe the patients as having persistent pain despite their current pain treatment, but their current treatment varies within and between studies and is usually described in terms of analgesics used (of example: insufficient pain relief despite NSAID treatment), but hardly ever mentions any non-pharmacological treatment, or the use of co-analgesics (e.g. antidepressants, anti-convulsants).</p> <p>Moreover, in a lot of trials, the previous analgesic medication is stopped before entering the trial. These trials are therefore not a comparison between starting opioids and the continuation of the non-opioid medication.</p> <p>We would suggest downgrading the level of evidence due to problems with directness.</p> <p>Some of the trials found in this systematic review were not included in other meta-analyses that searched for RCTs with similar populations and treatments. Some trials with similar populations and treatments were included in other meta-analyses, but not in this one. It is unclear whether this is because of active exclusion of these trials, or because they were not found in the respective searches.</p>

Results				
Ref	Comparison	N/n	Outcomes	Result
ref* Busse 2017 (9) Design: SR + MA Search date: april 2016	Opioids versus placebo/no opioids	N= 27 n= 13876 (Afilalo 2010, Bennett 2003, Breivik, 2010, Burch, 2007, Buynak 2010, DeLemos 2011, Emkey 2004, Friedmann, 2011, Gana 2006, Hale 2015, Hanna 2008, Katz 2010, Katz 2015, Peloso 2004, Rauck 2013, Rauck 2015, Rauck 2014, Rauck 2016, Ruoff 2003, Schwartz 2011, Steiner 2011, Trenkwalder 2015, Vinik 2014, Vojtassak 2011, Vorsanger 2008, Webster 2006, Wen 2015)	Pain (difference in patients who achieve the MID or greater) 3-6 months	Relative risk 1.25 (CI 95% 1.21 - 1.29) absolute effect estimate no opioid therapy 488 per 1000 opioid therapy 560 per 1000 Difference: 112 more per 1000 (CI 95% 94 more - 130 more) Quality of evidence assessed by Busse 2017 as HIGH
		N= 27 n=13876	Pain Measured by: 10 cm VAS Scale: 0-10 Lower better 3-6 months	Difference: 0.64 lower (MD) (CI 95% 0.76 lower - 0.53 lower) Quality of evidence assessed by Busse 2017 as HIGH
		N= 33 n= 12058 (Afilalo 2010, Bennett 2003, Breivik, 2010, Caldwell 2002, Chu 2012, Cloutier 2013, Buynak 2010, DeLemos 2011, Emkey 2004, Freeman 2007, Gana 2006, Gilron 2005, Gordon 2010, Gordon 2010, Hale 2010 Hale 2015, Katz 2010, Katz 2015, Lee 2013, Ma 2008, Matsumoto 2005, Peloso 2004, Rauck 2013, Rauck 2015, Rauck 2016, Ruoff 2003, Steiner 2011, Thorne 2008, Vinik 2014, Vojtassak	Physical function (difference in patients who achieve the MID or greater) 1-6 months	Relative risk 1.24 (CI 95% 1.17 - 1.30) absolute effect estimate no opioid therapy 424 per 1000 opioid therapy 526 per 1000 Difference: 102 more per 1000 (CI 95% 72 more - 127 more) Quality of evidence assessed by Busse 2017 as HIGH

		2011, Vorsanger 2008, Wen 2015, Zin 2010)		
		N= 33 n= 12058	Physical function Measured by: SF-36 physical component summary scale Scale: 0-100 High better 1-6 months	Difference: 2.16 higher (MD) (CI 95% 1.56 higher - 2.76 higher) Quality of evidence assessed by Busse 2017 as HIGH
		N= 36 n= 14449 Afilalo 2010, Bennett 2003, Boureau 2003, Breivik, 2010, Burch 2007, Cloutier 2013 Buynak 2010, DeLemos 2011, Fleischmann 2001, Freeman 2007, Friedmann 2011, Gana 2006, Gimbel 2003, Gordon 2010, Gordon 2010, Hale 2010, Hanna 2008, Hale 2015, Katz 2010, Langford 2006, Mangel 2008, Matsumoto 2005, Munera 2010, Norrbrink 2009, Peloso 2004, Rauck 2013, Ruoff 2003, Steiner 2011, Schwartz 2011, Thorne 2008, Trenkwalder 2015, Vinik 2014, Vondrackova 2008, Vorsanger 2008, Wen 2015, Zin 2010	Gastrointestinal side effects 4-26 weeks	Relative risk 3.08 (CI 95% 2.53 - 3.75) absolute effect estimate no opioid therapy 28 per 1000 opioid therapy 86 per 1000 Difference: 58 more per 1000 (CI 95% 43 more - 77 more) Quality of evidence assessed by Busse 2017 as HIGH

Characteristics of included studies					
Ref + design	n	Population	Duration	Comparison	Methodology
<p>Afilalo 2010 (82)</p> <p>Randomised controlled trial 3-arm parallel group design</p>	1030	<p>Participants with moderate-to-severe joint pain who needed analgesics for at least 3 months and were dissatisfied with their current treatment were eligible (non-opioids or opioids at doses equivalent to morphine 160 mg/day oral))</p> <p>previous opioid use: not reported</p> <p>Mean age: 58 y</p> <p>Analgesics other than study drugs allowed, but it was unclear whether intake was similar between groups</p>	15 w (3 w titration; 12 w treatment)	<p>Oral extended-release tapentadol, 100-250 mg twice daily</p> <p>vs</p> <p>Oral controlled-release oxycodone, 20-50 mg twice daily</p> <p>vs</p> <p>Placebo, twice daily</p>	<p>(assessed by Da Costa Bruno)</p> <p>ALLOCATION CONC:</p> <p>Low risk</p> <p>RANDO:</p> <p>Low risk</p> <p>BLINDING :</p> <p>Low risk</p> <p>ITT:</p> <p>High risk</p> <p>INDUSTRY FUNDING:</p> <p>yes</p> <p>completed study: 48,7%</p> <p>discontinued oxycodone: 64.9%</p> <p>- adverse event 40.6%</p> <p>- lack of efficacy 2.0%</p> <p>discontinued tapentadol: 47.1%</p> <p>- adverse event 17.6%</p> <p>- lack of efficacy 4.3%</p> <p>discontinued placebo: 39.5%</p> <p>- adverse event 6.5%</p> <p>- lack of efficacy 10.3%</p>
<p>Bennet 2003 (83)</p> <p>double-blind, randomized, placebo-controlled study</p>	315	<p>at least moderate pain from fibromyalgia,</p> <p>SSRI for depression, and zolpidem and flurazepam for sleep allowed</p> <p>excluded patients who had used other antidepressants, cyclobenzaprine, antiepileptic drugs for pain < 3w prior to enrollment,...</p>	91 d	<p>tramadol 37.5 mg + acetaminophen 325 mg vs placebo</p> <p>(max 8x/d)</p>	<p>ALLOCATION CONC:</p> <p>Low risk</p> <p>RANDO:</p> <p>Low risk</p> <p>BLINDING :</p> <p>Low risk</p> <p>ITT:</p> <p>High risk</p> <p>INDUSTRY FUNDING:</p> <p>no funding reported</p>

		3 w washout phase no information on use of other analgesics throughout trial			discontinued prematurely tramadol/acetaminophen 48,7% placebo 62.4%
Boureau 2003 (84)	127	postherpetic neuralgia ≥ 3 m patients treated with antidepressants, anticonvulsants, opioid analgesics or local/general anaesthetics within 7 days prior to the inclusion visit were excluded; local treatments and nerve block also excluded, only acetaminophen allowed	6 w	tramadol 100 mg (1 to 4x/d) vs placebo	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : unclear risk ITT: High risk INDUSTRY FUNDING: no funding reported
Breivik 2010 (85) Randomised controlled trial 2-arm parallel group design	199	Participants with insufficient relief of moderate-to-severe osteoarthritis pain using NSAIDs or COXIBs and without previous exposure to opioids were eligible Mean age: 63 y No analgesics other than study drugs allowed NSAID/COX-II were continued during study rescue medication: paracetamol	28 w (treatment duration 24 w)	Transdermal buprenorphine (Norspan; BuTrans), 5-20 μ g/hour vs Placebo, change of patch every 7 days	(assessed by Da Costa Bruno) ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Low risk ITT: High risk INDUSTRY FUNDING: yes discontinued throughout study BTDS 54% - adverse events 31% - lack of efficacy 7% placebo 34.3% - adverse events 2%

					lack of efficacy 12% Other methodological remarks. The author of this publication is the editor in chief of the journal in which it was published.
Burch 2007 (32) RCT double blind enriched enrollment	646	<p>osteoarthritis (OA) of the knee</p> <p>had to be taking NSAIDs, COX-2 inhibitors, or tramadol on a regular basis for OA pain during the 30 days that preceded enrollment.</p> <p>washed out any pre-study analgesics for a minimum of five drug half-lives and have a score of at least 4 on the 11-point Pain Intensity Numerical Rating Scale (PI-NRS) at screening with an increase of at least two points after analgesic washout.</p> <p>During the entire study, patients were not permitted to take pain medication other than the study drug, with the exception of short-acting analgesics for acute pain other than that due to OA</p> <p>open label run in with tramadol (n=1028), followed by wash out. Only patients with sufficiently increased pain after washout were eligible for randomisation</p>	12 w	<p>tramadol controlled release (contramid) once daily (titrated to 200 mg or 300 mg) vs placebo</p> <p><u>Results</u> pain PI-NRS (pain intensity numeric scale 0-10) tramadol improvement 3.03 (2.82 to 3.24) placebo improvement 2.29 (2.02 to 2.57) absolute difference -0.70 (-1.02 to -0.38)</p> <p>responders \geq 5 point improvement tramadol 45.1% placebo 30.1% $p < 0.001$</p> <p>Patient global impression of change (improvement) tramadol 80% placebo 69% $p = 0.0002$</p> <p>discontinuation due to AE tramadol 10% placebo 5%</p> <p>no statistical tests for adverse events</p>	<p>ALLOCATION CONC: unclear risk</p> <p>RANDO: Low risk</p> <p>BLINDING : Low risk, assessors: unclear risk</p> <p>ITT: no, but only 1 exclusion</p> <p>INDUSTRY FUNDING: unclear</p> <p>76% of those randomized completed 12 weeks (equally distributed between tramadol and placebo)</p> <p>dealing with missing values: LOCF</p>
Buynak 2010 (39)	981	Low back pain, ≥ 3 m	15 w (3 w	Tapentadol ER 100-250 mg twice daily	(assessment by Abdel Shaheed

randomized, double-blind, placebo- and active-controlled Phase III study	<p>taking analgesic medications for ≥ 3 months or dissatisfied with their current therapy (non-opioids or opioids at doses equivalent to morphine 160 mg/day oral)</p> <p>prior opioid use (taking opioid analgesics within 3 months of screening)</p> <p>placebo 53.9%</p> <p>tapentadol 56.0%</p> <p>oxycodone 50.3%</p> <p>Neuroleptics, tricyclic antidepressants, anticonvulsants, antiparkinsonian drugs, and serotonin norepinephrine reuptake inhibitors were prohibited within 14 days prior to the screening visit and during the study ; use of monoamine oxidase inhibitors was also prohibited within 14 days prior to the screening visit and during the study.</p> <p>SSRI allowed if stable dose and not used for pain treatment</p> <p>The use of concomitant analgesics, with the exception of allowed doses of acetaminophen (see Treatment schedule), was prohibited during the study</p> <p>Electrical Nerve Stimulation, acupuncture, physical therapy, packs, massages, and other interventional adjunctive therapy</p>	titration, 12w maintenance)	vs Oxycodone HCl 20-50 mg twice daily vs Placebo	<p>2016)</p> <p>ELEGIBILITY CRITERIA SPECIFIED: NO</p> <p>ALLOCATION CONC: NO</p> <p>RANDO: YES</p> <p>BLINDING : YES</p> <p>FOLLOW-UP $\geq 85\%$: NO</p> <p>ITT: NO</p> <p>INDUSTRY FUNDING: YES</p> <p>discontinued early</p> <p>tapentadol 152/321 47.4%</p> <p>-adverse event 15.9%</p> <p>- lack of efficacy 40%</p> <p>oxycodone 195/334 58.4%</p> <p>- adverse event 32.0%</p> <p>- lack of efficacy 2.1%</p> <p>placebo 167/326 51.2%</p> <p>- adverse event 4.6%</p> <p>- lack of efficacy 15.3%</p> <p>dealing with missing values: LOCF</p>
--	--	-----------------------------	---	--

		were permitted during the study if patients started the treatment ≥ 14 days prior to enrollment and continued on the same regimen during the study			
Caldwell 2002 (86) double-blind trial followed by an open-label extension	295	chronic, moderate-to-severe osteoarthritis pain who had failed to obtain adequate pain relief with NSAIDs and acetaminophen or had previously received intermittent opioid analgesic therapy washout period of up to seven days The use of analgesic preparations other than acetaminophen for non-OA symptomatology (up to 2000 mg/day for a maximum of 3 consecutive days) was prohibited in the double-blind trial	4w	once-daily, extended-release morphine formulation (morning vs evening dose) vs ms contin 15 mg twice daily vs placebo	(assessed by Da Costa Bruno) ALLOCATION CONC: Unclear risk RANDO: Unclear risk BLINDING : Low risk ITT: High risk INDUSTRY FUNDING: yes
Chu 2012 (87) randomized, double-blind, placebo controlled clinical trial	139	Chronic nonradicular low-back pain Participants were not currently taking opioid pain medication in excess of 30 mg oral morphine equivalents per day study designed to examine hypersensitivity and tolerance	1 m	oral sustained release morphine vs placebo	ALLOCATION CONC: Unclear risk RANDO: Unclear risk BLINDING : unclear risk ITT: no INDUSTRY FUNDING: no
Cloutier 2013 (88) crossover RCT	83	chronic low back pain Patients currently taking opioids or patients who had not previously responded to nonopioid therapy and now required opioids to control their	4w	CR oxycodone/CR naloxone vs placebo	ALLOCATION CONC: low risk RANDO: low risk BLINDING : low risk

		<p>a two- to seven-day opioid washout</p> <p>Patients who were receiving nonopioid analgesics (nonsteroidal anti-inflammatory drugs or muscle relaxants) that were stably dosed for two weeks and antidepressants or anticonvulsants that were stably dosed for eight weeks were permitted to continue these medications,</p> <p>Acetaminophen/codeine (300 mg/30 mg every 4 h to 6 h as needed) was provided as rescue medication.</p>			<p>ITT: no INDUSTRY FUNDING: yes</p>
<p>DeLemos 2011 (21)</p> <p>5-arm double blind RCT dose-ranging</p>	1011	<p>Adults with knee and/or hip osteoarthritis and baseline pain intensity of ≥ 40 on a 100-mm visual analog scale (0 = no pain, 100 = extreme pain)</p> <p>treatment with COX-2 inhibitors, NSAIDs, acetaminophen, or opioid analgesics for at least 75 of 90 days preceding the screening visit</p> <p>2-7 d washout of prior analgesics</p> <p>no rescue medication allowed (paracetamol allowed for pain other than osteoarthritis)</p> <p>patients were required to be able to discontinue acetaminophen, NSAIDs, COX-2 inhibitors, opioids, and other analgesics (except aspirin 325 mg once daily for cardiovascular prophylaxis) during the study.</p>	12 w (titration to fixed dose first weeks)	<p>once-daily tramadol ER 100 mg , 200 mg or 300 mg (titrated to fixed dose) vs celecoxib 200 mg (to test model sensitivity) vs placebo (n = 200)</p> <p>Results</p> <p>3 coprimary efficacy variables</p> <p>WOMAC pain subscale</p> <p>LSMD from baseline</p> <p>placebo 94.9 +/-8.9</p> <p>tramadol 100 82.5 +/-8.9</p> <p>tramadol 200 90.4 +/-8.9</p> <p>tramadol 300 117.8 +/-8.9</p> <p>celecoxib 200 130.0 +/-9.0</p> <p>overall p <0.001 (SS difference between treatment arms)</p> <p>pairwise p (tramadol different doses vs placebo: NS difference)</p> <p>WOMAC physical function subscale</p>	<p>ALLOCATION CONC: unclear</p> <p>RANDO: unclear</p> <p>BLINDING : patient low risk personnel low risk assessors unclear</p> <p>ITT: no</p> <p>INDUSTRY FUNDING: yes</p> <p>555/1011 (54.9%) completed study</p> <p>reasons for discontinuation</p> <p>placebo</p> <ul style="list-style-type: none"> - lack of efficacy 32.5% - adverse events 7.5% <p>tramadol 100</p> <ul style="list-style-type: none"> - lack of efficacy 25.4% - adverse events 12.4% <p>tramadol 200</p>

		<p>excluded if recent use of monoamine oxidase inhibitor, tricyclic antidepressant, other tricyclic compound, neuroleptic, selective serotonin reuptake inhibitor, serotonin/ norepinephrine reuptake inhibitor, anorectic, bupropion, carbamazepine, or quinidine</p>	<p>LSMD from baseline placebo 290.1 +/-29.1 tramadol 100 272.3 +/- 29.0 tramadol 200 271.0 +/-29.1 tramadol 300 357.2 +/- 29.0 celecoxib 200 429.2 +/- 29.3 overall p <0.001 (SS difference between treatment arms) pairwise p (tramadol different doses vs placebo: NS)</p> <p>patient global assessment of disease activity placebo 20.2 +/-2.0 tramadol 100 18.8 +/- 2.0 tramadol 200 20.6 +/- 2.0 tramadol 300 26.4 +/- 2.0 celecoxib 200 28.6 +/- 2.0 overall p < 0.001 (SS difference between treatment arms) pairwise p: only tramadol 300 vs placebo SS</p> <p>adverse events (in order previously established) Constipation, overall p <0.001 2.5% vs 11.4% vs 17.6% vs 20.1% vs 2.5% Nausea, overall p <0.001 8.5% vs 15.4% vs 20.6% vs 26.1% vs 7.9% Vomiting, overall p <0.001 2.5% vs 4.5% vs 7.0% vs 10.1% vs 1.5% Somnolence, overall p <0.001 1.0% vs 8.0% vs 12.1% vs 5.5% vs 0.5%</p> <p>There were no deaths or treatment related serious adverse events No suggestions of psychic dependence</p>	<p>- lack of efficacy 16.6% - adverse events 23.1% tramadol 300 - lack of efficacy 11.1% - adverse events 30.7% celecoxib 200 - lack of efficacy 14.9% - adverse events 9.9%</p> <p>handling missing values: LOCF</p>
--	--	--	--	--

				(ARCI questionnaire). physical dependence: (PDQ symptoms): overall p<0.05 (5-10% more with tramadol 200 and 300 vs placebo)	
Emkey 2004 (89) randomized, double- blind, placebo- controlled trial	307	Participants with more than one year of OA of hip or knee, receiving a COX-2 nonsteroidal antiinflammatory drug no access to full text	91 days	Tramadol (37.5 mg) plus paracetamol (325 mg) vs placebo Dose was increased up to 4 tablets/day on Day 10 and afterwards up to 8 tablets/day if needed Participants in both groups received COX-2 selective analgesics	(assessed by Cepeda 2006) ALLOCATION CONC: NO RANDO: yes BLINDING : YES GROUPS SIMILAR: YES ITT: NO <20% LOST: YES
Fleischmann (90) randomized, double- blind, placebocontrolled, parallel-group clinical trial	129	Participants with radiologically confirmed diagnosis of OA of knee, >= moderate pain used NSAIDs for >=3 months before study entry 10-day analgesic washout period of all analgesics, including nsaid	91 days	tramadol 50-mg increments up to 400mg/day if needed vs placebo	(assessed by Cepeda 2006) ALLOCATION CONC: NO RANDO: NO BLINDING : YES GROUPS SIMILAR: YES ITT: YES <20% LOST: YES
Freeman 2007 (91) RCT	313	painful diabetic peripheral neuropathy no access to full text	66 days	tramadol 37.5 mg/acetaminophen 325 mg vs placebo	
Friedmann 2011 (92) Randomised controlled trial 2-arm parallel group design enrichment design	412	Participants with moderate-to-severe osteoarthritis pain using NSAIDs or opioids were eligible mean age 58 y Unclear whether analgesics other than study drugs allowed	14 w Treatment duration: 12 weeks	Oral extended-release oxycodone (Remoxy), 5-20 mg twice daily vs Placebo, twice daily (tamper-resistant capsule gel form (not on the Belgian market)	(assessed by Da Costa Bruno) ALLOCATION CONC: unclear risk RANDO: unclear risk BLINDING : unclear risk ITT: high risk INDUSTRY FUNDING: yes

					discontinued in the open label period: 37%
Gana 2006 (31) RCT double blind	1020	adults with osteoarthritis of the knee or hip and baseline pain intensity ≥ 40 on a 100-mm pain visual analog scale insufficient pain relief from acetaminophen, NSAID, COX-2 inhibitor or opioid washout of previous analgesics 2-7 d rescue drug: paracetamol	12 w (titration to target dose in first few weeks)	<p>tramadol ER 100, 200, 300, or 400 mg once daily (titrated to fixed target dose) vs placebo</p> <p>Results 3 co-primary endpoints <u>WOMAC pain subscale</u> (0-500)(lower=better) change from baseline placebo 74.2 +/- 8.5 tramadol 100 107.2 +/-8.6 tramadol 200 111.5 +/-8.7 tramadol 300 103.9 +/-8.7 tramadol 400 107.8 +/- 8.7 overall p=0.009 individual doses vs placebo: all p<0.05 SS better with tramadol</p> <p><u>WOMAC function subscale</u> (0-1700)(lower = better) placebo 234.3+/- 28.1 tramadol 100 331.7 +/-28.5 tramadol 200 350.2 +/- 29.0 tramadol 300 336.1 +/- 28.8 tramadol 400 329.8 +/- 28.8 overall p=0.021 individual doses vs placebo: all p<0.05 SS better with tramadol</p> <p><u>Subject global assessment of disease activity</u> (0-100 mm VAS)(lower = better) NS p=0.079</p>	<p>RANDO: low risk ALLOC CONC low risk BLINDING patients low risk doctors low risk analysors unclear ITT ('subjects who took at least 1 dose...')</p> <p>INDUSTRY FUNDING yes</p> <p>558/1020 completed 12 weeks (54.7%)</p> <p>reasons for discontinuation tramadol 100 mg - lack of efficacy 15.3% tramadol 100-200-300-400 - adverse events 14.3%, 19.9%; 26.9%, 29.7% placebo - lack of efficacy 22.4% - adverse events 10.2%</p> <p>handling missing values: LOCF</p>

				<p>only 2 of 3 coprimary endpoints were SS</p> <p>SS more rescue medication in placebo vs tramadol 300 and 400</p> <p>Constipation 5.9% vs 12.9% vs 16.4% vs 22.4% vs 29.7% p<0.001</p> <p>Nausea 7.3% vs 14.9% vs 23.4% vs 24.4% vs 25.7% p<0.001</p> <p>Vomiting 2.9% vs 5.4% vs 7.5% vs 7.0% vs 9.4% p=0.094</p> <p>Somnolence 2.4% vs 8.4% vs 10.4% vs 9.0% vs 20.3% p<0.001</p> <p>also SS more discontinuation of tramadol for constipation, nausea and somnolence vs placebo and increased with increasing dose of tramadol</p>	
Gimbel 2003 (93) randomized, double-blind, placebo-controlled, parallel-group	159	<p>moderate to severe pain due to diabetic neuropathy</p> <p>Medications taken for diabetes control as well as adjuvant pain medications were continued at the same stable prestudy dose</p>	6 w	<p>oxycodone CR vs placebo</p>	<p>ALLOCATION CONC: LOW risk</p> <p>RANDO: unclear risk</p> <p>BLINDING : low risk</p> <p>ITT: low risk</p> <p>INDUSTRY FUNDING: unclear</p>
Gilron 2005 (94) randomized, double-blind, active placebo-controlled, four-period	57	<p>neuropathic pain (diabetic neuropathy or postherpetic neuralgia)</p> <p>Nonopioid drugs other than gabapentin</p>	5 w	<p>daily active placebo (lorazepam) vs sustained-release morphine vs</p>	<p>ALLOCATION CONC: unclear risk</p> <p>RANDO: low risk</p>

crossover trial,		were permitted at a steady dose throughout the trial; procedural pain therapies (e.g., nerve blocks) were forbidden		gabapentin vs a combination of gabapentin and morphine	BLINDING : high risk ITT: no INDUSTRY FUNDING: no
Gordon 2010 (95) randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase	78	<p>patients with moderate to severe chronic low back pain for >3 months; previously treated with ≥ 1 tablet daily of an opioid analgesic.</p> <p>2- to 7-day washout of previous opioid therapy</p> <p>Patients were permitted to continue nonopioid analgesics at doses that had been stable for 2 weeks before enrollment, and antidepressants or anticonvulsants at doses that had been stable for 8 weeks before enrollment.</p> <p>Rescue analgesia was provided as acetaminophen 325 mg to be taken as 1 or 2 tablets every 4 to 6 hours as needed</p>	4 w 6 month open label	7-day buprenorphine transdermal system (BTDS) 10 μ g/h (titrated to max 40 μ g/h) vs placebo	<p>ALLOCATION CONC: low risk</p> <p>RANDO: low risk</p> <p>BLINDING : low risk</p> <p>ITT: no</p> <p>INDUSTRY FUNDING: yes</p>
Gordon 2010 (96) Randomized, double-blinded, crossover study	79	<p>Low back pain of moderate or greater severity for at least six weeks.</p> <p>Nonopioid analgesics that had been administered at a stable dose for two weeks before enrollment were permitted at that stable dose throughout the study</p> <p>Prestudy analgesics were discontinued, with acetaminophen 300 mg/codeine</p>		7-day buprenorphine transdermal system 5 μ g/d (titrated to max vs placebo	<p>ALLOCATION CONC: low risk</p> <p>RANDO: low risk</p> <p>BLINDING : unclear risk</p> <p>ITT: no</p> <p>INDUSTRY FUNDING: yes</p>

		30 mg, one to two tablets every 4 h to 6 h as needed, for rescue analgesia.			
Hale 2010 (35) RCT double Blind enrichment design		<p>aged 18–75 years moderate-to-severe low back pain, non-neuropathic or neuropathic opioid tolerant: on daily opioid treatment with ≥ 60 mg oral morphine equivalent (≥ 12 mg hydromorphone), but ≤ 320 mg morphine (≤ 64 mg hydromorphone) per day within 2 months prior to the screening visits.</p> <p>all non-opioid analgesics or drugs with anticipated analgesic effects were discontinued before study entry</p> <p>conversion of current opioid to hydromorphone using 5:1 conversion ratio</p> <p>hydromorphone IR was permitted as rescue medication</p> <p>495 patients entered run-in</p>	<p>12 w (in which placebo group had 2 w tapering from hydromorphone run-in)</p>	<p>hydromorphone 12 – 64 mg/d vs placebo</p> <p>Results pain intensity NRS (0-10, higher = worse) change from baseline hydromorphone +0.2 placebo +1.2 SS $p < 0.001$</p> <p>RMDQ change from baseline hydromorphone 0 placebo +1.0 $p < 0.005$</p>	<p>(assessment by Abdel Shaheed 2016)</p> <p>ELEGIBILITY CRITERIA SPECIFIED: NO ALLOCATION CONC: YES RANDO: YES BLINDING : YES FOLLOW-UP $\geq 85\%$: NO ITT: NO INDUSTRY FUNDING: YES</p> <p>discontinued during open label period: 42% (97)</p> <p>discontinued during double blind phase hydromorphone 50.4% placebo 66.9% $p < 0.05$</p> <p>dealing with missing values</p> <p>for patients discontinuing due to opioid withdrawal symptoms, the baseline pain intensity NRS score was carried forward to the final visit; (2) for patients discontinuing due to AEs, the pain intensity NRS score at screening (highest pain intensity) was carried forward to the final visit; and (3) for patients discontinuing due to lack of efficacy or other reasons (e.g., administrative, withdrawal of consent), the last observation was</p>

					carried forward to the final visit.
Hale 2015 (98) double-blind, placebo- controlled study enriched enrollment	294	chronic moderate-to-severe low back or osteoarthritis pain open-label titration period. ; no additional analgesic medications were permitted during open-label titration rescue medication: hydrocodone/acetaminophen tablets 5/325 mg as needed, NSAID also permitted	12 w	hydrocodone extended release (ER) developed with abuse-deterrence technology (15-90 mg) vs placebo (this formulation is not on the Belgian market)	ALLOCATION CONC: low risk RANDO: low risk BLINDING : low risk ITT: no, but few exclusions INDUSTRY FUNDING: yes
Hanna 2008 (43) randomized, double- blind, placebo- controlled study	338	moderate to severe painful diabetic neuropathy despite receiving their maximum tolerated dose of gabapentin for > 1 month paracetamol was allowed as escape medication (1 dose = 1 g) patients taking NSAIDS and tricyclic antidepressants started at least 3 weeks prior to screening and continued at stable frequency and dose, aspirin for cardiovascular indication (max 300 mg/day) and any other medication not excluded by study exclusion criteria, were allowed as concomitant medication	12 w	oxycodone every 12 hours vs placebo, added on to existing gabapentin	ALLOCATION CONC: low risk RANDO: low risk BLINDING : low risk ITT: yes INDUSTRY FUNDING: yes
Katz 2015 (99) double-blind, placebo- controlled, enriched enrollment, randomized withdrawal design study	389	clinical diagnosis of moderate-to- severe CLBP for a minimum of 6 months Both opioid-experienced and opioid- naïve patients (failed previous therapy with APAP or NSAIDs (ie, had moderate-to-severe pain	12 w treatment	Xtamza ER (tamper-resistant oxycodone, 20 to 80 mg twice daily) vs placebo (this formulation is not on the Belgian market)	ALLOCATION CONC: low risk RANDO: low risk BLINDING : low risk ITT:

		<p>while on APAP and/or NSAIDs), or were unable to tolerate NSAIDs)</p> <p>a washout period during which all prohibited analgesic medications (ie, all analgesics with the exception of APAP [up to 2000 mg/d] rescue medication) were discontinued</p> <p>open label titration (n= 740)</p> <p>Any adjunct therapy for back pain such as physical therapy, biofeedback therapy, transcutaneous electrical nerve stimulation, acupuncture, nutraceuticals, herbal remedies, and water aerobics must have been unchanged for at least 4 weeks</p>			<p>no</p> <p>INDUSTRY FUNDING:</p> <p>yes</p> <p>discontinued during the open label period: 47% (97)</p>
<p>Katz 2010 (100)</p> <p>Randomised controlled trial</p> <p>2-arm parallel group design</p> <p>enriched enrollment</p>	344	<p>Participants with insufficient pain relief with non-opioids analgesics, tramadol, or other opioids at 40-mg morphine equivalent per day were eligible</p> <p>open label run-in titration (n=547)</p> <p>full text not available</p>	<p>treatment duration</p> <p>12 w</p>	<p>Morphine sulfate and naltrexone hydrochloride extended release vs placebo</p> <p>(this combination is not on the Belgian market)</p>	<p>(assessed by Da Costa Bruno)</p> <p>ALLOCATION CONC:</p> <p>low risk</p> <p>RANDO:</p> <p>unclear risk</p> <p>BLINDING :</p> <p>unclear risk</p> <p>ITT:</p> <p>high risk</p> <p>INDUSTRY FUNDING:</p> <p>yes</p>
<p>Langford 2006 (101)</p> <p>Randomised controlled trial</p> <p>2-arm parallel group design</p>	416	<p>osteoarthritis of hip or knee moderate-to-severe pain that had been inadequately controlled by weak opioids</p> <p>1 w pretreatment run-in</p>	<p>8 w</p> <p>(treatment duration 6 w)</p>	<p>Transdermal fentanyl (Durogesic), median dosage 25 µg/hour vs Placebo</p>	<p>(assessed by Da Costa Bruno)</p> <p>ALLOCATION CONC:</p> <p>low risk</p> <p>RANDO:</p> <p>low risk</p> <p>BLINDING :</p>

		<p>During study treatment, previously prescribed NSAIDs and simple analgesics were continued, but weak opioids were discontinued</p> <p>All patients had access to paracetamol and metoclopramide</p>			<p>low risk ITT: high risk INDUSTRY FUNDING: yes</p>
Mangel 2008 (102) double-blind, randomized, placebo- controlled trial	596	<p>irritable bowel syndrome mild or greater pain</p> <p>Other treatments for IBS, laxatives, anti-diarrhoeals, and macrolide antibiotics required a 7-day washout period prior to entering the screening period.</p> <p>anti-depressants, anxiolytics, anti-anginals, cholesterol lowering agents, oral sulfonylureas, antipsychotics, iron, fibre or acid suppressant therapy needed to be on a stable dose of medication for at least 30 days prior to screening. Anti-depressants or anxiolytics used as IBS treatments were exclusionary. rescue medication max 3D/ month: choice of investigator</p>	12 w treatment	<p>asimadoline 0.15 mg vs asimadoline 0.5 mg vs asimadoline 1.0 mg vs placebo</p> <p>(this drug is not available in Belgium)</p>	<p>ALLOCATION CONC: high risk RANDO: high risk BLINDING : unclear risk ITT: no INDUSTRY FUNDING: yes</p>
Hyup Lee 2013 (103) double-blind, placebo- controlled, parallel- group study	245	<p>chronic low back pain (≥ 3 m) insufficiently controlled by previous NSAIDs or cyclooxygenase-2-selective inhibitors</p> <p>Patients were required to have taken a stable dose of NSAIDs or COX-2-selective inhibitors from 7 days before study drug administration (screening</p>	4w	<p>extended-release tramadol hydrochloride 75-mg/acetaminophen 650-mg fixed-dose combination tablets vs placebo (note: this formulation is not available in Belgium)</p>	<p>ALLOCATION CONC: unclear risk RANDO: low risk BLINDING : low risk ITT: low risk INDUSTRY FUNDING:</p>

		period) and to maintain that same dose during the study period. exclusion if antidepressants, anticonvulsants, or cyclobenzaprine			yes
Ma 2008 (104) prospective, randomised, double-blind clinical trial	116	chronic neck pain patients with daily acute pain flares these patients did not respond to non-opioids, non-steroidal anti-inflammatory drugs (NSAIDs) and other regimens Breakthrough pain was treated with 325–650 mg acetaminophen every 4–6 h	4 w	oxycodone controlled release 5 or 10 mg 2x/d vs placebo note: patients could discontinue if oxycodone > 1 week and sufficient pain relief	ALLOCATION CONC: high risk RANDO: high risk BLINDING : unclear risk ITT: high risk INDUSTRY FUNDING: no
Matsumoto 2005(105) Randomised controlled trial 4-arm parallel group design		chronic osteoarthritis (OA) pain Patients must have taken either acetaminophen, a conventional NSAID, a COX-2 inhibitor, or an opioid analgesic for at least 75 of 90 days before the screening visit and must have had a suboptimal response to these agents. Eligible patients entered a 2- to 7-day washout period during which all analgesic medications were discontinued. Mean age: 62 years	4w	Oral extended-release oxymorphone, 20 mg twice daily vs Oral extended-release oxymorphone, 40 mg twice daily vs Oral controlled-release oxycodone, 20 mg twice daily vs Placebo, twice daily	(assessed by Da Costa Bruno) ALLOCATION CONC: unclear risk RANDO: low risk BLINDING : low risk ITT: high risk INDUSTRY FUNDING: yes
Munera 2010 (106)	315	Patients with OA pain inadequately controlled with nonsteroidal	4w	7 day buprenorphine transdermal system	(assessed by Da Costa Bruno)

Randomised controlled trial 2-arm parallel group design		antiinflammatory drugs or patients who had taken opioids for OA pain within the past year 7-day run-in period during which they took ibuprofen only No rescue medication was allowed during the study		vs placebo	ALLOCATION CONC: unclear risk RANDO: unclear risk BLINDING : low/unclear risk ITT: high risk INDUSTRY FUNDING: yes withdrew due to adverse events BTDS 36/152 (23.7%) placebo 18/163 (11.0%)
Norrbrink 2009 (107) Randomized, Double-blind, Placebo-controlled Trial	36	Neuropathic Pain After Spinal Cord Injury full text not available	4w	Tramadol (3x50 mg/d) vs placebo	
Peloso 2004(108) RCT double blind	338	chronic LBP requiring daily medication for > or = 3 months washout of current analgesics mean age 57.5 rescue medication (acetaminophen 500mg, up to 4 tablets daily) Excluded: any sedative hypnotics, shortacting analgesics, topical preparations/medications and anesthetics, or muscle relaxants for a period of less than 5 half-lives of the given medication	91 d	Combination tablet containing tramadol, 36.5 mg + paracetamol, 325 mg (max 8 doses/d) vs placebo (average 150 mg tramadol/d)	(assessed by Chaparro 2013) ALLOCATION CONC: unclear RANDO: unclear BLINDING : Participants low risk personnel low risk assessors unclear risk INCOMPLETE OUTCOME DATA high risk (drop out >20% in each group: 48% in tramadol/acetaminophen and 64% placebo) ITT yes SELECTIVE REPORTING unclear risk

		<p>prior to the double blind phase; use of medications that could reduce the seizure threshold within 3 weeks before the double blind phase; use of opioids or initiation of nutraceuticals within 6 weeks of the double blind phase</p> <p>permitted continuation of physiotherapy started prior to inclusion</p>			INFLUENCE OF CO-INTERVENTIONS low risk (only rescue med allowed)
Rauck 2013 (37) RCT Double blind	990	<p>OA of the hip or knee, reporting a target joint pain score of ≥ 5 on the NRS, who were unable to consistently control or treat their pain with nonopioid medications or who had received an opioid for pain treatment.</p> <p>washout of previous analgesics 2 weeks at study entry</p> <p>Acetaminophen (£ 2,000 mg daily) was permitted as supplemental analgesia during the titration, maintenance, and taper phases</p>	16 d titration, 12 w of treatment, 1 w of taper	<p>hydromorphone OROS ER 8mg vs hydromorphone OROS ER 16mg vs placebo</p> <p>Results: At Maintenance Week 12, the LS mean (standard error of the mean [SEM]) AUC ratios in patients receiving placebo, OROS hydromorphone ER 8 mg, and OROS hydromorphone ER 16 mg were 0.20 (0.015), 0.19 (0.016; P = 0.36 vs. placebo), and 0.19 (0.015; P = 0.55 vs. placebo), respectively</p> <p>pain intensity score (11 point Likert scale) LS mean change from baseline (LOCF) hydromorphone 8: - 2.0 hydromorphone 16: -2.5 placebo: -1.9 hydromorphone 8 vs placebo: NS hydromorphone 16 vs placebo: p=0.007</p> <p>patient global assessment LS mean score (LOCF)</p>	<p>ALLOCATION CONC: unclear risk RANDO: unclear risk BLINDING : unclear risk ITT: no INDUSTRY FUNDING: yes</p> <p>48.1% completed the study discontinued hydromorphone 8 and 16: 50.8% and 61.2% discontinued placebo 43.7%</p> <p>primary outcome was pain intensity score with BOCF imputation and area under the curve (AUC) time-interval weighted AUC divided by the maximum AUC benefit possible for an individual patient, or the observed baseline score multiplied by the planned study duration (ie, 14 weeks) for the pain intensity score. This endpoint aims to</p>

				<p>hydromorphone 8: NR (NS) hydromorphone 16: 1.41 placebo: 1.02 hydromorphone 16 vs placebo p=0.01</p> <p>WOMAC physical function subscale change from baseline hydromorphone 8: -1.6 hydromorphone 16: -1.7 placebo: -1.3 hydromorphone 8 vs placebo p=0.056 hydromorphone 16 vs placebo p=0.006</p> <p>discontinued due to lack of efficacy hydromorphone 8: 15.4% hydromorphone 16: 9.1% placebo: 25%</p> <p>discontinued due to AE hydromorphone 8: 25.7% hydromorphone 16: 38.5% placebo: 6.3%</p> <p>no statistical tests reported for individual adverse events</p>	<p>measure cumulative pain intensity differences from baseline for the Titration and Maintenance Phases and normalizes the pain intensity difference score to the maximum possible pain intensity difference score.²³ For example, an AUC ratio of 0.2 indicates that at a given time, patients experienced 20% of the maximum possible benefit.</p>
Rauck 2015 (109) RCT double blind enriched-enrollment randomized withdrawal (EERW) study	281	nonspecific moderate-to-severe CLBP for at least 3 months managing CLBP with a nonopioid analgesic, an “as-needed” opioid, or daily opioid therapy and who scored their daily average pain between 5 and 9 on the numeric rating scale (NRS-Pain) ¹⁴ for at least 4 of the last 7 days of the screening period were eligible to enter the 4- to 6-week open-label conversion and titration period (n=410).	12 w	ALO-02 (extended-release oxycodone surrounding sequestered naltrexone) vs placebo (this combination is not on the Belgian market)	<p>ALLOCATION CONC: unclear risk</p> <p>RANDO: unclear risk</p> <p>BLINDING : unclear risk</p> <p>ITT: no</p> <p>INDUSTRY FUNDING: yes</p>

		open label conversion and titration (n=663)			
Rauck 2014 (110) RCT double blind enriched enrollment, randomized withdrawal study	302	moderate-to-severe chronic low back pain opioid-experienced adults open-label conversion/titration phase (≤6 weeks) (n=510)	12 w treatment	hydrocodone extended-release capsules (20-100 mg 2x/d) vs placebo (this formulation is not on the Belgian market)	ALLOCATION CONC: unclear risk RANDO: unclear risk BLINDING : unclear risk ITT: no INDUSTRY FUNDING: yes
Rauck 2016 (111) double blind enriched-enrollment, randomized-withdrawal design		opioid-naïve adults (≥18 years of age) with CLBP for ≥6 months as their primary source of pain, including those with CLBP of nonneuropathic origin, neuropathic origin or after low back pain surgery as assessed by the Quebec Task Force Classification of Spinal Disorders a stable daily maintenance dose of non-opioid analgesics for ≥4 weeks, with ≤10 mg morphine sulfate equivalent (MSE) per day permitted; Roland Morris Disability Questionnaire (RMDQ) for low back pain score ≥10 at screening (scores range from 0 [no disability] to 24 [maximum disability]); and a mean of average daily pain intensity score ≥5 to <10 on a 11-point numerical rating scale (NRS).	12 w treatment	buprenorphine Hcl buccal film vs placebo (this formulation is not on the Belgian market)	ALLOCATION CONC: unclear risk RANDO: unclear risk BLINDING : unclear risk ITT: no INDUSTRY FUNDING: yes

		<p>open-label titration phase (up to 8 weeks) (n=749)</p> <p>All prior analgesic medications discontinued.</p> <p>hydrocodone/acetaminophen (HC/APAP) tablets as rescue medication during the first 2 weeks and acetaminophen 500-mg tablets thereafter</p>			
Ruoff 2003 (112) RCT double blind	322	<p>Patients with at least moderate lower back pain; daily medication was needed for >3 months</p> <p>excluded if they had taken antidepressants, cyclobenzaprine, or antiepileptic drugs for pain, or if they had received transcutaneous electrical nerve stimulation, chiropractic adjustments, or acupuncture within 3 weeks of the double-blind phase</p> <p>Patients were also excluded if they had taken sedative-hypnotics, short-acting analgesics, topical anesthetics, or muscle relaxants for a period of <5 half-lives of the specific medication before the double-blind phase.</p> <p>washout of previous analgesic drugs</p> <p>mean age 53.9</p>	91 d	<p>Combination tablet containing tramadol, 37.5 mg + paracetamol, 325 mg, 1-2 tablets 4 times/d vs placebo</p> <p>(average 150 mg tramadol/d)</p>	<p>(assessed by Chaparro 2013)</p> <p>ALLOCATION CONCEALMENT unclear risk</p> <p>RANDO low risk</p> <p>BLINDING patients low risk</p> <p>providers low risk</p> <p>assessors unclear risk</p> <p>INCOMPLETE OUTCOME DATA high risk</p> <p>% drop-out exceeded 20% in each group: 71/162 (43%) in the tramadol/APAP and 86/160 (53%) in the placebo group</p> <p>ITT yes</p> <p>SELECTIVE REPORTING unclear risk</p> <p>INFLUENCE OF CO-INTERVENTIONS unclear risk</p>
Schwartz 2011 (54)		3-month history of opioid and/or non-opioid analgesic use for DPN,	12 w treatment	tapentadol extended release (ER) 100-250 mg bid vs placebo	See chapter neuropathic pain

randomized-withdrawal, placebo-controlled trial enriched enrollment		dissatisfaction with current treatment, and an average pain intensity score of at least 5 on an 11-point numerical rating scale (NRS; 0 = 'no pain,' 10 = 'pain as bad as you can imagine') 3 w open label titration phase			discontinued during open label period: 33% (97)
Steiner 2011 (3) RCT double blind enrichment design	541	moderate to severe chronic low back pain (nonmalignant) (defined as ≥ 3 m) taking nonopioid analgesic medications for CLBP no benefit from nonopioid therapy or not tolerating nonopioid therapy all other pain medication stopped at screening rescue medication: acetaminophen max 2g/d and ibuprofen max 800 mg/d open label run-in (n=1024)	84 d	Transdermal buprenorphine, 10 µg/h once weekly vs placebo	(assessment by Abdel Shaheed 2016) ELEGIBILITY CRITERIA SPECIFIED: NO ALLOCATION CONC: YES RANDO: YES BLINDING : YES FOLLOW-UP $\geq 85\%$: NO ITT: NO INDUSTRY FUNDING: YES discontinued during the open label period: 47% See separate table for this RCT
Trenkwalder 2015 (113) double blind phase 2 study	202	severe pain in parkinson's disease	16 w	oxycodone + naloxone prolonged release vs placebo	ALLOCATION CONC: unclear risk RANDO: low risk BLINDING : low risk ITT: no INDUSTRY FUNDING: yes
Thorne 2008 (114) crossover RCT double blind	100	painful osteoarthritis analgesic washout for two to seven	4w 6 m open	oral controlled release tramadol (titrated 200 mg to 400 mg once daily) vs	ALLOCATION CONC: unclear risk RANDO:

		<p>days before random assignment</p> <p>acetaminophen was provided as a rescue analgesic</p> <p>All patients who completed the crossover study were eligible to receive open label CR tramadol for six months</p>	label	placebo	<p>unclear risk</p> <p>BLINDING : unclear risk</p> <p>ITT: no</p> <p>INDUSTRY FUNDING: yes</p>
<p>Vinik 2014 (55)</p> <p>randomized withdrawal, double-blind, parallel-group design</p> <p>enriched enrollment</p>	318	<p>Chronic Painful Diabetic Peripheral Neuropathy ≥ 6 m</p> <p>Optimized diabetic regimen for ≥ 3 months prior to screening</p> <p>3-month history of analgesic use for painful DPN and dissatisfaction with current analgesic treatment (if patients were taking an opioid, a dose equivalent of oral morphine ≤ 160 mg/day was required)</p> <p>The use of any analgesic except study drug or permitted rescue medication was prohibited throughout the study.</p> <p>Neuroleptics, serotonin-norepinephrine reuptake inhibitors, anticonvulsants, and antiparkinsonian drugs were prohibited during the study and within 14 days before screening because their use could confound the primary assessment of analgesic efficacy. Use of selective serotonin reuptake inhibitors was allowed if patients were on a stable dose for ≥ 3 months before screening.</p> <p>3 week open label run-in (n=459)</p>	12 w treatment	tapentadol extended release vs placebo	<p>ALLOCATION CONC: low risk</p> <p>RANDO: low risk</p> <p>BLINDING : low/unclear risk</p> <p>ITT: yes</p> <p>INDUSTRY FUNDING: yes</p> <p>discontinued during the open label period: 22%</p>

Vondrackova 2008 (40) randomized, double-blind, placebo- and active-controlled, parallel-group study	464	<p>moderate to severe chronic low back pain, adequately managed by an opioid analgesic for at least 2 weeks before study enrolment and if they received daily opioid analgesic treatment and were likely to benefit from chronic opioid therapy for the duration of the study.</p> <p>excluded: patients currently taking the equivalent of <10 mg or >40 mg/d oxycodone</p> <p>opioid titration run-in period (down-titration to assess the need of opioids, then up-titration (target dose 40 mg/d) of oxycodone IR to achieve stable dose and adequate analgesia.</p>	12 w double blind	<p>oxycodone in combination with naloxone in a prolonged release (PR) formulation vs vs oxycodone prolonged release vs placebo</p> <p>results <u>oxy/nalox vs placebo</u> The times to pain event were statistically significantly shorter in the placebo group compared with the oxycodone PR/naloxone PR group (P values between .0001 and .0003). The mean time to first pain event was 19.3 days in the placebo group and 32.2 days in the oxycodone PR/naloxone PR group.</p>	<p>ALLOCATION CONCEALMENT unclear RANDOMISATION unclear BLINDING described as 'identical placebo' ITT no INDUSTRY FUNDING yes</p> <p>note: this was a study in patients already on daily doses of opioids.</p> <p>discontinuations oxy+nalox 11.69% oxy 11.92% placebo 15.82%</p>
Vojtassak 2011 (36) randomised, parallel-	288	<p>Osteoarthritis of the Hip or the Knee Moderate-to-severe OA pain was defined as</p>	4 week titration, 12 w	<p>OROS hydromorphone hydrochloride 4mg once daily vs matched placebo</p>	<p>ALLOCATION CONCEALMENT: unclear risk RANDO:</p>

group, placebocontrolled, double-blind study		<p>a mean weekly score of ≥ 5 on a scale of 0–10 for “pain on average” on the BPI scale</p> <p>chronic pain ≥ 3 m</p> <p>not have been adequately controlled with daily analgesic (NSAIDs or paracetamol) treatment for the month before beginning the study.</p> <p>At the screening visit (week –1), subjects taking weak opioids discontinued their medication; subjects taking NSAIDs or paracetamol remained on a stable dose.</p> <p>Paracetamol was allowed as rescue medication</p> <p>baseline BPI average hydromorphone 6.6 +/-1.02 placebo 6.5 +/-0.94</p> <p>WOMAC pain hydromorphone 11.8 +/- 2.63 placebo 11.5 +/- 2.71</p> <p>WOMAC function hydromorphone 41.2 +/- 9.25 placebo 39.8 +/-9.46</p>	maintenan ce	<p>Results</p> <p>pain (BPI – Brief Pain inventory) average (scale 0-10, higher = worse) (mixed model for repeated measures) hydromorphone -2.4 (SD 2.1) placebo -2.6 (SD 2.3) P = .1212 NS</p> <p>WOMAC OA index pain (range 0-20, higher = worse) hydromorphone -3.74 (SD 4.49) placebo -3.86 (SD 4.52) NS</p> <p>WOMAC OA index function (range 0-68, higher = worse) hydromorphone -11.93 (SD 13.17) placebo -11.90 (SD 14.35) NS</p> <p>Discontinuation due to AE hydromorphone 25.9% placebo 4.7% SS</p>	<p>unclear risk BLINDING : unclear risk ITT: no (but low number of exclusions) INDUSTRY FUNDING: yes</p> <p>discontinued early: hydromorphone 55/139 (39.6%) placebo 33/149 (23.6%)</p> <p>handling missing values: MMRM</p>
Vorsanger 2008(115) RCT enrichment design	386	<p>adults with VAS Score $\geq 40/100$. CLBP > 6months. Requiring at least 90 days of NSAIDs, COX-2, opioids or muscle relaxant mean age 47.8 y</p> <p>VAS ≥ 40 mm</p>	12 w	<p>Tramadol ER 300 mg/d, VS tramadol ER 200 mg/d vs placebo</p>	<p>ALLOCATION CONCEALMENT unclear risk RANDO low risk BLINDING patients low risk personnel unclear risk</p>

		<p>619 patients in 3 w open label tramadol run-in</p> <p>Study authors did not allow patients to use NSAID corticosteroids, opioids, or other analgesic during the study, with the exception of low-dose aspirin or acetaminophen as described earlier. They also excluded neuroleptic, SSRIs, SNRIs, carbamazepine, or quinidine medications</p>			<p>assessors unclear risk INCOMPLETE OUTCOME DATA high risk % drop-out > 20% in each group: 42/128 (32%) in high dose tramadol, 61/129 (47%) in placebo group ITT modified itt SELECTIVE REPORTING unclear risk INFLUENCE OF CO-INTERVENTIONS low risk</p> <p>discontinued during open label period: 38% (97)</p>
Webster 2006 (38) double blind RCT	719 oxycodone 206 placebo 101	<p>persistent low back pain for at least 6 months requiring daily analgesics and a baseline pain intensity score of ≥ 5 at screening</p> <p>- 42.6% to 48.1% opioid use in preceding month - only 5% of patients were on high dose opioids (oxycodone equivalent ≥ 20mg/d)</p> <p>washout period of all analgesics except acetaminophen</p>	12 w	<p>Oxycodone + low-dose naltrexone 4 times/d vs oxycodone 4 times/d vs oxycodone + low-dose naltrexone twice a day, vs placebo</p>	<p>(assessment by Abdel Shaheed 2016)</p> <p>ELEGIBILITY CRITERIA SPECIFIED: NO ALLOCATION CONC: YES RANDO: YES BLINDING : YES FOLLOW-UP $\geq 85\%$: NO ITT: NO INDUSTRY FUNDING: YES</p> <p>discontinued oxycodone 105/206 51.0% 7.3% inadequate pain relief 23.8% adverse events</p> <p>placebo 59/101 58.4% 40% inadequate pain relief 5% adverse events</p> <p>handling missing values LOCF</p>
Wen 2015 (116) randomized, double-	588	opioid-naive and opioid-experienced patients with uncontrolled moderate to	12 w treatment	hydrocodone vs placebo	

blind, placebo-controlled study with an enriched enrollment, randomized withdrawal design		severe chronic low back pain open label titration (n=905)			
Zin 2010 (117) double-blind, placebo-controlled, parallel-group	62	postherpetic neuralgia (PHN) or painful diabetic neuropathy (PDN) 7-day washout	4 w	oxycodone vs placebo both treatment arms received pregabalin after 1 week	

19.2 Opioids vs placebo for chronic non-cancer pain: adverse events. Meta-analysis Els 2017

Methods

Systematic review/Meta-analysis: Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews

Inclusion criteria:

Cochrane Reviews of studies of medium- or long-term opioid use (2 weeks or more) for CNCP in adults aged 18 and over

Search strategy: Cochrane Database of Systematic Reviews (the Cochrane Library) Issue 3, 2017 on 8 March 2017

Assessment of quality of included trials: yes AMSTAR for SRs, GRADE for outcomes

Other methodological remarks:

- The authors considered a trial duration of 2 weeks to 2 months as medium term use and a duration > 2 months as long duration
- The authors only included trials from the reviews that met their inclusion criteria in the analyses. Duplicate trials were removed.
- Calculation of NNH: the authors calculated risk ratios (RRs) and numbers needed to treat for an additional harmful outcome (NNTH) from the pooled number of events using the method of Cook and Sackett (Cook 1995 - <https://www.bmj.com/content/310/6977/452>).
- Calculation of absolute event rates: the authors also calculated the proportion of participants experiencing adverse events and associated 95% CIs; if the lower bound of such a 95% CI was calculated as negative, we reported it as 0, following the methodology of Moore and McQuay (Moore 2005 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1257433/>).

Remarks

The average absolute event rate seems to be calculated using the crude rates from the individual trials.

It is unclear how the NNT was calculated. It seems that the authors used the crude absolute event rates to calculate the NNT. This is not how the GRADE approach advises the absolute event rates and NNTs to be calculated. This calculation of the NNT is also problematic because of the varying trial durations included in the meta-analysis.

Author's conclusions

"A number of adverse events, including serious adverse events, are associated with the medium- and long-term use of opioids for CNCP. The absolute event rate for any adverse event with opioids in trials using a placebo as comparison was 78%, with an absolute event rate of 7.5% for any serious adverse event. Based on the adverse events identified, clinically relevant benefit would need to be clearly demonstrated before long-term use could be considered in people with CNCP in clinical practice. A number of adverse events that we would have expected to occur with opioid use were not reported in the included Cochrane Reviews. Going forward, we recommend more rigorous identification and reporting of all adverse events in randomised controlled trials and systematic reviews on opioid therapy. The absence of data for many adverse events represents a serious limitation of the evidence on opioids. We also recommend extending study follow-up, as a latency of onset may exist for some adverse events." (23)

Results				
Ref	Comparison	N/n	Outcomes	Result (95% CI)
ref*Els 2017 • (23) Design: SR of SR's MA Search date: march 2017	Opioids vs placebo	N= 6 reviews n= 5004 (Reviews: Stannard 2016, Derry 2016, da Costa 2014, Whittle 2011, McNicol 2013, gaskell 2016)	Any adverse event	(risk ratio (RR) 1.42, 95% confidence interval (CI) 1.22 to 1.66) absolute event rate, average opioid 78.3% (76.8 to 79.7) placebo 54.5% (52.2 to 56.7) NNH 4.20 (3.78, 4.74) (as calculated by Els 2017) (duration of treatment not reported. Probably the average study duration) GRADE assessment by Els 2017 reported (MODERATE), but based on only 1 review with 1583 participants
		N= 6 reviews n= 4324 (Reviews: Stannard 2016, Derry 2016, Cepeda 2006, Santos 2015, da Costa 2014, Gaskell 2016)	Serious adverse event	RR 2.75, 95% CI 2.06 to 3.67 absolute event rate, average opioid 7.5% (6.5 to 8.4) placebo 4.0% (3 to 5) NNH 28.71 (20.50 to 47.88) (as calculated by Els 2017) (duration of treatment not reported. Probably the average study duration) GRADE assessment by Els 2017 reported (MODERATE), but based on only 1 review with 108 participants
		N= 10 reviews n=11511 (Reviews Haroutiunian 2012, Chaparro 2012, McNicol 2013, Cepeda 2006, Santos 2015, Derry 2016, da Costa 2014, Whittle	Withdrawal due to adverse events	RR 3.40, 95% CI 3.02 to 3.82 absolute event rate opioid 25.1% (24.1 to 26.1) placebo 7.1% (6.3 to 7.9) NNH 5.55 (5.19, 5.97) (as calculated by Els 2017) (duration of treatment not reported. Probably the average study

		2011, Gaskell 2016, Stannard 2016)		duration) GRADE assessment by Els 2017 reported (MODERATE), but based on only 4 review with 2375 participants
		N= 4 reviews n= 4255 (Reviews: Derry 2016, Chaparro 2013, McNicol 2013, Chaparro 2012)	Constipation	RR 2.23 (1.39 – 3.59) absolute risk (average) opioids 11.3% (10.1 to 12.6) placebo 5.4% (4.3 to 6.5) NNH 16.82 (13.20, 23.19) (as calculated by Els 2017) (duration of treatment not reported. Probably the average study duration) GRADE assessed by Els 2017 as MODERATE (serious risk of bias and serious indirectness)
		N= 3 Reviews n=4346 (Reviews Chaparro 2013, McNicol 2013, Chaparro 2012)	nausea	RR 2.46 (2.08-2.92) absolute risk (average) opioids 20.9% (20.9 to 20.9) placebo 8.4% (8.4 to 8.4) NNH 8.00 (6.88, 9.56) (as calculated by Els 2017) (duration of treatment not reported. Probably the average study duration) GRADE assessed by Els 2017 as MODERATE (serious risk of bias and serious indirectness)

		N=2 n=3368 (Reviews: Chaparro 2013, McNicol 2013)	vomiting	RR 4.29 (2.90 – 6.34) absolute risk (average) opioids 8.9% (8.9 to 8.9) placebo 2.1% (2.1 to 2.1) NNH 14.70 (12.10, 18.72) (as calculated by Els 2017) (duration of treatment not reported. Probably the average study duration) GRADE assessed by Els 2017 as LOW (serious risk of bias and VERY serious indirectness)
		n=3856 (Reviews Chaparro 2013, McNicol 2013, Chaparro 2012)	drowsiness (or somnolence)	RR 2.89 (95%CI 2.19 to 3.83) absolute risk (average) opioids 10.3% (9 to 11.5) placebo 3.7% (2.8 to 4.6) NNH 15.26 (12.34, 20.00) (as calculated by Els 2017) (duration of treatment not reported. Probably the average study duration) GRADE assessed by Els 2017 as MODERATE (serious risk of bias and serious indirectness)
			fatigue, dizziness, hot flushes, increased sweating, pruritis	there are also SS results for these endpoints
			addiction, cognitive dysfunction, depressive symptoms or mood disturbances, hypogonadism or other endocrine dysfunction, respiratory depression, sexual dysfunction, and sleep apnoea or sleep-disordered breathing	no data

Characteristics of included studies					
Ref + design	n	Population	Duration	Comparison	Methodology
Cepeda 2006 Cochrane SR + MA		Osteoarthritis Adults with primary or secondary osteoarthritis of the hip or knee	14 to 91 days	Tramadol or tramadol plus paracetamol	AMSTAR assessed by Els 2017 10
Chaparro 2012 Cochrane SR + MA		Neuropathic pain Adults	5 to 36 weeks (includes a crossover trial of 9 weeks with 4 conditions)	Compared combinations of 2 or more drugs against placebo or another comparator	AMSTAR assessed by Els 2017 9
Chaparro 2013 Cochrane SR + MA		CLBP (chronic low back pain) Adults with persistent pain in the low back for at least 12 weeks	4 to 15 weeks	Any opioid prescribed in an outpatient setting for 1 month or longer	AMSTAR assessed by Els 2017 9
da Costa 2014 Cochrane SR + MA		Adults with osteoarthritis of the knee or hip	2 to 30 weeks	Any type of opioid except tramadol	AMSTAR assessed by Els 2017 10
Derry 2016 Cochrane SR + MA		Neuropathic pain Adults with postherpetic neuralgia, complex regional pain syndrome, or chronic postoperative pain	94 to 113 days	Fentanyl at any dose, by any route	AMSTAR assessed by Els 2017 10
Gaskell 2016 Cochrane SR + MA		Chronic neuropathic pain Adults with painful diabetic neuropathy or postherpetic neuralgia	12 weeks	Any dose or formulation of oxycodone	AMSTAR assessed by Els 2017 10
Haroutiunian 2012 Cochrane SR + MA		CNCP (chronic non cancer pain), adults	40 to 119 days	Methadone by any route in randomised or quasi- randomised studies	AMSTAR assessed by Els 2017 10
McNicol 2013 Cochrane SR + MA		Adults with central or peripheral neuropathic pain of any aetiology	6 to 16 weeks (includes a 6- and 8- week cross- over trial with 2 conditions)	Opioid agonists used in an RCT	AMSTAR assessed by Els 2017 9
Santos 2015 Cochrane SR + MA		CNCP (chronic non cancer pain) Adults with osteoarthritis of the knee or	15 to 52 weeks	Tapentadol ER in doses of 100 to 500 mg/day	AMSTAR assessed by Els 2017 10

		hip, CLBP			
Stannard 2016 Cochrane SR + MA		Neuropathic pain Adults with 1 or more chronic neuropathic pain conditions	14 to 16 weeks	Hydromorphone at any dose, by any route	AMSTAR assessed by Els 2017 10
Whittle 2011 Cochrane SR + MA		Adults with rheumatoid arthritis pain	6 to 10 weeks	Opioids of any formulation at any dose, by any route	AMSTAR assessed by Els 2017 10

19.3 Opioids vs placebo for chronic non-cancer pain: quality of life. Meta-analysis Thornton 2017

Methods
<p>Systematic review/Meta-analysis: Health-related quality of life in patients receiving long-term opioid therapy: a systematic review with meta-analysis</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> - Physical Component Summary (PCS) score and Mental Component Summary (MCS) scores of a Health-Related Quality of Life instrument - adults without opioid use disorder - randomized controlled trial, at least one opioid intervention group, minimum of 4-week duration of opioid use, comparative control group - adults ≥ 18 years that do not have dominant disease (chronic kidney disease, HIV/AIDs, or cancer), - Chronic pain was defined as beyond the time of normal tissue healing or 3 months <p><u>Search strategy:</u> PubMed (MEDLINE), Scopus, and PsycINFO through april 2016</p> <p><u>Assessment of quality of included trials:</u> yes</p> <p><u>Other methodological remarks:</u></p> <p>the magnitude of effect sizes were interpreted as very small (0.01), small (0.2), medium (0.5), large (0.8), very large (1.2), and huge (2.0)</p> <p>To aid practical application, the number-needed-to treat (NNT) were calculated for those overall findings reported as statistically significant. For NNT, the method of Kraemer and Kupfer (25) was used versus a method based on control group risk given the lack of consensus regarding an appropriate control group risk for opioids and HRQoL.</p>

Results				
Ref	Comparison	N/n	Outcomes	Result (95% CI)
ref*Thornton 2017 (24) Design: SR/MA Search date: april 2016	Opioids versus placebo	N= 5 n= ? Afilalo 2013 (3 studies, 6 comparisons), Peloso 2004, Ruoff 2013	SF-36 Physical component summary	Hedge's g Effect size 0.18 (0.08, 0.28) SS in favor of opioids NNT = 10 (for 1 patient to have a larger improvement than the placebo group(25)) Cohen's U3 index percentile improvement 7.1
		N= 5 n= ? Afilalo 2013 (3 studies, 6 comparisons), Peloso 2004, Ruoff 2013	SF-36 Mental component summary	Hedge's g Effect Size -0.05 (-0.18, 0.08) NS

Characteristics of included studies					
Ref + design	n	Population	Duration	Comparison	Methodology
Afilalo 2013 (118), refers to these original articles:	1030	<p>Chronic osteoarthritis-related knee pain (n=502 reported by Thornton 2017)</p> <p>this trial was published in a full text article by Afilalo 2010 (82)</p> <p>randomized, double-blind, active- and placebo-controlled, parallel-arm, multicentre, phase III study</p> <p>Participants with moderate-to-severe joint pain who needed analgesics for at least 3 months and were dissatisfied with their current treatment were eligible (non-opioids or opioids at doses equivalent to morphine 160 mg/day oral))</p> <p>Previous opioid use: not reported Mean age: 58 y</p> <p>Neuroleptics, tricyclic antidepressants, anticonvulsants, antiparkinsonian drugs and serotonin-norepinephrine reuptake inhibitors were prohibited within 14 days prior to screening and during the study. Monoamine oxidase inhibitors were prohibited within 14 days prior to screening and during the study. Corticosteroids were prohibited during the trial</p> <p>The use of concomitant analgesics (except allowed doses of paracetamol) was prohibited during the study</p>	15 weeks (3 week titration, 12 week maintenance)	<p>Tapentadol ER 100-250 mg twice daily</p> <p>vs</p> <p>Oxycodone CR 20-50 mg twice daily</p> <p>vs</p> <p>Placebo</p>	<p>(from: Assessment by Santos 2015)</p> <p>ALLOCATION CONC: Low risk</p> <p>RANDO: Low risk</p> <p>BLINDING : Low risk</p> <p>INCOMPLETE OUTCOME DATA: Unclear risk (LOCF)</p> <p>SELECTIVE REPORTING: Low risk</p> <p>completed study: 48.7%</p> <p>discontinued oxycodone: 64.9%</p> <p>- adverse event 40.6%</p> <p>- lack of efficacy 2.0%</p> <p>discontinued tapentadol: 47.1%</p> <p>- adverse event 17.6%</p> <p>- lack of efficacy 4.3%</p> <p>discontinued placebo: 39.5%</p> <p>- adverse event 6.5%</p> <p>- lack of efficacy 10.3%</p>

	990	<p>Chronic osteoarthritis-related knee pain (n= 513 reported by Thornton 2017)</p> <p>This trial was published in a full-text article by Serrie 2017 (119))</p> <p>Osteoarthritis of the knee Participants who were dissatisfied with their prior analgesic therapy were eligible</p> <p>pain requiring analgesic medications (non-opioids or opioids) at the reference joint for >=3 months. Opioids equivalent to =<160mg oral morphine/day Mean age: 62 years Prior opioid use <3months before screening in 14.2% to 16.6% of participants</p> <p>concomitant analgesics were prohibited during the study. Neuroleptics, monoamine oxidase inhibitors, serotonin norepinephrine re-uptake inhibitors, tricyclic antidepressants, anti-epileptics, and anti-parkinsonian medications were not permitted within 14 days prior to screening and during the study. Corticosteroids were also not permitted.</p> <p>washout of previous analgesics</p> <p>limited use of paracetamol as rescue medication</p>	15 weeks (3 week titration, 12 week maintenance)	<p>3-7 day washout phase to discontinue analgesic medications</p> <p>3 week double blind titration phase</p> <p>Tapentadol ER 100-250 mg twice daily vs Oxycodone CR 20-50 mg twice daily vs Placebo</p>	<p>(from: Assessment by Santos 2015)</p> <p>ALLOCATION CONC: Low risk</p> <p>RANDO: Low risk</p> <p>BLINDING : Low risk</p> <p>INCOMPLETE OUTCOME DATA: unclear risk (LOCF) The original article does not state the number of patients with SF-36 results at 12 weeks. The methods section states that LOCF would be used for the missing values. Thornton reports numbers that are slightly lower than the number of patients that completed the trial.</p> <p>completed study: 48,7% discontinued oxycodone: 64.9% - adverse event 40.6% - lack of efficacy 2.0% discontinued tapentadol: 47.1% - adverse event 17.6% - lack of efficacy 4.3% discontinued placebo: 39.5% - adverse event 6.5% - lack of efficacy 10.3%</p>
--	-----	--	--	--	---

	981	<p>Chronic low back pain (n= 451 reported by Thornton 2017)</p> <p>This trial was pulished in a full text article by Buynak 2010 (39)</p> <p>Low back pain, >=3 m taking analgesic medications for ≥ 3 months or dissatisfied with their current therapy (non-opioids or opioids at doses equivalent to morphine 160 mg/day oral)</p> <p>prior opioid use (taking opioid analgesics within 3 months of screening) placebo 53.9% tapentadol 56.0% oxycodone 50.3%</p> <p>Neuroleptics, tricyclic antidepressants, anticonvulsants, antiparkinsonian drugs, and serotonin norepinephrine reuptake inhibitors were prohibited within 14 days prior to the screening visit and during the study ; use of monoamine oxidase inhibitors was also prohibited within 14 days prior to the screening visit and during the study.</p> <p>SSRI allowed if stable dose and not used for pain treatment</p> <p>The use of concomitant analgesics, with the exception of allowed doses of acetaminophen (see Treatment schedule), was prohibited during the study</p> <p>Electrical Nerve Stimulation, acupuncture,</p>	15 weeks (3 week titration, 12 week maintenance)	<p>Tapentadol ER 100-250 mg twice daily vs Oxycodone HCl 20-50 mg twice daily vs Placebo</p>	<p>ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Low risk INCOMPLETE OUTCOME DATA: Unclear risk (LOCF) SELECTIVE REPORTING: Low risk</p> <p>discontinued early tapentadol 152/321 47.4% -adverse event 15.9% - lack of efficacy 40% oxycodone 195/334 58.4% - adverse event 32.0% - lack of efficacy 2.1% placebo 167/326 51.2% - adverse event 4.6% - lack of efficacy 15.3%</p>
--	-----	--	--	--	--

		physical therapy, packs, massages, and other interventional adjunctive therapy were permitted during the study if patients started the			
Peloso 2004 (108) RCT double blind enriched enrollment	338	chronic LBP requiring daily medication for > or = 3 months washout of current analgesics mean age 57.5 rescue medication (acetaminophen 500mg, up to 4 tablets daily) Excluded: any sedative hypnotics, shortacting analgesics, topical preparations/medications and anesthetics, or muscle relaxants for a period of less than 5 half-lives of the given medication prior to the double blind phase; use of medications that could reduce the seizure threshold within 3 weeks before the double blind phase; use of opioids or initiation of nutraceuticals within 6 weeks of the double blind phase permitted continuation of physiotherapy started prior to inclusion	91 d	Combination tablet containing tramadol, 36.5 mg + paracetamol, 325 mg (max 8 doses/d) vs placebo (average 150 mg tramadol/d)	(assessed by Chaparro 2013) ALLOCATION CONC: unclear RANDO: unclear BLINDING : Participants low risk personnel low risk assessors unclear risk INCOMPLETE OUTCOME DATA high risk (drop out >20% in each group: 48% in tramadol/acetaminophen and 64% placebo) ITT yes SELECTIVE REPORTING unclear risk INFLUENCE OF CO-INTERVENTIONS low risk (only rescue med allowed)
Ruoff 2003 (112) RCT double blind	322	Patients with at least moderate lower back pain daily medication was needed for >3 months excluded if they had taken antidepressants,	91 d	Combination tablet containing tramadol, 37.5 mg + paracetamol, 325 mg, 1-2 tablets 4 times/d	(assessed by Chaparro 2013) ALLOCATION CONCEALMENT unclear risk RANDO low risk BLINDING

		<p>cyclobenzaprine, or antiepileptic drugs for pain, or if they had received transcutaneous electrical nerve stimulation, chiropractic adjustments, or acupuncture within 3 weeks of the double-blind phase.</p> <p>Patients were also excluded if they had taken sedative-hypnotics, short-acting analgesics, topical anesthetics, or muscle relaxants for a period of <5 half-lives of the specific medication before the double-blind phase.</p> <p>washout of previous analgesic drugs</p> <p>mean age 53.9</p>		vs placebo	<p>patients low risk</p> <p>providers low risk</p> <p>assessors unclear risk</p> <p>INCOMPLETE OUTCOME DATA</p> <p>high risk</p> <p>% drop-out exceeded 20% in each group:</p> <p>71/162 (43%) in the tramadol/APAP and</p> <p>86/160 (53%) in the placebo group</p> <p>ITT yes</p> <p>SELECTIVE REPORTING unclear risk</p> <p>INFLUENCE OF CO-INTERVENTIONS</p> <p>unclear risk</p>
--	--	--	--	------------	--

Remarks
The authors were only able to include studies with tapentadol, tramadol and oxycodone for this outcome. The authors found moderate heterogeneity.
Author's conclusions
"PCS scores improve with no change in MCS scores. However, long-term opioid trials are rare..."(24)

20 Appendix. Evidence tables. Opioids versus placebo for specific musculoskeletal pain conditions

20.1 Opioids vs placebo for chronic pain in osteoarthritis of the knee or hip. Meta-analysis da Costa Bruno 2014

Methods
<p>Systematic review/Meta-analysis: Oral or transdermal opioids for osteoarthritis of the knee or hip (26)</p> <p><u>Inclusion criteria:</u></p> <p>Randomised or quasi-randomised controlled trials that compared oral or transdermal opioids with placebo or no treatment in people with knee or hip osteoarthritis.</p> <p>Excluded: studies of tramadol.</p> <p>No language restrictions</p> <p><u>Search strategy:</u> Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and CINAHL (up to 28 July 2008, with an update performed on 15 August 2012), conference proceedings, reference lists, and contacted authors</p> <p><u>Assessment of quality of included trials:</u> yes, GRADE</p> <p><u>Other methodological remarks:</u></p>
Remarks
<p>This systematic review found 22 trials with <u>opioids</u> in knee and hip osteoarthritis. Almost half of the trials (representing half of the treatment arms) were ≥ 12 weeks. The other trials were shorter than specified in the inclusion criteria for our Consensus Conference literature review, or included opioids that are not available on the Belgian market. We reported the results of the meta-analysis, with the caveat that slightly more than half of the trials did not meet the inclusion criteria for our Consensus Conference literature review and the caveat that tramadol was not included in this meta-analysis.</p> <p>This systematic review found 3 trials with <u>codeine</u>. These were all <12 weeks. This is shorter than specified in the inclusion criteria for our Consensus Conference literature review. Therefore we did not report the results for codeine.</p> <p>This systematic review found 2 trials with <u>morphine</u>. One was <12 weeks, the other used a combination of morphine + naltrexone. Both these trials did not meet the inclusion criteria for our Consensus Conference literature review. Therefore we did not report the results for morphine.</p> <p>This systematic review found 1 trial with <u>hydromorphone</u>. This trial was at that time published in peer reviewed literature (NCT00980798). We reported the results that were provided by Cochrane Da Costa Bruno in the table 'Characteristics of included studies'. Since the publication of this Cochrane review, this trial has been published (Vojtassak 2011 (36)).</p> <p>This systematic review found 10 trials with <u>oxycodone</u>. 5 trials were ≥ 12 weeks. One of these trials was not published in peer reviewed literature (NCT00486811) at the time of the cochrane review. It has since been published (118, 119). We reported the results that were provided by Cochrane Da Costa Bruno. The other five trials were < 12 weeks. We will report the results of the meta-analysis by Da Costa Bruno (see separate results table below), with the caveat that half of the trials were of insufficient length for our Consensus Conference literature review.</p>

This systematic review found 4 trials with tapentadol. 2 of these trials were ≥ 12 weeks. One of these was unpublished at the time of the Cochrane review (NCT00486811). It has since been published (118, 119). The 2 other trials were < 12 weeks.

We did not report the results of this meta-analysis, because the meta-analysis by Santos 2015 (see elsewhere in this document) provides results to this research question and includes only trials ≥ 12 weeks.

This systematic review found 4 trials with transdermal buprenorphine. 3 of these trials were ≥ 12 weeks. One of these was unpublished at the time of the Cochrane review (NCT00531427). We report the results that were provided by Cochrane Da Costa Bruno. The remaining trial was < 12 weeks. We will report the results of the meta-analysis by Da Costa Bruno, with the caveat that one trial was of insufficient length for our Consensus Conference literature review.

This systematic review found 1 trial with transdermal fentanyl. It was < 12 weeks. This is shorter than specified in the inclusion criteria for our Consensus Conference literature review. Therefore we did not report these results.

Author's conclusions

"The small mean benefit of non-tramadol opioids are contrasted by significant increases in the risk of adverse events. For the pain outcome in particular, observed effects were of questionable clinical relevance since the 95% CI did not include the minimal clinically important difference of 0.37 SMDs, which corresponds to 0.9 cm on a 10-cm VAS."(26)

20.1.1 Non-tramadol opioids for chronic pain in osteoarthritis of the knee or hip

Results				
Ref	Comparison	N/n	Outcomes	Result (95% CI)
ref* (26) Design: SR + MA Search date: (aug 2012)	Opioids versus placebo in knee or hip osteoarthritis	N= 22 n= 8275 (Breivik 2010, Munera 2010, NCT00531427, Shannon 2005, Kjaersgaard-Andersen 1990, Peloso 2000, Quiding 1992, Langford 2006, NCT00980798, Caldwell 2002, Katz 2010, Afilalo 2010, Chindalore 2005, Etropolski 2011, Fidelholtz 2011, Friedmann 2011, Hartrick 2009, Markenson 2005, Matsumoto 2005, NCT00486811, Zautra 2005, Kivitz 2006, Matsumoto 2005, Afilalo 2010, Etropolski 2011, Hartrick 2009, NCT00486811	Pain intensity. Various pain scales (median follow-up: 4 weeks)	<p>Result for all trials SMD -0.28 (-0.35 to -0.20)</p> <p>Assumed risk placebo -1.8 cm change on 10 cm VAS (29% improvement) (Median reduction as observed across placebo groups in large osteoarthritis trials) corresponding risk (opioids) -2.5 cm change on 10 cm VAS (41% improvement) estimated difference: -0.7 cm (-0.9 to -0.5)</p> <p>NNT 10 (95% CI 8 to 14) for treatment response (50% improvement in scores) (Absolute response risks for pain in the control groups were assumed 31%) quality assessed by Cochrane Da Costa Bruno: GRADE: HIGH</p> <p>Result for trials > 1 month (N=10) SMD -0.15 (-0.22 to -0.08)</p>
		N= 12 n= 3553 (Breivik 2010, Munera 2010, Kjaersgaard-Andersen 1990, Peloso 2000, langford 2006, Caldwell 2002, Katz 2010, Afilalo 2010, Markenson 2005, Matsumoto 2005, NCT00486811, Kivitz 2006, Matsumoto 2005, Afilalo 2010, NTC 00486811	Function Various validated function scales (median follow-up: 5 weeks)	<p>SMD -0.26 (-0.35 to -0.17)</p> <p>Assumed risk placebo -1.2 units on WOMAC (range 0 to 10) (Median reduction as observed across placebo groups in large osteoarthritis trials) Corresponding risk opioids -1.8 units on WOMAC estimated difference: -0.6 (-0.8 to -0.4)</p> <p>NNT 12 (95% CI 10 to 18)</p>

				<p>(Absolute response risks for function in the control groups were assumed 26%)</p> <p>quality assessed by Cochrane Da Costa Bruno: GRADE: HIGH</p> <p>Result for trials > 1 month (N=6) SMD -0.25 (-0.41 to - 0.09)</p>
		<p>N= 9 n= 4898 (Breivik 2010, Peloso 2000, Langford 2006, Katz 2010, Afilalo 2010, Etropolski 2011, Hartrick 2009, Markenson 2005, Matsumoto 2005, NCT00486811, matsumoto 2005, Afilalo 2010, Etropolski 2011, Hartrick 2009, NCT00486811</p>	<p>Number of participants experiencing any adverse event (median follow-up: 8 weeks)</p>	<p>RR 1.49 (1.35 to 1.63)</p> <p>Assumed risk placebo 150 per 1000 participant-years (Median control risk across placebo groups in large osteoarthritis trials) Corresponding risk opioids 224 per 1000 participant-years (203 to 245)</p> <p>NNH 14 (95% CI 11 to 19)</p> <p>quality assessed by Cochrane Da Costa Bruno: GRADE: MODERATE (downgraded due to suspicion of selective outcome reporting)</p>
		<p>N=19 n=7712 (Breivik 2010, Munera 2010, NCT00531427, Shannon 2005, Kjaersgaard-Andersen 1990, Peloso 2000, Quiding 1992, Langford 2006, NCT00980798, Caldwell 2002, Katz 2010, Afilalo 2010, Chindalore 2005, Etropolski 2011, Friedman 2011, hartrick 2009, Markenson 2005, Matsumoto 2005, NCT00486811, Zautra 2005, Kivitz 2006, Matusmoto 2005, Afilalo 2010, Etropolski 2011, Hartrick 2009,</p>	<p>Number of participants who withdrew because of adverse events (median follow-up: 6 weeks)</p>	<p>RR 3.76 (2.93 to 4.82)</p> <p>Assumed risk placebo 17 per 1000 participantyears (Median control risk across placebo groups in large osteoarthritis trials) Corresponding risk opioids 64 per 1000 participantyears (50 to 82)</p> <p>NNH 21 (95% CI 15 to 30)</p> <p>quality assessed by Cochrane Da Costa Bruno: GRADE: HIGH</p>

		NCT00486811		
		N=3 n=681 Kjaersgaard-Andersen 1990, Langford 2006, Markenson 2005	Number of participants experiencing any serious adverse event (median follow-up: 8 weeks)	RR 3.35 (0.83 to 13.56) Assumed risk placebo 4 per 1000 participantyears (Median control risk across placebo groups in large osteoarthritis trials) Corresponding risk opioids 13 per 1000 participantyears (3 to 54) quality assessed by Cochrane Da Costa Bruno: GRADE: LOW (downgraded due to selective outcome reporting and imprecision)
		N=3 n=1151 Afilalo 2010, Katz 2010, Langford 2006	Withdrawal symptoms (median follow-up: 16 weeks)	OR 2.67 (2.02 to 3.77) Assumed risk placebo 9 per 1000 participantyears (Median risk across control groups in included trials) Corresponding risk opioids 24 per 100 participant-years (18 to 33) NNH 65 (95% CI 42 to 110) quality assessed by Cochrane Da Costa Bruno: GRADE: MODERATE (downgraded due to selection bias) note: 88% of weight derived from 1 trial (Langford 2006)

20.1.2 Oxycodone for chronic pain in osteoarthritis of the knee or hip

Results				
Ref	Comparison	N/n	Outcomes	Result
ref* (26) Design: SR + MA Search date: (aug 2012)	oxycodone vs placebo in knee or hip osteoarthritis	N= 10 n= 2943 (Afilalo 2010, Chindalore 2005, Etropolski 2011, Fidelholtz 2011, Friedmann 2011, Hartrick 2009, Markenson 2005, Matsumoto 2005, NCT00486811, Zautra 2005)	Pain	SMD -0.31 [-0.47, -0.15]
		N= 4 n= 680 (Afilalo 2010, Markenson 2005, Matsumoto 2005, NCT00486811)	Function	SMD -0.30 [-0.58, -0.01]
		N= 6 n=1779 (Afilalo 2010, Etropolski 2011, Hartrick 2009, Markenson 2005, Matsumoto 2005, NCT00486811)	Number of participants experiencing any adverse event	RR 1.69 [1.47, 1.95]
		N=9 n= 2653 (Afilalo 2010, Chindalore 2005, Etropolski 2011, Friedmann 2011, Hartrick 2009, Markenson 2005, Matsumoto 2005, NCT00486811, Zautra 2005)	Number of participants who withdrew because of adverse events.	RR 5.55 [3.47, 8.87]
		N=1 n= 107 (markenson 2005)	Number of participants experiencing any serious adverse event	RR 6.39 [0.34, 120.71]
		N=1 n= NR (Afilalo 2010)	Withdrawal symptoms	OR 2.18 [0.61, 7.81]

20.1.3 Transdermal buprenorphine for chronic pain in osteoarthritis of the knee or hip

Results				
Ref	Comparison	N/n	Outcomes	Result
ref* (26) Design: SR + MA Search date: (aug 2012)	Transdermal buprenorphine versus placebo in knee or hip osteoarthritis	N= 4 n= 1401 (Breivik 2010, Munera 2010, NCT00531427, Shannon 2005)	Pain	SMD - 0.19 [-0.30, -0.09]
		N= 2 n= 501 (Breivik 2010, Munera 2010)	Function	SMD -0.23 [-0.40, -0.05]
		N= 1 n= 199 (Breivik 2010)	Number of participants experiencing any adverse event	RR 1.25 [1.09, 1.42]
		N=4 n= 1407	Number of participants who withdrew because of adverse events	RR 3.10 [1.38, 6.94]

Characteristics of included studies						
Ref + design	n	Population	Duration	Comparison	Results (as reported by Cochrane Da Costa Bruno 2014)	Methodology as assessed by Cochrane Da Costa Bruno 2014
Afilalo 2010 (82) Randomised controlled trial 3-arm parallel group design	1030	<p>Participants with moderate-to-severe joint pain who needed analgesics for at least 3 months and were dissatisfied with their current treatment were eligible (non-opioids or opioids at doses equivalent to morphine 160 mg/day oral))</p> <p>previous opioid use: not reported</p> <p>Mean age: 58 y</p> <p>Analgesics other than study drugs allowed, but it was unclear whether intake was similar between groups</p>	15 w (3 w titration; 12 w treatment)	<p>Oral extended-release tapentadol, 100-250 mg twice daily vs Oral controlled-release oxycodone, 20-50 mg twice daily vs Placebo, twice daily</p>	<p><u>oxycodone</u> pain SMD -0.13 [-0.31, 0.06] function SMD -0.29 [-0.59, 0.01] number of participants with adverse events RR 1.43 [1.26, 1.63] Number of participants who withdrew because of adverse events RR 6.56 [3.66, 11.77] withdrawal symptoms OR 2.18 [0.61, 7.81]</p> <p><u>tapentadol</u> pain SMD -0.30 [-0.48, -0.11] function SMD -0.31 [-0.58, -0.03] number of participants with adverse events RR 1.24 [1.09, 1.42] Number of participants who withdrew because of adverse events RR 2.95 [1.60, 5.43] Withdrawal symptoms OR 0.99 [0.25, 3.97]</p>	<p>ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Low risk ITT: High risk INDUSTRY FUNDING: yes</p> <p>completed study: 48.7% discontinued oxycodone: 64.9% - adverse event 40.6% - lack of efficacy 2.0% discontinued tapentadol: 47.1% - adverse event 17.6% - lack of efficacy 4.3% discontinued placebo: 39.5% - adverse event 6.5% - lack of efficacy 10.3%</p> <p>LOCF</p>
Breivik 2010(85) Randomised controlled	199	Participants with insufficient relief of moderate-to-severe osteoarthritis pain using	28 w (treatment duration 24 w)	Transdermal buprenorphine 7-day patch (Norspan;	<p>reported by da costa Bruno: pain SMD -0.24 [-0.52, 0.04] NS</p>	<p>ALLOCATION CONC: Low risk RANDO: Low risk</p>

trial 2-arm parallel group design		NSAIDs or COXIBs and without previous exposure to opioids were eligible Mean age: 63 y NSAID/COX-II were continued during study rescue medication: paracetamol		BuTrans), 5-20 µg/hour (titrated to adequate pain relief/tolerance) vs Placebo	function -0.24 [-0.53, 0.05] NS Number of participants experiencing any adverse event RR 1.25 [1.09, 1.42] Number of participants who withdrew because of adverse events RR 15.35 [3.77, 62.39]	BLINDING : Low risk but not described as double- dummy ITT: High risk INDUSTRY FUNDING: yes discontinued throughout study BTDS 54% - adverse events 31% - lack of efficacy 7% placebo 34.3% - adverse events 2% lack of efficacy 12% Other methodological remarks. The author of this publication is the editor in chief of the journal in which it was published.
Caldwell 2002 (86) Randomised controlled trial 4-arm parallel group design	295	Participants with prior suboptimal analgesic response to NSAIDs/paracetamol or previous intermittent opioid therapy were eligible washout period of up to seven days No analgesics other than study drugs allowed	4 w	Oral morphine (Avinza), 30 mg once daily in the morning vs Oral morphine (Avinza), 30 mg once daily in the evening vs Oral morphine sulphate (Contin), 15 mg twice daily vs Placebo, twice daily	We do not report these results because the trial duration does not meet the inclusion criteria for our Consensus Conference literature review	ALLOCATION CONC: Unclear risk RANDO: Unclear risk BLINDING : Low risk ITT: High risk INDUSTRY FUNDING: yes

Chindalore 2005 (120) Randomised controlled trial 4-arm parallel group design phase II	362	<p>Participants with moderate to severe hip or knee pain while taking ≥ 1 oral analgesic medication were eligible</p> <p>Patients were excluded for a daily opioid dose equivalent to >20 mg oxycodone for 2 or more days within the previous 4 weeks; administration of an opioid within 72 hours;</p> <p>Analgesics other than study drugs allowed, but it was unclear whether intake was similar between groups</p>	4w (3w treatment)	<p>Oral oxycodone, 10 mg 4 times daily vs Oral oxycodone, 2.5 mg 4 times daily, plus naltrexone 0.001 mg 4 times daily vs Oral oxycodone, 2.5 mg 4 times daily, plus natronex 0.001 mg twice daily vs Placebo, twice daily</p>	We do not report these results because the trial duration does not meet the inclusion criteria for our Consensus Conference literature review	<p>ALLOCATION CONC: unclear risk RANDO: unclear risk BLINDING : low risk ITT: high risk INDUSTRY FUNDING: yes</p> <p>41/52 completed placebo 70/103 completed oxycodone</p>
Etropolski 2011 (121) Randomised controlled trial 4-arm parallel group design	598	<p>Participants with joint disease requiring surgery and insufficient pain relief by stable analgesic regimens were eligible (who step 2 or step 3)</p> <p>A similar percentage of patients across treatment groups reported previous opioid use (33%-40%)</p> <p>Analgesics other than study drugs allowed and intake was similar between groups</p>	8 w (treatment duration 2 weeks)	<p>Oral immediate-release tapentadol, 50 mg 3-6 times daily vs Oral immediate-release tapentadol, 75 mg 3-6 times daily vs Oral immediate-release oxycodone, 10 mg 3-6 times daily vs Placebo, 3-6 times daily</p>	We do not report these results because the trial duration does not meet the inclusion criteria for our Consensus Conference literature review	<p>ALLOCATION CONC: low risk RANDO: low risk BLINDING : low risk ITT: high risk INDUSTRY FUNDING: yes</p>

Fidelholtz 2011 (122) Randomised controlled trial 4-arm parallel group design	NR	Participants with moderate-to-severe osteoarthritis pain of knees or hips were eligible use nonopioids or opioids up to 90 mg/d in morphine equivalents, but this therapy had not provided adequate pain relief, had not been tolerated, or the patient was a candidate for invasive intervention such as total hip or knee replacement. Unclear whether analgesics other than study drugs allowed	unclear outcome assessed at 8 w	Oral oxycodone, 10-40 mg twice daily vs Placebo (tanezumab vs placebo, oxycodone controlled study)	We do not report these results because the trial duration does not meet the duration inclusion criteria for our Consensus Conference literature review	ALLOCATION CONC: unclear RANDO: unclear BLINDING : unclear risk ITT: unclear risk INDUSTRY FUNDING: yes discontinued (16 weeks) oxycodone 136/158 placebo 113/141 major reason: study terminated by sponsor still in study at 8 weeks oxycodone 61/158 38.6% placebo 62/141 44.0%
Friedmann 2011 (92) Randomised controlled trial 2-arm parallel group design enrichment design	412	Participants with moderate-to-severe osteoarthritis pain using NSAIDs or opioids were eligible mean age 58 y Unclear whether analgesics other than study drugs allowed	14 w Treatment duration: 12 weeks	Oral extended-release oxycodone (Remoxy), 5-20 mg twice daily vs Placebo, twice daily tamper-resistant capsule gel form (not on the Belgian market)	pain SMD -0.26 [-0.46, -0.07] Number of participants who withdrew because of adverse events RR 2.01 [1.25, 3.24]	ALLOCATION CONC: unclear risk RANDO: unclear risk BLINDING : unclear risk ITT: high risk INDUSTRY FUNDING: yes discontinued in the open label period: 37%
Hartrick 2009 (123) Randomised	674	Participants with insufficient relief of moderate-to-severe	2 w (treatment duration 1 w)	Oral immediate-release tapentadol, 50 mg	We do not report these results because the trial duration does not meet the inclusion criteria for our Consensus	ALLOCATION CONC: unclear risk RANDO:

controlled trial 4-arm parallel group design		osteoarthritis pain (who step II or higher) who were candidates for joint replacement surgery were eligible mean age 61 y Analgesics other than study drugs allowed, but it was unclear whether intake was similar between groups		every 4-6 hours vs Oral immediate-release tapentadol, 75 mg every 4-6 hours vs Oral oxycodone, 10 mg every 4-6 hours vs Placebo, every 4-6 hours	Conference literature review	low risk BLINDING : unclear risk ITT: high risk INDUSTRY FUNDING: yes discontinued tapentadol 50 17.4% tapentadol 75 25.4% oxycodone 34.9% all mostly due to adverse events placebo 9.9%
Katz 2010 (100) Randomised controlled trial 2-arm parallel group design enriched enrollment	344	Participants with insufficient pain relief with non-opioids analgesics, tramadol, or other opioids at 40-mg morphine equivalent per day were eligible open label run-in titration (n=547)	14 w (treatment duration 12 w)	Oral morphine sulphate and naltrexone hydrochloride (EMBEDA), 20-80 mg twice daily vs Placebo, twice daily	We do not report these results because the pharmaceutical combination does not meet the inclusion criteria for our Consensus Conference literature review	ALLOCATION CONC: low risk RANDO: unclear risk BLINDING : unclear risk ITT: high risk INDUSTRY FUNDING: yes
Kivitz 2006 (124) Randomised controlled trial 4-arm parallel group design	370	Participants with suboptimal analgesic response to NSAIDs/paracetamol or previous opioid therapy were eligible No analgesics other than study drugs allowed	2 w	Oral extended-release oxymorphone, 10 mg twice daily vs Oral extended-release oxymorphone, 40 mg twice daily vs Oral extended-	We do not report these results because the trial duration does not meet the inclusion criteria for our Consensus Conference literature review	ALLOCATION CONC: low risk RANDO: low risk BLINDING : low risk ITT: high risk INDUSTRY FUNDING: yes

				release oxymorphone, 50 mg twice daily vs Placebo, twice daily		
Kjaersgaard- Andersen 1990 (125) Randomised controlled trial 2-arm parallel group design	158	Participants with chronic pain requiring analgesic treatment were eligible	4w	Oral codeine 60 mg plus paracetamol 1000 mg, 3 times daily vs Paracetamol 1000 mg, 3 times daily	We do not report these results because the trial duration does not meet the inclusion criteria for our Consensus Conference literature review	ALLOCATION CONC: unclear risk RANDO: unclear risk BLINDING : low/unclear risk ITT: high risk INDUSTRY FUNDING: no information
Langford 2006 (101) Randomised controlled trial 2-arm parallel group design	416	osteoarthritis of hip or knee moderate-to-severe pain that had been inadequately controlled by weak opioids 1 w pretreatment run-in During study treatment, previously prescribed NSAIDs and simple analgesics were continued, but weak opioids were discontinued All patients had access to paracetamol and metoclopramide°	8 w (treatment duration 6 w)	Transdermal fentanyl (Durogesic), median dosage 25 µg/hour vs Placebo	We do not report these results because the trial duration does not meet the inclusion criteria for our Consensus Conference literature review	ALLOCATION CONC: low risk RANDO: low risk BLINDING : low risk ITT: high risk INDUSTRY FUNDING: yes
Markenson 2005 (126)	109	Participants with moderate- to-severe pain while taking	13 w	Oral oxycodone (OxyContin), 10	Results as reported by Cochrane Da Costa Bruno	ALLOCATION CONC: low risk

Randomised controlled trial 2-arm parallel group design		NSAIDs/paracetamol, with contraindications to NSAID therapy or with previous oral opioid therapy (≤ 6 mg equivalent oxycodone) were eligible mean age 63 y 54% to 65% prior opioid use Analgesics other than study drugs allowed and intake assessed, but it was unclear whether intake was similar		mg twice daily vs Placebo, twice daily	pain SMD -0.43 [-0.82, -0.05] function SMD -0.80 [-1.19, -0.40] Number of participants experiencing any adverse event RR 1.69 [1.31, 2.19] Number of participants who withdrew because of adverse events RR 9.11 [2.24, 37.05] Number of participants experiencing any serious adverse event RR 6.39 [0.34, 120.71]	RANDO: low risk BLINDING : low risk ITT: high risk INDUSTRY FUNDING: yes discontinued oxycodone 58.9% - adverse event 36% - ineffective treatment 16% placebo 74.5% - adverse event 4% - ineffective treatment 67%
Matsumoto 2005 (105) Randomised controlled trial 4-arm parallel group design	491	chronic osteoarthritis (OA) pain Patients must have taken either acetaminophen, a conventional NSAID, a COX-2 inhibitor, or an opioid analgesic for at least 75 of 90 days before the screening visit and must have had a suboptimal response to these agents. Eligible patients entered a 2- to 7-day washout period during which all analgesic medications were discontinued. Mean age: 62 years	4w	Oral extended-release oxymorphone, 20 mg twice daily vs Oral extended-release oxymorphone, 40 mg twice daily vs Oral controlled-release oxycodone, 20 mg twice daily vs Placebo, twice daily	We do not report these results because the trial duration does not meet the inclusion criteria for our Consensus Conference literature review	ALLOCATION CONC: unclear risk RANDO: low risk BLINDING : low risk ITT: high risk INDUSTRY FUNDING: yes

Munera 2010 (106) Randomised controlled trial 2-arm parallel group design	315	Participants with inadequate pain control using NSAIDs were eligible 7 day ibuprofen run-in No analgesics other than study drugs allowed	4w	Transdermal buprenorphine, 5, 10, or 20 µg/hour vs Placebo	We do not report these results because the trial duration does not meet the inclusion criteria for our Consensus Conference literature review	ALLOCATION CONC: unclear risk RANDO: unclear risk BLINDING : low/unclear risk ITT: high risk INDUSTRY FUNDING: yes withdrew due to adverse events BTDS 36/152 (23.7%) placebo 18/163 (11.0%)
NCT00486811 (118, 119) Randomised controlled trial 3-arm parallel group design this study was unpublished at the time of the Cochrane review	987	Participants who were dissatisfied with their prior analgesic therapy were eligible pain requiring analgesic medications (non-opioids or opioids) at the reference joint for ≥3 months. Opioids equivalent to ≤160mg oral morphine/day Mean age: 62 years Prior opioid use <3months before screening in 14.2% to 16.6% of participants concomitant analgesics were prohibited during the study. Neuroleptics, monoamine oxidase inhibitors, serotonin norepinephrine re-uptake	15 w (3 w titration, 12 w maintenance)	Oral extended-release tapentadol, 100-250 mg twice daily vs Oral controlled-release oxycodone, 20-50 mg twice daily vs Placebo, twice daily	Results extracted from Cochrane Da Costa Bruno Oxycodone pain SMD 0.05 [-0.14, 0.23] function SMD -0.05 [-0.31, 0.22] Number of participants experiencing any adverse event RR 1.58 [1.38, 1.81] Number of participants who withdrew because of adverse events RR 4.89 [2.91, 8.22] Tapentadol pain SMD -0.14 [-0.33, 0.04] function SMD 0.0 [-0.24, 0.24] Number of participants experiencing any adverse event RR 1.20 [1.03, 1.40]	assessed by bcfi authors ALLOCATION CONC: low risk RANDO: low risk BLINDING : low risk ITT: no OUTCOME REPORTING: LOCF INDUSTRY FUNDING: yes completed study: 53.3% discontinued oxycodone: 63.6% - adverse event 42.3% - lack of efficacy 3.6% discontinued tapentadol: 41.6% - adverse event 18.8% - lack of efficacy 6.7% discontinued placebo: 34.4% - adverse event 8.3%

		<p>inhibitors, tricyclic antidepressants, anti-epileptics, and anti-parkinsonian medications were not permitted within 14 days prior to screening and during the study.</p> <p>washout of previous analgesics</p> <p>limited use of paracetamol as rescue medication</p>			<p>Number of participants who withdrew because of adverse events RR 2.26 [1.30, 3.93]</p>	<p>- lack of efficacy 12.8%</p> <p>handling missing values: The last observation carried forward (LOCF) approach for missing data in the event of discontinuation was used for primary and secondary end-points, except for WOMAC and responder rates. For the latter, subjects who prematurely discontinued were considered non-responders</p>
<p>NCT00531427 see Da Costa Bruno 2014 (26) Randomised controlled trial 2-arm parallel group design</p>	570	<p>Participants with suboptimal analgesic response to opioids were eligible</p> <p>Mean age: 59 years</p> <p>Analgesics other than study drugs allowed and intake was similar between groups</p>	unclear (treatment duration 12 w)	<p>Transdermal buprenorphine, 10 or 20 µg/hour vs placebo</p>	<p>pain SMD -0.14 [-0.30, 0.02] Number of participants who withdrew because of adverse events RR 1.48 [0.96, 2.29]</p>	<p>ALLOCATION CONC: unclear risk RANDO: unclear risk BLINDING : low/unclear risk ITT: low risk INDUSTRY FUNDING: yes</p> <p>withdrew due to adverse events BTDS 44/282 (15.6%) placebo 30/285 (10.6%)</p>
<p>NCT00980798 see Da Costa Bruno 2014 (26) Randomised controlled</p>	288	<p>Participants with insufficient pain relief using NSAIDs, paracetamol, or a weak opioid were eligible</p> <p>Analgesics other than study drugs allowed, but it was</p>	unclear (treatment duration 16 w)	<p>Oral hydromorphone (OROS), 4-32 mg once daily vs Placebo, once daily</p>	<p>pain SMD 0.04 [-0.19, 0.28] Number of participants who withdrew because of adverse events RR 5.51 [2.54, 11.98]</p>	<p>ALLOCATION CONC: unclear risk RANDO: unclear risk BLINDING : low risk ITT: high risk</p>

trial 2-arm parallel group design note: this study was later published: Vojtassak 2011 (36)		unclear whether intake was similar between groups Mean age: 65 years				INDUSTRY FUNDING: yes
Peloso 2000 (127) Randomised controlled trial 2-arm parallel group design	103	Participants with osteoarthritis symptoms requiring therapy with paracetamol, anti- inflammatory agents or opioids were eligible Mean age: 62 years Analgesics other than study drugs allowed and intake assessed, but it was unclear whether intake was similar between groups	4 w	Oral codeine (Contin), 100 mg twice daily Control intervention Placebo, twice daily	We do not report these results because the trial duration does not meet the inclusion criteria for our Consensus Conference literature review	ALLOCATION CONC: unclear risk RANDO: unclear risk BLINDING : low/unclear risk ITT: high risk INDUSTRY FUNDING: yes
Quiding 1992 (128) Randomised controlled trial 3-arm cross- over design	27	Participants in need of analgesic medication for hip osteoarthritis were eligible Mean age: 53 years No analgesics other than study drugs allowed	1w	Oral codeine 30 mg plus ibuprofen 200 mg, 6 times in 32 hours vs Ibuprofen 200 mg, 6 times in 32 hours	We do not report these results because the trial duration does not meet the inclusion criteria for our Consensus Conference literature review	ALLOCATION CONC: unclear risk RANDO: unclear risk BLINDING : low/unclear risk ITT: unclear risk INDUSTRY FUNDING: no information

Shannon 2005 (129) Randomised controlled trial 2-arm parallel group design	327	Participants with moderate-to-severe pain while taking paracetamol, non-steroidal anti-inflammatory agents or opioids were eligible Mean age: 61 years Analgesics other than study drugs allowed, but it was unclear whether intake was similar between groups	30 w (treatment duration 4 w, open label extension) extracted outcomes at 30 w reported	Transdermal buprenorphine (Butrans), 5, 10 or 20 µg/hour vs Placebo	pain SMD -0.32 [-0.54, -0.10] Number of participants who withdrew because of adverse events RR 7.90 [1.00, 62.47]	ALLOCATION CONC: unclear risk RANDO: unclear risk BLINDING : low/unclear risk ITT: high risk INDUSTRY FUNDING: yes withdrew due to adverse events BTDS 8/164 (4.9%) placebo 1/162 (0.6%)
Zautra 2005 (130) Randomised controlled trial 2-arm parallel group design	107	osteoarthritis moderate to severe pain pain for at least 1 month before day 0 (baseline) or after the patients had discontinued their as-needed opioid; and 2) pain during the week before day 0 with an average score of ≥ 5 (≥ 3 if receiving as-needed opioids) Patients were excluded if taking opioids at an average daily dose of >60 mg of oxycodone equivalent during the month prior to the study Mean age: 63 years Analgesics other than study drugs allowed, but it was	13 w	Oral oxycodone (Oxycontin), 10 mg twice daily vs Placebo, twice daily	results extracted by Cochrane: global pain after 13 weeks pain SMD -0.81 [-1.21, -0.41] Number of participants who withdrew because of adverse events RR 8.91 [2.19, 36.19] (primary outcome of study: coping efficacy/helplessness/pain after 2 weeks)	ALLOCATION CONC: low risk RANDO: unclear risk BLINDING : low/unclear risk ITT: high risk INDUSTRY FUNDING: yes discontinuation oxycodone 59% - lack of efficacy 16% - adverse events 36% placebo 75% - lack of efficacy 67% - adverse events 4%

		unclear whether intake was similar between groups (Stable regimens of acetaminophens, nonsteroidal antiinflammatory drugs (NSAIDs), or oral steroids were allowed; however, rescue medication was not permitted)				
--	--	--	--	--	--	--

20.2 Opioids vs placebo for chronic low back pain. Systematic review Chou 2016 and 2017

Methods
Systematic review: Noninvasive Treatments for Low Back Pain. Comparative effectiveness review(29, 30). <u>Inclusion criteria:</u> systematic reviews of randomized trials of pharmacological treatments (acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs] opioids, skeletal muscle relaxants, benzodiazepines, antidepressants, antiseizure medications, and systemic corticosteroids) and nonpharmacological treatments (psychological therapies, multidisciplinary rehabilitation, spinal manipulation, acupuncture, massage, exercise and related therapies, and various physical modalities) 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. We also included randomized trials that were not in systematic reviews. The quality of included studies was assessed, data were extracted, and results were summarized qualitatively based on the totality of the evidence <u>Search strategy:</u> 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 <u>Assessment of quality of included trials:</u> yes <u>Other methodological remarks:</u> no meta-analysis performed
Remarks
This systematic review discussed results from Cochrane Chaparro 2013(28). It found 4 new RCTs and 1 older RCT that was missed by Cochrane Chaparro 2013. None of these additional RCTs met our inclusion criteria for duration.

20.3 Opioids vs placebo for chronic low back pain. Meta-analysis Abdel Shaheed 2016

Methods
Systematic review/Meta-analysis: Efficacy, Tolerability, and Dose-Dependent Effects of Opioid Analgesics for Low Back Pain A Systematic Review and Meta-analysis (7) <u>Inclusion criteria:</u> Placebo-controlled RCTs in any language; single- ingredient or combination medicines containing an opioid analgesic for nonspecific acute or chronic low back pain. Study selection was not restricted by pain duration, comorbid condition(s), or concurrent nonopioid or nonanalgesic medication use (eg, to treat hypertension) provided that participants were stabilized on these medications and the pattern of use was unchanged throughout the study. Placebo controlled RCTs and RCTs comparing 2 drugs from the same class or different doses of the same drug were eligible for inclusion. Trials were included if they reported pain, disability, or adverse events outcomes. <u>Search strategy:</u> Medline, EMBASE, CENTRAL, CINAHL, and PsycINFO (inception to September 2015) with citation tracking from eligible randomized clinical trials (RCTs) <u>Assessment of quality of included trials:</u> yes, 11-item PEDRO scale <u>Other methodological remarks:</u> - Studies were pooled according to study duration: short(<12 w) vs intermediate (12w) - studies were pooled according to design (enriched enrolment versus no enriched enrolment)
Remarks
Abdel Shaheed 2016(7) is of a later search date than the previously reported Cochrane Chaparro 2013. Abdel Shaheed 2016 analyses the studies according to study duration and reports separately all trials ≥ 12 weeks duration. For this reason, it responds better to our selection criteria for inclusion of trials. No new trials were found by Abdel Shaheed 2016 when compared to Cochrane Chaparro 2013. Chaparro 2013 analyses more outcomes (more trials analysed for disability; also analyses for adverse events) We will report Abdel Shaheed's results for ≥ 12 week studies only.
Author's conclusions
"In people with chronic low back pain, opioid analgesics provide short and/or intermediate pain relief, though the effect is small and not clinically important even at higher doses. Many trial patients stopped taking the medicine because they did not tolerate or respond to the medicine."(7)

Results				
Ref	Comparison	N/n	Outcomes	Result (95% CI) reported by Abdel Shaheed
ref* Abdel Shaheed 2016 (7) Design: SR + MA Search date: (sept 2015)	Opioid vs placebo for low back pain	N= 4 (5 study-arms) n= 1392 (Steiner 2011, Vorsanger 2008, Katz 2007, Hale 2010)	Pain outcome (0 to 100 scale) Intermediate duration (12 weeks) Enrichment design	MD - 7.6 (-11.5 to -3.6)
		N= 2 (6 study-arms) n= 1213 (Webster 2006, Buynak 2010)	Pain outcome (0 to 100 scale) Intermediate duration (12 weeks) Non-enrichment design	MD -9.2 (-12.2 to -6.2)
		N= 6 (10 study-arms) n= 2605 (Steiner 2011, Vorsanger 2008, Katz 2007, Hale 2010, Webster 2006, Buynak 2010)	Pain outcome (0 to 100 scale) Intermediate duration (12 weeks) All study designs	MD -8.1 (-10.2 to -6.0) quality of evidence assessed as HIGH
	opioid (tramadol) + paracetamol vs placebo	N=2 n= (Ruoff 2003) (Peloso 2004)	Pain outcome (0 to 100 scale) Intermediate duration (12 weeks)	MD -11.9 [-19.3, -4.4] quality of evidence assessed by Abdel Shaheed 2016 as MODERATE (downgraded due to publication bias)
		N=1 (Ruoff 2003)	Disability Intermediate duration (12 weeks)	MD -3.7 [-11.8, 4.4] quality of evidence assessed by Abdel Shaheed 2016 as VERY LOW (downgraded for imprecision, inconsistency and publication bias)

Characteristics of included studies						
Ref + design	n	Population	Duration	Comparison	Results (95% CI)	Methodology (assessed by Abdel Shaheed 2016, PEDRO rating)
Buynak 2010 (39) RCT	981 oxycodone 334 placebo 326	<p>Low back pain, ≥ 3 m taking analgesic medications for ≥ 3 months or dissatisfied with their current therapy (non-opioids or opioids at doses equivalent to morphine 160 mg/day oral)</p> <p>prior opioid use (taking opioid analgesics within 3 months of screening) placebo 53.9% tapentadol 56.0% oxycodone 50.3%</p> <p>Neuroleptics, tricyclic antidepressants, anticonvulsants, antiparkinsonian drugs, and serotonin norepinephrine reuptake inhibitors were prohibited within 14 days prior to the screening visit and during the study ; use of monoamine oxidase inhibitors was also prohibited within 14 days prior to the screening visit and during the study.</p> <p>SSRI allowed if stable dose and</p>	15 w (3 w titration, 12w maintenance)	Tapentadol ER 100-250 mg twice daily vs Oxycodone HCl 20-50 mg twice daily vs Placebo	<p><u>Reported by Abdel Shaheed 2016</u> <u>oxycodone vs placebo</u> pain (converted to 0-100) MD -8.9 (-12.8 to - 5.0)</p> <p>constipation TER: 0.3 (88/328) PER: 0.1 (16/319) RR 5.4 ($p < 0.0$)</p> <p>nausea TER: 0.3 (113/328) PER: 0.1 (29/319) RR 3.8 (< 0.0)</p> <p>somnolence TER: 0.2 (53/328) PER: 0.0 (8/319) 6.4 (< 0.0)</p> <p>adverse event rate oxycodone: 84.5% Placebo: 59.6%</p> <p><u>Reported by Buynak 2010</u> mean change in pain intensity from baseline to week 12 LSMD -0.9 [-1.24 to -0.49]; $p < 0.001$; LOCF</p>	<p>ELEGIBILITY CRITERIA SPECIFIED: NO ALLOCATION CONC: NO RANDO: YES BLINDING : YES FOLLOW-UP $\geq 85\%$: NO ITT: NO INDUSTRY FUNDING: YES</p> <p>discontinued early tapentadol 152/321 47.4% - adverse event 15.9% - lack of efficacy 40% oxycodone 195/334 58.4% - adverse event 32.0% - lack of efficacy 2.1% placebo 167/326 51.2% - adverse event 4.6% - lack of efficacy 15.3%</p> <p>dealing with missing values: LOCF sensitivity analyses were performed using other imputation methods. Mostly, for tapentadol, statistically significant differences remained, but the size of the effect was generally smaller. for oxycodone, significant differences remained for some but not all pain score</p>

		<p>not used for pain treatment</p> <p>The use of concomitant analgesics, with the exception of allowed doses of acetaminophen (see Treatment schedule), was prohibited during the study</p> <p>Electrical Nerve Stimulation, acupuncture, physical therapy, packs, massages, and other interventional adjunctive therapy were permitted during the study if patients started the</p>		<p>mean change in pain intensity from baseline over the entire maintenance period LSMD -0.8 [-1.16 to -0.46]; $p < 0.001$; LOCF</p> <p>$\geq 30\%$ improvement oxycodone 30.4% placebo 27.1% $p = 0.365$ NS</p> <p>$\geq 50\%$ improvement oxycodone 23.3% placebo 18.9% $p = 0.174$ NS</p> <p>BPI pain interference LSMD vs pla -0.4 (SE 0.19) $p = 0.023$ LOCF</p> <p>SF-36 physical component summary (0-100? Not reported) LSMD vs pla -2.3 (SE 0.65) < 0.001 LOCF</p> <p>SF-36 mental component summary LSMD vs pla -0.7 (SE 0.69) $p = 0.285$ NS LOCF</p> <p>adverse events (placebo – oxycodone) Constipation (5.0%) (26.8%) Vomiting (1.6%) (19.2%) Nausea (9.1%) (34.5%) Somnolence (2.5%) (16.2%) <u>tapentadol vs placebo</u> see separate table Tapentadol (Santos 2015)</p>	outcomes.
--	--	--	--	--	-----------

Hale 2010(35) RCT enrichment design	294	<p>aged 18–75 years moderate-to-severe low back pain, non-neuropathic or neuropathic opioid tolerant: on daily opioid treatment with ≥ 60 mg oral morphine equivalent (≥ 12 mg hydromorphone), but ≤ 320 mg morphine (≤ 64 mg hydromorphone) per day within 2 months prior to the screening visits.</p> <p>all non-opioid analgesics or drugs with anticipated analgesic effects were discontinued before study entry</p> <p>conversion of current opioid to hydromorphone using 5:1 conversion ratio</p> <p>hydromorphone IR was permitted as rescue medication</p> <p>495 patients entered run-in</p>	12 w (in which placebo group had 2 w tapering from hydromorp hone run- in)	hydromorphone 12 – 64 mg/d vs placebo	<p>NRS (0-10) (results presented by Abdel Shaheed 2016 in a 0-100 scale) MD -9.0 (-13.6 to - 4.4)</p> <p>constipation TER: 0.1 (10/134) PER: 0.0 (5/134) RR 2.0 (p 0.20)</p> <p>nausea TER: 0.1(12/134) PER: 0.1 (10/134) RR 1.2 (p 0.7)</p> <p>somnolence TER: 0.0 (1/134) PER: 0.0 (0/134) RR 3.00 (p 0.50)</p> <p>Adverse event rate hydromorphone: 47.8% placebo: 54.5%</p>	<p>ELEGIBILITY CRITERIA SPECIFIED: NO ALLOCATION CONC: YES RANDO: YES BLINDING : YES FOLLOW-UP $\geq 85\%$: NO ITT: NO INDUSTRY FUNDING: YES</p> <p>discontinued during open label period: 42% (97)</p> <p>discontinued during double blind phase hydromorphone 50.4% placebo 66.9% p<0.05</p> <p>dealing with missing values</p> <p>for patients discontinuing due to opioid withdrawal symptoms, the baseline pain intensity NRS score was carried forward to the final visit; (2) for patients discontinuing due to AEs, the pain intensity NRS score at screening (highest pain intensity) was carried forward to the final visit; and (3) for patients discontinuing due to lack of efficacy or other reasons (e.g., administrative, withdrawal of consent), the last observation was carried</p>
--	-----	---	---	---	---	--

						forward to the final visit.
Katz 2007(131) RCT double blind enrichment design	325	Chronic LBP, mean age 49.8y	12 w	Oxymorphone MR, 39.2 mg/d (mean stabilized dose) vs placebo	not available in Belgium	ELEGIBILITY CRITERIA SPECIFIED: YES ALLOCATION CONC: YES RANDO: YES BLINDING : YES FOLLOW-UP >=85%: NO ITT: NO INDUSTRY FUNDING: YES
Peloso 2004(108) RCT double blind	338	chronic LBP requiring daily medication for > or = 3 months washout of current analgesics mean age 57.5 rescue medication (acetaminophen 500mg, up to 4 tablets daily) Excluded: any sedative hypnotics, shortacting analgesics, topical preparations/medications and anesthetics, or muscle relaxants for a period of less than 5 half- lives of the given medication prior to the double blind phase; use of medications that could reduce the seizure threshold within 3 weeks before the double blind phase; use of opioids or initiation of nutraceuticals within 6 weeks of the double blind phase	91 d	Combination tablet containing tramadol, 36.5 mg + paracetamol, 325 mg (max 8 doses/d) vs placebo (average 150 mg tramadol/d)	PAIN (VAS) (results presented by Abdel Shaheed 2016 in a 0-100 scale) MD -15.5 (-18.8 to -12.2) Constipation TER: 0.1 (17/167) PER: 0.0 (2/169) RR 8.6 (p <0.01) Nausea TER: 0.1 (20/167) PER: 0.0 (3/169) RR 6.7 (p <0.01) dizziness TER: 0.11 (18/167) PER: 0.0 (1/169) RR 18.2 (p<0.01) Somnolence TER: 0.1 (15/167) PER: 0.0 (3/169) RR 5.1 (p <0.0)	ELEGIBILITY CRITERIA SPECIFIED: YES ALLOCATION CONC: YES RANDO: YES BLINDING : YES FOLLOW-UP >=85%: YES ITT: YES INDUSTRY FUNDING: YES

		permitted continuation of physiotherapy started prior to inclusion				
Ruoff 2003(112) RCT double blind	322	<p>Patients with at least moderate lower back pain daily medication was needed for >3 months</p> <p>excluded if they had taken antidepressants, cyclobenzaprine, or antiepileptic drugs for pain, or if they had received transcutaneous electrical nerve stimulation, chiropractic adjustments, or acupuncture within 3 weeks of the double-blind phase</p> <p>Patients were also excluded if they had taken sedative-hypnotics, short-acting analgesics, topical anesthetics, or muscle relaxants for a period of <5 half-lives of the specific medication before the double-blind phase.</p> <p>washout of previous analgesic drugs</p> <p>mean age 53.9</p>	91 d	Combination tablet containing tramadol, 37.5 mg + paracetamol, 325 mg, 1-2 tablets 4 times/d vs placebo	<p>PAIN (VAS) (results presented by Abdel Shaheed 2016 in a 0-100 scale) MD -7.9 (- 12.4 to -3.4)</p> <p>RMDQ (results presented by Abdel Shaheed 2016 in a 0-100 scale?) MD -3.7 (-11.8 to 4.4)</p> <p>Constipation TER: 0.1 (18/161) PER: 0.1 (8/157) RR 2.2 (p 0.1)</p> <p>nausea TER: 0.1(21/161) PER: 0.0(5/157) RR 4.1(p <0.01)</p> <p>dizziness TER: 0.1(12/161) PER: 0.0(3/157) RR 3.9 (p 0.0)</p> <p>somnolence TER: 0.1(13/161) PER: 0.0 (1/157) RR 12.7 (p <0.0)</p> <p>adverse event rate Tramadol/paracetamol 68.9%</p>	<p>ELEGIBILITY CRITERIA SPECIFIED: NO ALLOCATION CONC: YES RANDO: YES BLINDING : YES FOLLOW-UP >=85%: NO ITT: NO INDUSTRY FUNDING: YES</p>

					Placebo 46.5%	
Steiner 2011 (3) RCT double blind enrichment design	541	<p>moderate to severe chronic low back pain (nonmalignant) (defined as ≥ 3 m) taking nonopioid analgesic medications for CLBP no benefit from nonopioid therapy or not tolerating nonopioid therapy</p> <p>all other pain medication stopped at screening</p> <p>rescue medication: acetaminophen max 2g/d and ibuprofen max 800 mg/d</p> <p>open label run-in (n=1024)</p>	84 d	Transdermal buprenorphine, 10 µg/h once weekly vs placebo	See separate table Steiner 2011	<p>ELEGIBILITY CRITERIA SPECIFIED: NO ALLOCATION CONC: YES RANDO: YES BLINDING : YES FOLLOW-UP $\geq 85\%$: NO ITT: NO INDUSTRY FUNDING: YES</p> <p>discontinued during the open label period: 47%</p> <p>See separate table for this RCT</p>
Vorsanger 2008(115) RCT enrichment design	386	<p>adults with VAS Score $\geq 40/100$. CLBP > 6 months. Requiring at least 90 days of NSAIDs, COX-2, opioids or muscle relaxant mean age 47.8 y VAS ≥ 40 mm</p> <p>619 patients in 3 w open label tramadol run-in</p> <p>Study authors did not allow patients to use NSAID corticosteroids, opioids, or other analgesic during the study, with the exception of low-dose aspirin or acetaminophen as described earlier. They also</p>	12 w	Tramadol MR, 300 mg/d, or tramadol MR, 200 mg/d vs placebo	<p>PAIN (VAS) (results presented by Abdel Shaheed 2016 in a 0-100 scale) Tramadol ER 300 mg vs pla MD -6.0 (-12.1 to 0.1) Tramadol ER 200 mg vs pla MD -1.0 (-7.4 to 5.4)</p> <p><u>Tramadol 300 mg vs pla</u> Constipation TER: 0.2 (19/128) PER: 0.0 (1/129) RR 19.2 (p <0.01) nausea TER: 0.2 (25/128) PER: 0.1 (9/129) RR 2.8 (p <0.01) dizziness</p>	<p>ELEGIBILITY CRITERIA SPECIFIED: NO ALLOCATION CONC: YES RANDO: YES BLINDING : YES FOLLOW-UP $\geq 85\%$: NO ITT: NO INDUSTRY FUNDING: YES</p>

		excluded neuroleptic, SSRIs, SNRIs, carbamazepine, or quinidine medications			<p>TER: 0.1 (18/128) PER: 0.1 (12/129) RR 1.5 (p 0.2)</p> <p>adverse event rate 80.6% had adverse events during the run in period</p>	
Webster 2006 (38) double blind RCT	719 oxycodone 206 placebo 101	<p>persistent low back pain for at least 6 months requiring daily analgesics and a baseline pain intensity score of ≥ 5 at screening</p> <p>- 42.6% to 48.1% opioid use in preceding month - only 5% of patients were on high dose opioids (oxycodone equivalent ≥ 20mg/d)</p> <p>washout period of all analgesics except acetaminophen</p>	12 w	<p>Oxycodone + low-dose naltrexone 4 times/d vs oxycodone 4 times/d vs oxycodone + low-dose naltrexone twice a day, vs placebo</p>	<p><u>oxycodone 4x/d vs placebo</u> pain (converted to 0-100)(results from Abdel Shaheed 2016) MD -12.0 (- 18.9 to -5.1) SS</p> <p><u>Results from Webster 2006</u> pain was reported as the percentage change from baseline oxycodone -46% (SD 33.60) placebo -32.2% (SD 38.04) p<0.05</p> <p>function SF-12 physical component reported as significant (p<0.01) but no results shown SF-12 mental component reported as NS</p> <p>number of moderate-to severe opioid related adverse events per patient (oxy vs pla) constipation 0.71 vs 0.28 (p<0.05) somnolence 0.37 vs 0.13 (p<0.05) nausea 0.60 vs 0.21 (p<0.05) vomiting 0.23 vs 0.09 (p<0.05)</p>	<p>ELEGIBILITY CRITERIA SPECIFIED: NO ALLOCATION CONC: YES RANDO: YES BLINDING : YES FOLLOW-UP $\geq 85\%$: NO ITT: NO INDUSTRY FUNDING: YES</p> <p>discontinued oxycodone 105/206 51.0% 7.3% inadequate pain relief 23.8% adverse events</p> <p>placebo 59/101 58.4% 40% inadequate pain relief 5% adverse events</p> <p>handling missing values LOCF</p>

20.4 Opioids vs placebo for chronic low back pain. Meta-analysis Chaparro 2013

Methods

Systematic review/Meta-analysis: Opioids compared to placebo or other treatments for chronic low-back pain (28)

Inclusion criteria:

We included randomized controlled trials (RCTs) that assessed the use of opioids (as monotherapy or in combination with other therapies) in adults with CLBP that were at least four weeks in duration. We included trials that compared non-injectable opioids to placebo or other treatments. We excluded trials that compared different opioids only.

Search strategy:

the Cochrane Back Review Group's Specialized Register, CENTRAL, CINAHL and PsycINFO, MEDLINE, and EMBASE from January 2006 to October 2012; reference lists of these trials and other relevant systematic reviews for potential trials for inclusion.

Assessment of quality of included trials: yes, GRADE

Other methodological remarks:

a difference of 0.2 SD was considered a small effect

a difference of 0.5 SD was considered a moderate effect

Remarks

This Cochrane Review is of an earlier search date than SR Abdel Shaheed 2016(7). Abdel Shaheed 2016 analyses the studies according to study duration and reports separately all trials ≥ 12 weeks duration. For this reason, it responds better to our selection criteria for inclusion of trials.

No new trials were found by Abdel Shaheed 2016 when compared to Cochrane Chaparro 2013.

Chaparro 2013 analyses more outcomes (more trials analysed for disability; also analyses for adverse events)

Chaparro 2013 also reports outcomes for individual opioids. We decided to report these when relevant for our literature review. See chapters on individual opioids in this report for more information.

Author's conclusions

"The included trials in this review had high drop-out rates, were of short duration, and had limited interpretability of functional improvement. They did not report any serious adverse effects, risks (addiction or overdose), or complications (sleep apnea, opioid-induced hyperalgesia, hypogonadism). In general, the effect sizes were medium for pain and small for function....There is some evidence (very low to moderate quality) for short-term efficacy (for both pain and function) of opioids to treat CLBP compared to placebo. The very few trials that compared opioids to non-steroidal anti-inflammatory drugs (NSAIDs) or antidepressants did not show any differences regarding pain and function. The initiation of a trial of opioids for long-term management should be done with extreme caution, especially after a comprehensive assessment of potential risks. There are no placebo-RCTs supporting the effectiveness and safety of long-term opioid therapy for treatment of CLBP." (28)

20.4.1 Strong opioids vs placebo in chronic low back pain

Results				
Ref	Comparison	N/n	Outcomes	Result (95%CI)
ref*Cochrane Chaparro 2013 (28) Design: SR + MA Search date: oct 2012	Strong opioids vs placebo	N= 6 n= 1887 (Buynak 2010, Chu 2012, Hale 2010, Katz 2007, Khoromi 2007, Webster 2006)	mean pain intensity numeric scale lower score = less pain	Std MD -0.43 [-0.52, -0.33] 'The magnitude of this difference is in the range of small to moderate' levels of evidence assessed by Chaparro as MODERATE (downgraded due to attrition bias)
		N= 3 n= 819 (Buynak 2010, Katz 2007, Khoromi 2007)	At least 30% of pain relief	OR 1.91 [1.41, 2.58] illustrative comparative risks placebo 327 per 1000 opioids 481 per 1000 (406 to 556) 'The magnitude of this OR is large' levels of evidence assessed by Chaparro as MODERATE (downgraded due to attrition bias, performance bias)
		N= 4 n= 1375 (Buynak 2010, Chu 2012, Hale 2010, Khoromi 2007)	Disability higher score = more disability various instruments	Std MD -0.26 [-0.37, -0.15] 'The magnitude of this difference is small.' levels of evidence assessed by Chaparro as MODERATE (downgraded due to attrition bias)
	Strong opioids vs placebo	2346 (5 studies) (Buynak 2010, Gordon 2010, Katz 2007, Khoromi 2007, Steiner 2011)	Nausea	RD 12% (5%to 19%) illustrative comparative risks placebo 102 per 1000 opioids 223 per 1000 (151 to 291) levels of evidence assessed by Chaparro as LOW (downgraded due to

				attrition bias, some performance bias, unclear random in 1 trials)
		2346 (5 studies) (Buynak 2010, Gordon 2010, Katz 2007, Khoromi 2007, Steiner 2011)	Constipation	RD 11% (4% to 19%) illustrative comparative risks placebo 36 per 1000 opioids 148 per 1000 (76 to 226) levels of evidence assessed by Chaparro as VERY LOW (downgraded due to attrition bias, low number of events, heterogeneity, some performance bias, unclear random in 1 trials)
		2346 (5 studies) (Buynak 2010, Gordon 2010, Katz 2007, Khoromi 2007, Steiner 2011)	Somnolence	RD 6% (2% to 10%) illustrative comparative risks placebo 25 per 1000 opioids 86 per 1000 (45 to 125) levels of evidence assessed by Chaparro as VERY LOW (downgraded due to attrition bias, low number of events, some performance bias, unclear random in 1 trials)

Characteristics of included studies					
Ref + design	n	Population	Duration	Comparison	Methodology
Buynak 2010 (39) randomized, double-blind, placebo- and active-controlled Phase III study	981	<p>Low back pain, ≥ 3 m taking analgesic medications for ≥ 3 months or dissatisfied with their current therapy (non-opioids or opioids at doses equivalent to morphine 160 mg/day oral)</p> <p>prior opioid use (taking opioid analgesics within 3 months of screening) placebo 53.9% tapentadol 56.0% oxycodone 50.3%</p> <p>Neuroleptics, tricyclic antidepressants, anticonvulsants, antiparkinsonian drugs, and serotonin norepinephrine reuptake inhibitors were prohibited within 14 days prior to the screening visit and during the study ; use of monoamine oxidase inhibitors was also prohibited within 14 days prior to the screening visit and during the study. SSRI allowed if stable dose and not used for pain treatment</p> <p>The use of concomitant analgesics, with the exception of allowed doses of acetaminophen (see Treatment schedule), was prohibited during the study</p> <p>Electrical Nerve Stimulation, acupuncture, physical therapy, packs, massages, and other interventional adjunctive therapy</p>	15 w (3 w titration, 12w maintenance)	Tapentadol ER 100-250 mg twice daily vs Oxycodone HCl 20-50 mg twice daily vs Placebo	<p>(assessment by Abdel Shaheed 2016) ELEGIBILITY CRITERIA SPECIFIED: NO ALLOCATION CONC: NO RANDO: YES BLINDING : YES FOLLOW-UP $\geq 85\%$: NO ITT: NO INDUSTRY FUNDING: YES</p> <p>discontinued early tapentadol 152/321 47.4% -adverse event 15.9% - lack of efficacy 40% oxycodone 195/334 58.4% - adverse event 32.0% - lack of efficacy 2.1% placebo 167/326 51.2% - adverse event 4.6% - lack of efficacy 15.3%</p> <p>dealing with missing values: LOCF</p>

		were permitted during the study if patients started the treatment ≥ 14 days prior to enrollment and continued on the same regimen during the study			
Chu 2012 (87) randomized, double-blind, placebo controlled clinical trial	139	Chronic nonradicular low-back pain Participants were not currently taking opioid pain medication in excess of 30 mg oral morphine equivalents per day study designed to examine hypersensitivity and tolerance	1m	oral sustained release morphine vs placebo	ALLOCATION CONC: Unclear risk RANDO: Unclear risk BLINDING : unclear risk ITT: no INDUSTRY FUNDING: no
Hale 2010 (35) RCT double Blind enrichment design		aged 18–75 years moderate-to-severe low back pain, non-neuropathic or neuropathic opioid tolerant: on daily opioid treatment with ≥ 60 mg oral morphine equivalent (≥ 12 mg hydromorphone), but ≤ 320 mg morphine (≤ 64 mg hydromorphone) per day within 2 months prior to the screening visits. all non-opioid analgesics or drugs with anticipated analgesic effects were discontinued before study entry conversion of current opioid to hydromorphone using 5:1 conversion ratio hydromorphone IR was permitted as rescue medication 495 patients entered run-in	12 w (in which placebo group had 2 w tapering from hydromorphone run-in)	hydromorphone 12 – 64 mg/d vs placebo	(assessment by Abdel Shaheed 2016) ELEGIBILITY CRITERIA SPECIFIED: NO ALLOCATION CONC: YES RANDO: YES BLINDING : YES FOLLOW-UP $\geq 85\%$: NO ITT: NO INDUSTRY FUNDING: YES discontinued during open label period: 42% (97) discontinued during double blind phase hydromorphone 50.4% placebo 66.9% $p < 0.05$ dealing with missing values

					for patients discontinuing due to opioid withdrawal symptoms, the baseline pain intensity NRS score was carried forward to the final visit; (2) for patients discontinuing due to AEs, the pain intensity NRS score at screening (highest pain intensity) was carried forward to the final visit; and (3) for patients discontinuing due to lack of efficacy or other reasons (e.g., administrative, withdrawal of consent), the last observation was carried forward to the final visit.
Katz 2007(131) RCT double blind enrichment design	325	Chronic LBP, mean age 49.8y	12 w	Oxymorphone MR, 39.2 mg/d (mean stabilized dose) vs placebo	(assessment by Abdel Shaheed 2016) ELEGIBILITY CRITERIA SPECIFIED: YES ALLOCATION CONC: YES RANDO: YES BLINDING : YES FOLLOW-UP >=85%: NO ITT: NO INDUSTRY FUNDING: YES
Khoromi 2007 cross over	55	Chronic sciatica Opioids and antidepressants were not allowed. NSAIDs and acetaminophen were used as rescue medications	9 w	BID ER morphine (15 to 90 mg; mean 62 mg), nortriptyline (25 to 100 mg; mean 84 mg), their combination (morphine 49 mg and NT 55 mg) or benztropine-active placebo (0.25 to 1 mg);	assessed by Chaparro 2013 RANDO low risk ALLOCATION CONC low risk BLINDING low/unclear risk INCOMPLETE OUTCOME DATA- drop outs - high risk
Webster 2006 (38) RCT double blind	719	persistent low back pain for at least 6 months requiring daily analgesics washout period of all analgesics except acetaminophen	12 w	Oxycodone + low-dose naltrexone 4 times/d vs oxycodone 4 times/d vs oxycodone + low-dose	(assessment by Abdel Shaheed 2016) ELEGIBILITY CRITERIA SPECIFIED: NO ALLOCATION CONC: YES RANDO: YES BLINDING : YES FOLLOW-UP >=85%: NO

				naltrexone twice a day, vs placebo	ITT: NO INDUSTRY FUNDING: YES
Steiner 2011 (3) RCT double blind enrichment design	541	moderate to severe chronic low back pain (nonmalignant) (defined as ≥ 3 m) taking nonopioid analgesic medications for CLBP no benefit form nonopioid therapy or not tolerating nonopioid therapy all other pain medication stopped at screening rescue medication: acetaminophen max 2g/d and ibuprofen max 800 mg/d open label run-in (n=1024)	84 d	Transdermal buprenorphine, 10 μ g/h once weekly vs placebo	(assessment by Abdel Shaheed 2016) ELEGIBILITY CRITERIA SPECIFIED: NO ALLOCATION CONC: YES RANDO: YES BLINDING : YES FOLLOW-UP $\geq 85\%$: NO ITT: NO INDUSTRY FUNDING: YES discontinued during the open label period: 47% See separate table for this RCT

20.4.2 Tramadol vs placebo in chronic low back pain

Results				
Ref	Comparison	N/n	Outcomes	Result (95%CI)
ref*Cochrane Chaparro 2013 (28) Design: SR + MA Search date: oct 2012	Tramadol vs placebo	N= 5 n= 1378 (Peloso 2004, Ruoff 2003, Schnitzer 2000, Uberall 2012, Vorsanger 2008)	Pain intensity (higher = worse)	Standardised mean difference -0.55 [-0.66, -0.44] SS high heterogeneity I ² 86% (Uberall deviates most towards no effect, Peloso deviates most to higher effect) GRADE assessed by Chaparro as LOW (attrition bias, possible performance and detection bias, heterogeneity, effect size crosses 0.5)
		N= 5 n= 1348 (Peloso 2004, Ruoff 2003, Schnitzer 2000, Uberall 2012, Vorsanger 2008)	Disability (higher = worse)	Standardised mean difference -0.18 [-0.29, -0.07] SS GRADE assessed by Chaparro as MODERATE (attrition bias, possible performance and detection bias)
		N= 5 n= 1401 (Peloso 2004, Ruoff 2003, Schnitzer 2000, Uberall 2012, Vorsanger 2008)	Nausea	Risk difference 0.09 [0.05, 0.13] SS
		N= 5 n= 1102 (Peloso 2004, Ruoff 2003, Schnitzer 2000, Uberall 2012, Vorsanger 2008)	Constipation	Risk difference 0.05 [0.02, 0.09] SS
		N=3 n=911 (Peloso 2004, Ruoff 2003, Vorsanger 2008)	Somnolence	0.06 [-0.01, 0.13] NS Heterogeneity: Vorsanger (no effect) differs from Ruoff and Peloso (more somnolence with tramadol)

Characteristics of included studies					
Ref + design	n	Population	Duration	Comparison	Methodology (assessed by Chaparro 2013)
Peloso 2004(108) RCT double blind	338	<p>chronic LBP requiring daily medication for > or = 3 months</p> <p>washout of current analgesics</p> <p>mean age 57.5</p> <p>rescue medication (acetaminophen 500mg, up to 4 tablets daily)</p> <p>Excluded: any sedative hypnotics, shortacting analgesics, topical preparations/medications and anesthetics, or muscle relaxants for a period of less than 5 half-lives of the given medication prior to the double blind phase; use of medications that could reduce the seizure threshold within 3 weeks before the double blind phase; use of opioids or initiation of nutraceuticals within 6 weeks of the double blind phase</p> <p>permitted continuation of physiotherapy started prior to inclusion</p>	91 d	<p>Combination tablet containing tramadol, 36.5 mg + paracetamol, 325 mg (max 8 doses/d) vs placebo</p> <p>(average 150 mg tramadol/d)</p>	<p>ALLOCATION CONC: unclear</p> <p>RANDO: unclear</p> <p>BLINDING : Participants low risk personnel low risk assessors unclear risk</p> <p>INCOMPLETE OUTCOME DATA high risk (drop out >20% in each group: 48% in tramadol/acetaminophen and 64% placebo)</p> <p>ITT yes</p> <p>SELECTIVE REPORTING unclear risk</p> <p>INFLUENCE OF CO-INTERVENTIONS low risk (only rescue med allowed)</p>
Ruoff 2003(112) RCT double blind	322	<p>Patients with at least moderate lower back pain; daily medication was needed for >3 months</p> <p>excluded if they had taken antidepressants, cyclobenzaprine, or antiepileptic drugs for pain, or if they had received transcutaneous electrical nerve stimulation, chiropractic</p>	91 d	<p>Combination tablet containing tramadol, 37.5 mg + paracetamol, 325 mg, 1-2 tablets 4 times/d vs placebo</p> <p>(average 150 mg tramadol/d)</p>	<p>ALLOCATION CONCEALMENT unclear risk</p> <p>RANDO low risk</p> <p>BLINDING patients low risk providers low risk assessors unclear risk</p> <p>INCOMPLETE OUTCOME DATA</p>

		<p>adjustments, or acupuncture within 3 weeks of the double-blind phase</p> <p>Patients were also excluded if they had taken sedative-hypnotics, short-acting analgesics, topical anesthetics, or muscle relaxants for a period of <5 half-lives of the specific medication before the double-blind phase.</p> <p>washout of previous analgesic drugs</p> <p>mean age 53.9</p>			<p>high risk</p> <p>% drop-out exceeded 20% in each group:</p> <p>71/162 (43%) in the tramadol/APAP and 86/160 (53%) in the placebo group</p> <p>ITT yes</p> <p>SELECTIVE REPORTING unclear risk</p> <p>INFLUENCE OF CO-INTERVENTIONS unclear risk</p>
Schnitzer 2000 randomized, double-blind, control trial (enrichment design)	254	<p>patients with CLBP severe enough to require medications for greater than 3 months</p> <p>open label tramadol run-in: 380 patients</p> <p>“Patients were told to maintain a constant level of exercise throughout the study. Physiotherapy started before entrance into the open label/run-in phase was continued throughout both the open label and double blind phases of the study. Physiotherapy could not be initiated during the open label or double blind phases of the study”</p>	4 w	<p>Tramadol 50 mg, max 8/d vs placebo</p> <p>(average 242 mg/d)</p>	<p>ALLOCATION CONCEALMENT unclear risk</p> <p>RANDO low risk</p> <p>BLINDING patients low risk providers low risk assessors unclear risk</p> <p>INCOMPLETE OUTCOME DATA high risk</p> <p>% drop-out >20% in each group: 36/127 (28.3%) in the tramadol group, 72/127 (56.7%) in the placebo group</p> <p>SS more patients discontinued in the placebo group due to inadequate pain relief</p> <p>ITT yes</p> <p>SELECTIVE REPORTING unclear risk</p> <p>INFLUENCE OF CO-INTERVENTIONS low risk</p>
Vorsanger 2008(115) RCT enrichment design	386	<p>adults with VAS Score $\geq 40/100$. CLBP > 6months. Requiring at least 90 days of NSAIDs, COX-2, opioids or muscle relaxant</p> <p>mean age 47.8 y</p> <p>VAS ≥ 40 mm</p>	12 w	<p>Tramadol ER 300 mg/d, VS tramadol ER 200 mg/d vs placebo</p>	<p>ALLOCATION CONCEALMENT unclear risk</p> <p>RANDO low risk</p> <p>BLINDING patients low risk</p>

		<p>619 patients in 3 w open label tramadol run-in</p> <p>Study authors did not allow patients to use NSAID corticosteroids, opioids, or other analgesic during the study, with the exception of low-dose aspirin or acetaminophen as described earlier. They also excluded neuroleptic, SSRIs, SNRIs, carbamazepine, or quinidine medications</p>			<p>personnel unclear risk assessors unclear risk INCOMPLETE OUTCOME DATA high risk % drop-out > 20% in each group: 42/128 (32%) in high dose tramadol, 61/129 (47%) in placebo group ITT modified itt SELECTIVE REPORTING unclear risk INFLUENCE OF CO-INTERVENTIONS low risk</p> <p>discontinued during open label period: 38% (97)</p>
<p>Uberall 2012 Randomized, double-blind, placebo-controlled, and active-controlled study.</p>		<p>Adults aged 18 to 75 years, with LBP > 3 months. Patients who were taking analgesics for LBP but the treatment was not satisfactory, reporting at least moderate pain (> 3/10)</p> <p>washout 1 week</p> <p>rescue medication: diclofenac</p> <p>Uberall 2012 used tramadol as the active control arm and evaluated the efficacy of flupirtine</p>	4w	<p>Flupirtine 400 mg once daily vs tramadol 200 mg once daily vs placebo</p>	<p>ALLOCATION CONCEALMENT unclear risk RANDO patients low risk providers unclear risk assessors unclear risk BLINDING INCOMPLETE OUTCOME DATA high risk % drop-out > 20% in each group: 33/118 (27%) in the tramadol group, 28/123 (22%) in the flupirtine group and 26/122 (21%) in the placebo group ITT yes SELECTIVE REPORTING low risk INFLUENCE OF CO-INTERVENTIONS low risk</p>

21 Appendix. Evidence tables. Individual opioids versus placebo for chronic non-cancer pain

21.1 Tramadol (+/-paracetamol) vs placebo for chronic pain in osteoarthritis

Methods
Systematic review/Meta-analysis: Cochrane Review -Tramadol for osteoarthritis (27) <u>Inclusion criteria:</u> randomized controlled trials (RCTs) that evaluated the effect of tramadol or tramadol plus paracetamol on pain levels and/or physical function in people with osteoarthritis <u>Search strategy:</u> Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and LILACS databases up to August 2005 <u>Assessment of quality of included trials:</u> yes <u>Other methodological remarks:</u> <ul style="list-style-type: none">- studies comparing tramadol to placebo and tramadol/paracetamol to placebo were analysed together- follow-up ranged from 10 days to 91 days. Trials were analysed together. A separate analysis exists for long duration trials only (> =8 w).
Remarks
<ul style="list-style-type: none">- Pooling of studies with tramadol only and tramadol + paracetamol, as well as including studies with a very short duration limits the applicability of these results.- Previous analgesic treatment not reported by Cepeda 2006 for most studies.- this Cochrane review also included studies comparing tramadol to active control. None of the included studies met our inclusion criteria for study duration.
Author's conclusions
<i>"Tramadol or tramadol/paracetamol decreases pain intensity, produces symptom relief and improves function, but these benefits are small. Adverse events, although reversible and not life threatening, often cause participants to stop taking the medication and could limit tramadol or tramadol plus paracetamol usefulness." (27)</i>

Results				
Ref	Comparison	N/n	Outcomes	Result (95% CI)
ref (27) Design: SR/MA Search date: (aug 2005)	tramadol or tramadol/paracetamol vs placebo	N=3 n=645 (Babul 2004, Emkey 2004, Malonne 2004) (tr and tr/pctm)	Pain intensity (all study durations) 0-100 scale	MD -8.47 (95%CI -12.05 to -4.90) SS
		N= 2 n= 553 (Babul 2004, Emkey 2004)	Pain intensity (long duration studies only: >=8w) 0-100 scale	MD -9.06 (-13.68, -4.44) SS
		N=4 n=836 (Emkey 2004, Fleischman 2001, Malonne 2004, Silverfield 2002)	Proportion of subjects with at least moderate (>=50%*) improvement (all study durations) *defined by the Cochrane authors	RR 1.37 (95% CI 1.2 to 1.5) SS NNT = 6; 95% CI 4 to 9
		N= 2 n= 436 (Emkey 2004, Fleischman 2001)	Proportion of subjects with at least moderate (>=50%) improvement (long duration studies only: >=8w)	RR 1.36 (1.05, 1.75) SS
		N=4 n=990 (Babul 2004, Emkey 2004, Fleischmann 2001, Silverfield 2002) t rand tr/pctm	WOMAC index score (0-10 scale) (pain –stiffness-physical function)	MD -0.34 (95%CI -0.49 to -0.19) SS

		<p>N= 4 n=953 (Babul 2004, Emkey 2004, Malonne 2004, Silverfield 2002)</p>	<p>Proportion of subjects with minor adverse events (all study durations)</p>	<p>RR 2.17 [1.77, 2.66] SS</p>
		<p>N= 7 n=1338 (Babul 2004, Bianchi 2003, Emkey 2004, Fleischmann 2001, malonne 2004, Schnitzer 1999, Silverfield 2002)</p>	<p>Proportion of subjects with Major adverse events, or: Discontinuation due to adverse events (all study durations) <i>(“We defined major adverse effects as events of sufficient severity to cause participants to stop taking the medication”)</i></p>	<p>RR 2.67 [1.96, 3.63] <i>NNH= 8 (95% CI 7 to 12)</i></p>

Characteristics of included studies						
Ref + design	n	Population	Duration	Comparison	Results (reported by Cepeda 2006)	Methodology (assessed by Cepeda 2006)
Babul 2004 (132) Parallel Multicenter Double blind RCT	246	Participants at least 18 years old with OA of knee Participants met the American College of Rheumatology (ACR) diagnostic criteria; treatment with acet-aminophen, COX-2 inhibitors, NSAIDs, tramadol, or opioid analgesics for at least 75 of 90 days prior to the study washout of all analgesics no rescue medication permitted (paracetamol for other pain than osteoarthritis limited use only)	84 days	Tramadol extended-release (ER) 100 mg twice daily, up to 400 mg/d vs placebo	Pain intensity (0-100 point scale) MD -12.70 [-20.17, -5.23] Withdrawals due to adverse events: 33 of 124 in tramadol group; 9 of 122 in placebo group	ALLOCATION CONC: NO RANDO: YES BLINDING : YES GROUPS SIMILAR: YES ITT: YES <20% LOST: NO withdrawn before end of study tramadol 63/124 (50.8%) placebo 59/122 (48.4%) dealing with missing values: unclear
Fleischman 2001 (90) Parallel Multicenter Double blind RCT	129	Participants with radiologically confirmed diagnosis of OA of knee, NSAID≥3 m before study entry excluded: recent intraarticular corticosteroids or hyaluronic acid; oral steroids or glucosamine washout of all NSAID	91 days	tramadol 50-mg increments up to 400mg/day if needed vs placebo	Proportion of subjects with at least moderate improvement RR 1.61 [1.00, 2.59] Withdrawals due to adverse events: 14 of 63 in tramadol group; 10 of 66 in placebo group	ALLOCATION CONC: NO RANDO: yes BLINDING : YES GROUPS SIMILAR: YES ITT: NO <20% LOST: YES discontinued before end of study tramadol 68.3% placebo 74.2%) dealing with missing values:

		no rescue medication permitted				unclear (LOCF?)
Emkey 2004 (89) Parallel Multicenter Double blind RCT	307	<p>Participants with more than one year of OA of hip or knee, receiving cox-II inhibitor and inadequate pain relief</p> <p>washout of all non cox-II analgesics</p> <p>excluded if antidepressants, cyclobenzaprine, or antiepileptic drugs for pain SSRI for depression permitted to continue. Also excluded: recent use of sedative hypnotics, short-acting analgesics, topical medications and anesthetics, and/or muscle relaxants, intraarticular injections of corticosteroids, hyaluronan injections, physical therapy</p>	91 days	<p>Tramadol (37.5 mg) plus paracetamol (325 mg) vs placebo</p> <p>Dose was increased up to 4 tablets/day on Day 10 and afterwards up to 8 tablets/day if needed</p> <p>Participants in both groups received COX-2 selective analgesics</p>	<p>Pain intensity (0-100 point scale) -6.80 [-12.68, -0.92]</p> <p>Proportion of subjects with at least moderate improvement 1.24 [0.92, 1.67]</p> <p>Withdrawals due to adverse events: 20 of 153 in tramadol group; 6 of 154 in placebo group</p>	<p>ALLOCATION CONC: NO RANDO: NO BLINDING : YES GROUPS SIMILAR: YES ITT: YES <20% LOST: YES</p> <p>discontinued before end of study tramadol/pctm 41/153 (26.8%) placebo 39/153 (25.5%) dealing with missing values: LOCF</p>
Bianchi 2003 (133)	20	Adult participants with OA of knee	7d	tramadol vs paracetamol		<p>ALLOCATION CONC: NO RANDO: YES BLINDING : YES GROUPS SIMILAR: YES ITT: YES <20% LOST: YES</p>
Malonne 2004 (134)	92	Adult participants between 45 and 80 years old with OA of hip or knee	14 d	tramadol vs placebo		<p>ALLOCATION CONC: NO RANDO: YES BLINDING : YES GROUPS SIMILAR: YES</p>

						ITT: NO <20% LOST: YES
Schnitzer 1999 (135)	nr	Adult participants with symptomatic OA of knee	8 w	tramadol vs placebo (+ naproxen in both groups)		ALLOCATION CONC: NO RANDO: NO BLINDING : YES GROUPS SIMILAR: YES ITT: NO <20% LOST: YES
Silverfield 2002 (136)	308	Adult participants between 35 and 75 years old with symptomatic OA of hip or knee	10 d	tramadol + paracetamol vs placebo		ALLOCATION CONC: YES RANDO: YES BLINDING : YES GROUPS SIMILAR: YES YES ITT: YES <20% LOST: YES

21.2 Tramadol vs placebo for chronic low back pain

See 'Characteristics of included studies' Busse 2017, Chaparro 2013, Abdel Shaheed 2016

21.3 Buprenorphine vs placebo for chronic non-cancer pain: Systematic review Ayer 2017

Methods
<p>Systematic review: Treatment of Chronic Pain With Various Buprenorphine Formulations: A Systematic Review of Clinical Studies (137)</p> <p>No meta-analysis performed</p> <p><u>Inclusion criteria:</u></p> <p>RCTs, comparison of buprenorphine against an active analgesic or placebo for treatment of chronic pain (duration of at least 3 months)</p> <p><u>Search strategy:</u> MEDLINE In-Process & Other Non-Indexed Citations (all using the OvidSP Platform); Cochrane Database of Systematic Reviews; PROSPERO; and Cochrane Central Register of Controlled Trials for potential reviews or trials, respectively, that may have been published but missed during the initial search on MEDLINE and EMBASE; www.clinicaltrials.gov</p> <p><u>Assessment of quality of included trials:</u> yes</p>

Remarks
<p>No studies comparing sublingual buprenorphine to placebo or non-opioid treatments were found by Ayer.</p> <p>Only 4 publication comparing buprenorphine to placebo in chronic noncancer pain (and non-neuropathic pain) met our criteria for study duration. Of these, 2 had a low number of participants. 1 study was a post-hoc publication.</p> <p>After exclusion, only 1 trial comparing buprenorphine to placebo was selected for our review: Steiner 2011 (3). See further chapter for full evidence table.</p> <p>For information on buprenorphine in neuropathic pain and cancer pain, see other chapters</p>

Information retrieved from supplementary appendix Ayer 2017 (137)									
Studies comparing buprenorphine transdermal versus placebo									
Author	Year	Subjects	Study Duration	N	Buprenorphine Dose	Comparator	Scale	Mean/Median Pain Score (when calculated)	Outcome and Results
Steiner <i>et al</i> ²³	2011	Moderate to severe low back pain persisting for a minimum of three months	12 weeks	541	10 or 20 µg /h	Placebo	11-point scale (0=no pain, 10= "pain as bad as you can imagine")	Mean pain score in buprenorphine group 6.9 ± 1.21; placebo group: 6.8 ± 1.26	Patients receiving buprenorphine transdermal patch reported statistically significantly lower pain scores compared to placebo (p=0.010)

21.4 Buprenorphine vs placebo for chronic pain in osteoarthritis

See higher under da Costa Bruno 2014

21.5 Buprenorphine vs placebo for chronic low back pain. RCT Steiner 2011

Study details	n/Population	Comparison	Outcomes		Methodological
Ref(3) Steiner 2011 Design: RCT DB PG enriched enrollment	open label run-in n= 1024 randomised n= 541 (53%) Mean age: 49.4y screening mean pain score BTDS 7.2+/-1.26 placebo 7.2+/- 1.22	Run-in phase: 27 d open label run-in with 7 day BTSD 10µg/20µg then: BTDS 5 for 3 d, BTDS 10 for 10+/- 2 d, if analgesic response too little: BTDS 20 10+/-2 d if not tolerant or insufficient analgesic response: not randomised No additional analgesics were permitted during run-in period <u>randomized</u> <u>treatment</u> 84 d 10 or 20 µg/hour in a <u>7-day</u> transdermal patch Vs	<u>Efficacy</u> average pain over the last 24 hours (11 point scale) (0 = no pain, 10 = pain as bad as you can imagine) (PO) Sleep disturbance (Medical Outcomes Study subscale) at weeks 4, 8 and 12 (mixed effect repeated- measure general linear model) (higher= worse) (range not reported. Probably converted to 0- 100) (SO) Mean daily number of tablets of supplemental analgesic medication from Weeks 2 through 12 (only patients who took at least 1 dose; n=317) (SO) Responder analysis: improvement in pain scores of >=30% (SO)	BTDS: LSM 3.81+/- 0.166 Placebo: LSM 4.39 +/-0.152 LSMD = -0.58 (-1.02 to -0.14) (P = 0.0104) SS in favour of BTDS BTDS: LSM 35.1 Placebo: LSM 39.5 LSMD -4.4 (-7.5 to -1.3) (P = 0.0062) SS in favor of BTDS BTDS: LSM 0.620 Placebo: LSM 0.743 LSMD -0.124 (-0.296 to 0.048) NS discontinuations classified as non- responders BTDS: 53% Placebo: 46% P = 0.1075 discontinuations hybrid imputation (primary analysis) BTDS 64%	RANDO: unclear ALLOCATION CONC: unclear BLINDING : Participants: yes Personnel: yes Assessors: unclear FOLLOW-UP: Lost-to follow-up: <1% Drop-out and Exclusions: 66 % completed BTDS discontinued due to adverse event: 16% lack of therapeutic effect 9% other 9% 70 % completed placebo discontinued due to adverse event 7% lack of therapeutic effect 13% other: 10% drop out in open label run-in: 47% Adverse event 23% Lack of therapeutic effect 14% Other 10% HANDLING DROP OUTS hybrid baseline observation carried forward (BOCF)/last observation carried forward (LOCF) imputation method, depending on
Duration of follow-up: 12 weeks	Previous/current pain treatment: ibuprofen (244 patients, 45%), acetaminophen (144 patients, 27%), naproxen sodium (75 patients, 14%), and hydrocodone/ acetaminophen (53 patients, 10%) No information on adjuvant treatment or non-drug treatments <u>Inclusion</u> - moderate to severe chronic low back pain (nonmalignant) (defined as >= 3 m)				

<p>- “average pain over the past 14 days” score of 5 or more on an 11-point numerical rating scale</p> <p>- >=18y</p> <p>- opioid naïve (no history of 5 mg daily oxycodone or equivalent in the 3 months prior to screening, <5mg oxycodone or equivalent in 14 days prior to screening)</p> <p>- no benefit from nonopioid therapy or not tolerating nonopioid therapy</p> <p><u>Exclusion</u></p> <p>radicular symptoms, acute spinal cord compression, acute compression fracture, seronegative spondyloarthropathy, acute nerve root compression, cauda equina compression, fibromyalgia, reflex sympathetic dystrophy or causalgia (complex regional pain syndrome), diabetic amyotrophy, meningitis, discitis, gout, pseudogout, psoriatic arthritis, active Lyme</p>	<p>placebo</p>		<p>placebo 53%</p> <p>P = 0.0157</p>	<p>the specific reason for dropout: The screening mean pain was carried forward for discontinuations caused by AEs (BOCF), and the last nonmissing observation (LOCF) was carried forward for discontinuations caused by other reasons</p> <p>ITT?</p> <p>full analysis population, which consisted of all patients who were randomized and received at least one dose of double-blind study drug safety population (all patients who received BTDS and had at least one safety assessment during the open-label period randomized safety population (n=539 all patients from the full analysis population who had at least one safety assessment during the doubleblind phase).</p> <p>SELECTIVE REPORTING: no</p> <p>Other important methodological remarks</p> <p>- enriched enrollment design</p> <p>- several sensitivity analyses performed</p> <p>- disability, physical and mental health measured but no statistical analysis</p> <p>Sponsor: Purdue Pharma L.P.</p>	
	<p><u>rescue medication</u></p> <p>sponsor-provided immediate-release oxycodone 5 mg capsules, up to 10 mg/day the first six days of the double-blind phase (to counteract possible withdrawal symptoms in placebo group).</p>	<p>other pain/function/QOL outcomes</p> <p>(exploratory)</p>	<p>PGI (patient global impression of change) %</p> <p>much improved or very much improved</p> <p>BTDS 61%</p> <p>placebo 42%</p> <p>p<0.001 post hoc analysis</p> <p>ODI (Oswestry Disability Index)(0-50, higher=worse)</p> <p>BTDS 19.1 (n=166)</p> <p>placebo 24.8 (n=197)</p> <p>BPI-severity (higher=worse)</p> <p>Scale range not reported</p> <p>BTDS 2.4 (n=166)</p> <p>placebo 3.5 (n=196)</p> <p>BPI-interference (higher=worse)</p> <p>BTDS 2.0 (n=166)</p> <p>placebo 2.9 (n=196)</p> <p>SF-36 physical health (higher=better)</p> <p>Scale range not reported</p> <p>BTDS 43.2 (n=166)</p> <p>placebo 39.5 (n=196)</p> <p>SF-36 mental health (higher = better)</p> <p>BTDS 51.8 (n=166)</p> <p>placebo 48.4 (n=196)</p> <p>no statistical test (described as ‘better with BTDS’)</p>		
	<p>acetaminophen max 2g/d and ibuprofen max 800 mg/d for Weeks 2 - 12</p>				
	<p><u>Use of other pain treatment:</u></p> <p>All nonopioid analgesics, other medications, or opioids taken at doses of <5 mg oxycodone (or equivalent) per day that were</p>				
		<p>Safety</p>			
		<p>Total adverse events</p>	<p>run in period (n= 1024)</p>		

	<p>disease, rheumatoid arthritis or other inflammatory arthritis, trochanteric bursitis, ischial tuberosity bursitis, neuropathic conditions, or back pain caused by secondary infection, tumor, or postherpetic neuralgia; surgery to treat their back pain within six months of screening or had planned to have such surgery during the study conduct period; QTc value of <480 milliseconds and eukalemic</p> <p>all previous analgesics stopped at screening for duration of study</p>	<p>specifically being used for chronic pain were stopped at screening for the duration of the study</p> <p>Adjunct stable therapies for back pain, such as physical therapy, biofeedback therapy, acupuncture, or herbal remedies were allowed if initiated at least 14 days prior to study entry.</p> <p>antidepressants and anticonvulsants for uses other than pain treatment were allowed</p>		<p>BTDS 55%</p> <p>randomised period (n=539)</p> <p>BTDS 55%</p> <p>Placebo 52%</p> <p>NT</p>	
			gastro-intestinal (nausea, vomiting, constipation, other)	<p>run in period (n= 1024)</p> <p>BTDS 31%</p> <p>randomised period (n=539)</p> <p>BTDS 21%</p> <p>Placebo 16%</p> <p>NT</p>	
			Nausea	<p>run in period (n= 1024)</p> <p>BTDS 23%</p> <p>randomised period (n=539)</p> <p>BTDS 13%</p> <p>Placebo 11%</p> <p>NT</p>	
			Constipation	<p>run in period (n= 1024)</p> <p>BTDS 7%</p> <p>randomised period (n=539)</p> <p>BTDS 4%</p> <p>Placebo 1%</p> <p>NT</p>	
			Administration site conditions	<p>run in period (n= 1024)</p> <p>BTDS 17%</p> <p>randomised period (n=539)</p> <p>BTDS 17%</p> <p>Placebo 16%</p>	
			Nervous system disorders (dizziness, headache, somnolence, other)	<p>run in period (n= 1024)</p> <p>BTDS 25 %</p> <p>randomised period (n=539)</p> <p>BTDS 14%</p> <p>Placebo 11%</p> <p>NT</p>	
			Somnolence	<p>run in period (n= 1024)</p> <p>BTDS 8%</p>	

				<p>randomised period (n=539)</p> <p>BTDS 2%</p> <p>Placebo 2%</p> <p>NT</p>	
			Opioid abuse/misuse	<p>No patients were suspected of abuse of BTDS. One patient was discontinued from the study for suspected oxycodone abuse, and this was recorded as an SAE.</p> <p>Nine patients either did not return for study visits or did not return study drug and were thus suspected of study drug diversion. Of these nine cases, six involved open-label BTDS, two involved oxycodone, and one involved acetaminophen</p> <p>NT</p>	

21.6 Methadone vs placebo for chronic non-cancer pain

Methods
Systematic review/Meta-analysis: Cochrane Review Methadone for chronic non-cancer pain in adults <u>Inclusion criteria:</u> randomized controlled trials (RCTs) and non-randomized studies of methadone use in chronic pain <u>Search strategy:</u> Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library 2011, issue 11, MEDLINE (1950 to November 2011), and EMBASE (1980 to November 2011), together with reference lists of retrieved papers and reviews <u>Assessment of quality of included trials:</u> yes
Remarks
This Cochrane Review included two RCTs, both of insufficient duration and sample size to be included in our review, in neuropathic pain, and one non-randomised study.

21.7 Hydromorphone vs placebo for chronic non-cancer pain: systematic review Quigley 2013

Methods
<p>Systematic review/Meta-analysis: Hydromorphone for acute and chronic pain</p> <p>Cochrane review Quigley 2013(34) (retracted due to failure to update)</p> <p>Cochrane review Quigley 2002 (138)</p> <p><u>Inclusion criteria:</u> RCTs which involved the administration of hydromorphone, for both acute and chronic pain conditions, in adults and children, were included.</p> <p><u>Search strategy:</u> The following electronic databases have been searched for this review:</p> <ul style="list-style-type: none">• MEDLINE (1966 to November 2006);• EMBASE (1974 to November 2006);• CINAHL (November 2006);• The Cochrane Controlled Trials Register (CENTRAL/CCTR) (November 2006);• The Oxford Pain Relief Database (1954 to 1994).
Remarks
<p>This publication was retracted in 2013 due to failure to provide an update.</p> <p>The last search dates from 2006. Studies in chronic pain were all performed in cancer patients. No studies were found in chronic non-cancer pain.</p> <p>For information on hydromorphone in neuropathic pain or cancer pain: see other chapters.</p>

21.8 Hydromorphone vs placebo for chronic musculoskeletal pain

See 'Characteristics of included studies' Busse 2017, Chaparro 2013, Abdel Shaheed 2016

21.9 Oxycodone vs placebo for chronic pain in osteoarthritis

See higher under da Costa Bruno 2014

21.10 Oxycodone vs placebo for chronic low back pain

See 'Characteristics of included studies' Busse 2017, Chaparro 2013, Abdel Shaheed 2016

21.11 Tapentadol vs placebo for chronic musculoskeletal pain

Methods
Systematic review/Meta-analysis:(41) <i>Cochrane Review. Tapentadol for chronic musculoskeletal pain in adults. (41)</i>
<u>Inclusion criteria:</u> <ul style="list-style-type: none">• moderate-to-severe musculoskeletal pain of any cause, for at least three months• Randomised controlled trials (RCTs) of tapentadol compared to placebo or active control• Tapentadol extended release only (not immediate release) <p><u>Search strategy:</u> electronic databases (the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and Web of Science) to March 2014, unrestricted by language, as well as trials registers and reference lists from retrieved studies; contact with drug manufacturers for further information</p> <p><u>Assessment of quality of included trials:</u> yes</p> <p><u>Other methodological remarks:</u></p>
Remarks
Exclusion of patients with a history of substance abuse, liver disease, kidney disease... No information on previous analgesic use reported in this SR. Information in the above table was found in the original articles. All trials had high withdrawal rates (ranging from 48% to 56%)
Author's conclusions
<i>"Tapentadol extended release was associated with a reduction in pain intensity in comparison to placebo ... However, the clinical significance of the results is uncertain due to the following reasons: modest difference between interventions in efficacy outcomes, high heterogeneity in some comparisons and outcomes, high withdrawals rates, lack of data for the primary outcome in some studies, and the impossibility of using BOCF as the imputation method." (41).</i>

Results				
Ref	Comparison	N/n	Outcomes	Result (95% CI)
ref* (41) Design: Search date: (month-year)	Tapentadol extended release versus placebo	N= 3 n= 3001	Change in pain intensity from baseline at week 12 (11-point numerical rating scale)	MD (on the 11 point NRS) -0.56 (-0.92, -0.20] SS less pain with tapentadol I2 65%
		N= 2 n=2011 (Afilalo 2010, Bunyak 2010)	Responder rate (at least 50% pain reduction)	RR 1.36 (1.13, 1.64) SS more responders with tapentadol NNT for 12 weeks: 16, 95% CI 9 to 57
		N= 2 n=2011 (Afilalo 2010, Bunyak 2010)	SF-36 physical component summary score (range not reported. probably 0-100)	MD 2.57 (1.69 to 3.44) SS better score with tapentadol
		N=3 n= 3001	Other functional health status and well-being scores (EQ-5D, WOMAC)	NS (no numbers reported)
		N= 3 n= 3001	Study discontinuation due to treatment- emergent adverse effects	RR 2.68 (2.05, 3.52) SS more discontinuations with tapentadol NNH 10; 95% CI 7 to 12, for 12 weeks
		N=2 n=2011 (Afilalo 2010, Bunyak 2010)	Adverse effects	RR 1.25 (1.16, 1.35) SS more adverse events with tapentadol
		N=3 n= 3001	Serious adverse effects	1.01 (0.47, 2.16) NS
		N=3 n= 3001	Specific adverse events	"Tapentadol was associated with a higher risk of constipation (RR 2.43, 95% CI 1.86 to 3.17), nausea (RR 2.81, 95% CI 2.18 to 3.62, vomiting (RR 2.77, 95% CI 1.83 to 4.21; dry mouth (RR 3.08, 95% CI 1.92 to 4.94), somnolence (RR 3.27, 95% CI 2.26 to 4.73), dizziness (RR 2.73, 95% CI 2.08 to 3.60), and fatigue (RR 2.15, 95% CI 1.48 to 3.11). There were no differences for diarrhoea (RR 0.85, 95% CI 0.59 to 1.23), headache (RR 1.13, 95% CI 0.91 to 1.40), and pruritus (RR 2.67, 95% CI 0.85 to 8.37)"

Characteristics of included studies					
Ref + design	n	Population	Duration	Comparison	Methodology (according to Cochrane Santos 2015)
<p>Afilalo 2010 (82) RCT DB</p> <p>NCT00421928</p>	1030	<p>Chronic osteoarthritis-related knee pain Participants with moderate-to-severe joint pain who needed analgesics for at least 3 months and were dissatisfied with their current treatment were eligible (non-opioids or opioids at doses equivalent to morphine 160 mg/day oral))</p> <p>previous opioid use: not reported</p> <p>Mean age: 58 y</p> <p>Neuroleptics, tricyclic antidepressants, anticonvulsants, antiparkinsonian drugs and serotonin-norepinephrine reuptake inhibitors were prohibited within 14 days prior to screening and during the study. Monoamine oxidase inhibitors were prohibited within 14 days prior to screening and during the study. Corticosteroids were prohibited during the trial</p> <p>washout (3–7 days, during which patients were to discontinue all analgesic medication) The use of concomitant analgesics (except allowed doses of paracetamol) was prohibited during the study</p>	15 weeks	<p>Tapentadol ER 100-250 mg twice daily vs Oxycodone CR 20-50 mg twice daily vs Placebo</p>	<p>ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Low risk INCOMPLETE OUTCOME DATA: Unclear risk (LOCF) SELECTIVE REPORTING: Low risk</p> <p>completed study: 48,7% discontinued oxycodone: 64.9% - adverse event 40.6% - lack of efficacy 2.0% discontinued tapentadol: 47.1% - adverse event 17.6% - lack of efficacy 4.3% discontinued placebo: 39.5% - adverse event 6.5% - lack of efficacy 10.3%</p>
<p>Afilalo 2013 (118) RCT DB</p> <p>Note: these results were published in a full</p>	990	<p>osteoarthritis of the knee</p> <p>Participants who were dissatisfied with their prior analgesic therapy were eligible</p>	<p>15 w (3 w titration, 12 w maintenance)</p>	<p>3-7 day washout phase to discontinue analgesic medications</p> <p>3 week double blind titration</p>	<p>ALLOCATION CONC: Low risk (assessed by BCFI redaction) RANDO: Low risk BLINDING :</p>

article in 2017 by Serrie (119)		<p>pain requiring analgesic medications (non-opioids or opioids) at the reference joint for ≥ 3 months. Opioids equivalent to ≤ 160mg oral morphine/day Mean age: 62 years Prior opioid use < 3 months before screening in 14.2% to 16.6% of participants</p> <p>concomitant analgesics were prohibited during the study. Neuroleptics, monoamine oxidase inhibitors, serotonin norepinephrine re-uptake inhibitors, tricyclic antidepressants, anti-epileptics, and anti-parkinsonian medications were not permitted within 14 days prior to screening and during the study.</p> <p>washout of previous analgesics</p> <p>limited use of paracetamol as rescue medication</p>		<p>phase</p> <p>Tapentadol ER 100-250 mg twice daily vs Oxycodone CR 20-50 mg twice daily vs Placebo</p>	<p>Low risk INCOMPLETE OUTCOME DATA: Unclear risk (LOCF) SELECTIVE REPORTING: Low risk OUTCOMES High risk (choice of outcomes, no responder rates)*</p> <p>* note: responder rates were reported in the subsequent full article publication, but were not available to the Cochrane authors</p> <p>unpublished study at the time of the publication of the Cochrane review by Santos 2015. It has been published since then (119)</p> <p>Study assessed as having high risk of bias by Cochrane authors (41)</p> <p>completed study: 53.3% discontinued oxycodone: 63.6% - adverse event 42.3% - lack of efficacy 3.6% discontinued tapentadol: 41.6% - adverse event 18.8% - lack of efficacy 6.7% discontinued placebo: 34.4% - adverse event 8.3% - lack of efficacy 12.8%</p> <p>handling missing values: The last observation carried forward (LOCF) approach for missing data in the event of discontinuation was used for</p>
---------------------------------	--	--	--	--	--

					primary and secondary end-points, except for WOMAC and responder rates. For the latter, subjects who prematurely discontinued were considered non-responders
Buynak 2010 (39) RCT DB	981	<p>Low back pain, ≥ 3 m taking analgesic medications for ≥ 3 months or dissatisfied with their current therapy (non-opioids or opioids at doses equivalent to morphine 160 mg/day oral)</p> <p>prior opioid use (taking opioid analgesics within 3 months of screening) placebo 53.9% tapentadol 56.0% oxycodone 50.3%</p> <p>Neuroleptics, tricyclic antidepressants, anticonvulsants, antiparkinsonian drugs, and serotonin norepinephrine reuptake inhibitors were prohibited within 14 days prior to the screening visit and during the study ; use of monoamine oxidase inhibitors was also prohibited within 14 days prior to the screening visit and during the study. SSRI allowed if stable dose and not used for pain treatment</p> <p>3- to 7-day washout period of all previous analgesics</p> <p>The use of concomitant analgesics, with the exception of allowed doses of acetaminophen (see Treatment schedule), was prohibited during the study</p> <p>Electrical Nerve Stimulation, acupuncture, physical therapy, packs, massages, and</p>	15 w (3 w titration, 12w maintenance)	<p>Tapentadol ER 100-250 mg twice daily</p> <p>vs</p> <p>Oxycodone HCl 20-50 mg twice daily</p> <p>vs</p> <p>Placebo</p>	<p>ALLOCATION CONC: Low risk</p> <p>RANDO: Low risk</p> <p>BLINDING : Low risk</p> <p>INCOMPLETE OUTCOME DATA: Unclear risk (LOCF)</p> <p>SELECTIVE REPORTING: Low risk</p> <p>discontinued early tapentadol 152/321 47.4% -adverse event 15.9% - lack of efficacy 40% oxycodone 195/334 58.4% - adverse event 32.0% - lack of efficacy 2.1% placebo 167/326 51.2% - adverse event 4.6% - lack of efficacy 15.3%</p> <p>dealing with missing values: LOCF sensitivity analyses were performed using other imputation methods. Mostly, for tapentadol, statistically significant differences remained, but the size of the effect was generally smaller. for oxycodone, significant differences remained for some but not all pain score outcomes.</p>

		other interventional adjunctive therapy were permitted during the study if patients started the			
--	--	---	--	--	--

22 Appendix. Evidence tables. Opioids for neuropathic pain

22.1 Opioids for neuropathic pain. Systematic review McNicol 2013

Methods
<p>Systematic review/Meta-analysis: Opioids for neuropathic pain in adults. (42)</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none">• RCT's with an opioid agonist (not partial agonists or agonist-antagonists)• Tramadol, tapentadol, and opioids combined with drugs other than opioid agonists (e.g. codeine with paracetamol) were excluded• Patients with central or peripheral neuropathic pain of any aetiology <p><u>Search strategy:</u> The authors searched CENTRAL, on <i>The Cochrane Library</i> (Issue 10 of 12, 2012), MEDLINE (1966 to Oct week 3, 2012), and EMBASE (1980 to 2012, week 42) for articles in any language, and reference lists of reviews and retrieved articles. Searches were originally run in 2005, then again in 2010 and 2012.</p> <p><u>Assessment of quality of included trials:</u> yes <u>Other methodological remarks:</u> /</p>
Remarks
<p>In this cochrane review, included studies were divided in “short-term” studies and “intermediate-term” studies. From the 14 intermediate-term studies, only 1 met our inclusion criterion for study duration (≥12 weeks). This study (43) has already been discussed in another section of this document</p>
Author's conclusions
<p>“Since the last version of this review, new studies were found providing additional information. Data were reanalyzed but the results did not alter any of our previously published conclusions. Short-term studies provide only equivocal evidence regarding the efficacy of opioids in reducing the intensity of neuropathic pain. Intermediate-term studies demonstrated significant efficacy of opioids over placebo, but these results are likely to be subject to significant bias because of small size, short duration, and potentially inadequate handling of dropouts. Analgesic efficacy of opioids in chronic neuropathic pain is subject to considerable uncertainty. Reported adverse events of opioids were common but not life-threatening. Further randomized controlled trials are needed to establish unbiased estimates of long-term efficacy, safety (including addiction potential), and effects on quality of life.” (42)</p>

22.2 Combination pharmacotherapy versus placebo/active comparator for neuropathic pain. Systematic review Chaparro 2012

<p>Methods</p> <p>Systematic review/Meta-analysis: Combination pharmacotherapy for the treatment of neuropathic pain in adults (Review). (44)</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none"> • Double-blind RCT's comparing combinations of ≥ 2 drugs (systemic or topical) to placebo and/or 1 other comparator • Patients ≥ 18 years old with a diagnosis of neuropathic pain <p><u>Search strategy:</u> The authors identified randomised controlled trials (RCTs) of various drug combinations for neuropathic pain from CENTRAL, MEDLINE, EMBASE and handsearches of other reviews and trial registries. The most recent search was performed on 9 April 2012.</p> <p><u>Assessment of quality of included trials:</u> yes <u>Other methodological remarks:</u> /</p>
<p>Remarks</p> <p>This Cochrane review studied various combinations of drugs, also not containing opioids, and included 21 studies. From these 21 studies, 5 studies met our inclusion criterion in terms of intervention. From these 5 studies, only 1 study (43) met our inclusion criterion for study duration (≥ 12 weeks) and has already been discussed in another section of this document.</p>
<p>Author's conclusions</p> <p>"Multiple, good-quality studies demonstrate superior efficacy of two-drug combinations. However, the number of available studies for any one specific combination, as well as other study factors (e.g. limited trial size and duration), preclude the recommendation of any one specific drug combination for neuropathic pain. Demonstration of combination benefits by several studies together with reports of widespread clinical polypharmacy for neuropathic pain surely provide a rationale for additional future rigorous evaluations. In order to properly identify specific drug combinations which provide superior efficacy and/or safety, we recommend that future neuropathic pain studies of two-drug combinations include comparisons with placebo and both single-agent components. Given the apparent adverse impact of combining agents with similar adverse effect profiles (e.g. CNS depression), the anticipated development and availability of non-sedating neuropathic pain agents could lead to the identification of more favourable analgesic drug combinations in which side effects are not compounded." (44)</p>

22.3 Codeine/dihydrocodeine +paracetamol vs placebo for neuropathic pain. Systematic review Wiffen 2016

Methods
Systematic review/Meta-analysis: Paracetamol (acetaminophen) with or without codeine or dihydrocodeine for neuropathic pain in adults. (45)
<u>Inclusion criteria:</u> <ul style="list-style-type: none">• Double blind RCT's, ≥2 weeks treatment• Patients ≥18 years with cancer-related neuropathy; central neuropathic pain; complex regional pain syndrome (CRPS) Type II; HIV neuropathy; painful diabetic neuropathy; phantom limb pain; postherpetic neuralgia; postoperative or traumatic neuropathic pain; spinal cord injury; and trigeminal neuralgia.
<u>Search strategy:</u> The 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.
<u>Assessment of quality of included trials:</u> yes
<u>Other methodological remarks:</u> /
Remarks
No study satisfied the inclusion criteria of this Cochrane review.
Author's conclusions
"There is insufficient evidence to support or refute the suggestion that paracetamol alone, or in combination with codeine or dihydrocodeine, works in any neuropathic pain condition." (45)

22.4 Tramadol for neuropathic pain. Systematic review Duehmke Rudolf 2017

Methods
<p>Systematic review/Meta-analysis: Tramadol for neuropathic pain in adults. (47)</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none">• Double blind RCT's, ≥ 2 weeks treatment• Patients ≥ 18 years with cancer-related neuropathy; central neuropathic pain; complex regional pain syndrome (CRPS) Type II; HIV neuropathy; painful diabetic neuropathy; phantom limb pain; postherpetic neuralgia; postoperative or traumatic neuropathic pain; spinal cord injury; and trigeminal neuralgia. <p><u>Search strategy:</u> CENTRAL, MEDLINE, and Embase were searched for randomised controlled trials from inception to January 2017. The reference lists of retrieved studies and reviews, and online clinical trial registries were also searched.</p> <p><u>Assessment of quality of included trials:</u> yes</p> <p><u>Other methodological remarks:</u> /</p>
Remarks
<p>In January 2017, the authors searched for clinical trials in which tramadol was used to treat neuropathic pain in adults. Six studies met the inclusion criteria, randomising 438 participants to treatment with tramadol or placebo. Study duration was between four and six weeks.</p> <p>None of these studies met our inclusion criterion for study duration (≥ 12 weeks).</p>
Author's conclusions
<p>"There is only modest information about the use of tramadol in neuropathic pain, coming from small, largely inadequate studies with potential risk of bias. That bias would normally increase the apparent benefits of tramadol. The evidence of benefit from tramadol was of low or very low quality, meaning that it does not provide a reliable indication of the likely effect, and the likelihood is very high that the effect will be substantially different from the estimate in this systematic review." (47)</p>

22.5 Tramadol for diabetic neuropathy. Systematic review Dy 2017

Methods
Systematic review/Meta-analysis: Preventing complications and treating symptoms of diabetic peripheral neuropathy. (46) <u>Inclusion criteria:</u> For the treatment of diabetic peripheral neuropathy symptoms, the authors included a systematic review of primary parallel or crossover randomized controlled trials that were blinded for interventions where blinding was possible. <u>Search strategy:</u> PubMed and the Cochrane Database of Systematic Reviews for systematic reviews was searched from January 1, 2011, to October 12, 2015. For questions for which high-quality relevant systematic reviews were identified, primary studies using PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to May 24, 2016. ClinicalTrials.gov was searched for pharmacologic treatment of diabetic peripheral neuropathy symptoms. <u>Assessment of quality of included trials:</u> yes <u>Other methodological remarks:</u> /
Remarks
A meta-analysis was conducted for “atypical opioids (tramadol and tapentadol)” vs placebo. Five studies were identified: 2 with tramadol and 3 with tapentadol. The Standardized mean difference was -0.68 (95% CI: -.80 to -0.56). Standardized mean difference ranged from -7.0 to -0.36 (from -1.43 to -0.46 for tapentadol and from -7.0 to -0.36 for tramadol). Both studies with tramadol did not meet our inclusion criterion for study duration (≥12 weeks).
Author’s conclusions
“Overall, based on the available data, atypical opioids are more effective than placebo for reducing pain. We considered the strength of evidence low for atypical opioids overall due to precise but inconsistent findings across the studies, as well as concerns about study methodology. There were particular concerns for the tapentadol studies as they were inconsistent with standards for pain trials, including using nonstandard primary pain outcomes and withdrawal study methodology (of concern for studies of opioids, where withdrawal causes additional symptoms). For individual drugs, we considered the strength of evidence low for use of tapentadol to reduce pain due to these issues, and low for tramadol due to inconsistency across the studies and unclear risk of bias.” (46) General conclusion for the treatment of diabetic neuropathy symptoms: “For reducing pain, the only class with moderate strength of evidence was serotonin-noradrenaline reuptake inhibitors; pregabalin and oxcarbazepine, atypical opioids, botulinum toxin, alpha-lipoic acid and spinal cord stimulation are more effective than placebo but with low SOE. However, studies were generally short term with unclear risk of bias, we could not draw conclusions for quality of life, all oral drugs had significant side effects, opioids have significant long-term risks including abuse, and spinal cord stimulation has risks of serious complications.” (46)

22.6 Buprenorphine for neuropathic pain. Systematic review Wiffen 2015

Methods
<p>Systematic review/Meta-analysis: Buprenorphine for neuropathic pain in adults. (49)</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none">• Double-blind RCT's; ≥2 weeks study duration• Any oral dose or formulation of buprenorphine• Patients ≥18 years with cancer-related neuropathy; central neuropathic pain; complex regional pain syndrome (CRPS) Type II; HIV neuropathy; painful diabetic neuropathy; phantom limb pain; postherpetic neuralgia; postoperative or traumatic neuropathic pain; spinal cord injury; and trigeminal neuralgia. <p><u>Search strategy:</u> The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE from inception to 11 June 2015, together with reference lists of retrieved papers and reviews, and two online study registries.</p> <p><u>Assessment of quality of included trials:</u> yes</p> <p><u>Other methodological remarks:</u></p>
Remarks
<p>The authors identified 10 published studies, and one study with results in ClinicalTrials.gov. None of these 11 studies satisfied the inclusion criteria of the authors and so no studies were included in this cochrane review. Reasons for exclusion included: no primary clinical trial data; mixed pain conditions with no separate results for neuropathic pain; not double-blind or not randomized.</p>
Author's conclusions
<p>"There was insufficient evidence to support or refute the suggestion that buprenorphine has any efficacy in any neuropathic pain condition." (49)</p>

22.7 Transdermal buprenorphine versus placebo for diabetic peripheral neuropathic pain. RCT Simpson 2016

Study details	n/Population	Comparison	Outcomes		Methodological
Ref(48)	n= 168	buprenorphine Vs placebo	Efficacy		RANDO:
Design: RCT (DB) (PG)	Mean age: 62.6 (SD 9.6) vs 63.3 (SD 93.3)		30% reduction in pain at week 12 (PO)	ITT analysis: Buprenorphine: 51.7% (46/89) Placebo: 41.3% (38/92) OR: 1.56 (95%: 0.82-2.97) NS; p= 0.175	Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: unclear
Duration of follow-up: assessment after 12 weeks	Mean pain score (11-point NRS) at baseline: Buprenorphine group: 5.7 (SD 1.1) Placebo group: 5.9 (SD 1.3)	<u>Titration phase:</u> 12 weeks A flexible dosage titration regimen was allowed during this 12-week period.	(NRS: 0 = no pain, 10 = worst possible pain)	Per protocol analysis: Buprenorphine: 86.3% (44/51) Placebo: 55.6% (35/63) OR: 6.88 (95%: 2.20-21.47) SS; p< 0.001 (in favour of buprenorphine)	Drop-out <ul style="list-style-type: none">Described: yesBalanced across groups: no
	<u>Inclusion</u> -type1 or 2 diabetes -stable glycemic control for the past 3 months -DPNP > 6 months - stable conventional nonopioid analgesic therapy - eligible pts had pain of at least moderate intensity <u>Exclusion</u> Patients who had currently or previously treated their DPNP with a strong opioid (e.g., oxycodone, morphine) or	<u>Downward-titration phase:</u> Blinded and for 3 weeks <u>Use of other pain treatment:</u> Concomitant use of antiepileptics or antidepressants during study: Buprenorphine group: 61.3% Placebo group: 68.8%	Secondary endpoints (ITT population) (n=89 vs n=92)		<u>Discontinuation</u> Buprenorphine group: 39.8% Main reasons: adverse events: 30.1% inadequate pain control: 3.2%
			At least 50% reduction in pain intensity from baseline at week 12 (proportion)	34.8% vs 20.7% SS, p<0.05 in favour of buprenorphine NNT 7.05	
			Neuropathic Pain Symptom Inventory(NPSI): change from baseline	Total pain intensity score: -22.50 (17.70) vs -20.10 (21.68) SS, p<0.05, in favour of buprenorphine Paroxymal pain: -2.12 (2.73) vs -1.96 (2.89) SS, p<0.05, in favour of buprenorphine No SS difference for burning spontaneous pain, pressing spontaneous pain, evoked pain, and parathesia/dysthesia pain	<u>Discontinuation</u> Placebo group: 25.8% Main reasons: adverse events: 6.5% inadequate pain control: 9.7%
			Brief Pain Inventory interference scale	Sleep: -3.52 (2.87) vs -2.18 (3.07) SS, p<0.05, in favour of buprenorphine	<u>Dealing with missing values:</u> For the primary outcome, patients who had dropped out of the study or had missing values at week 12 were considered non-responders.

were currently taking a strong opioid for any condition were excluded from the study.	Pts were allowed to continue stable doses of antidepressants, antiepileptics, or other medications with activity against neuropathic pain. However, the use of weak opioid analgesics (e.g., codeine containing, propoxyphene containing, tramadol), nonsteroidal antiinflammatory drugs, and any topical DPNP therapies or other nondrug therapies for DPNP were discontinued at the screening visit. Paracetamol (500–1,000 mg) up to four times per day was available for use as a rescue analgesic.		No SS differences for general activity, mood, walking ability, normal work, relationships, enjoyment of life.	ITT: “The ITT population included all participants randomized to receive at least one dose of study medication and had at least one valid after-treatment efficacy measurement.” SELECTIVE REPORTING: no Sponsor: Mundipharma, Sydney, NSW, Australia.
		HRQoL (MOS 36-item SF): change from baseline	Bodily pain: 17.26 (19.43) vs 10.00 (20.56) SS, p<0.05, in favour of buprenorphine No SS differences for physical functioning, physical role, general health, vitality, social functioning, emotional role, and mental health	
		Participant Global Impression of Change(PGIC)	2.37 (1.09) vs 3.03 (1.35) SS, p<0.05, in favour of buprenorphine	
		Clinician Global Impression of Change(CGIC)	2.39 (1.19) vs 2.91 (1.21) NS, p=0.25	
		Mean number of paracetamol 500 mg taken per day as rescue medication	1.56 (2.22) vs 1.77 (2.39) NS, p=0.73	
		Safety		
		At least 1 adverse event (AE) (mostly mild and moderate)	93.6% (87/93) vs 81.7% (76/93) NT Most reported AE’s: Buprenorphine group: -Nausea: 43.0% -Constipation: 31.2% Placebo group: -Upper respiratory infection: 12.9% -headache: 9.7%	
		Severe AE’s	10 vs 9 reports NT	
		Serious adverse events (SAE)	Buprenorphine: 17 SAE’s in 7 pts Relation drug:	

				-Related: 1 SAE vomiting -Possibly related: 1 case each of supraventricular tachycardia, depression, and diarrhea. Placebo: 5 SAE's in 5 pts 1 SAE (respiratory failure) related to placebo	
--	--	--	--	---	--

Note: Interaction analyses were done to assess the effect of antidepressant or anti-epileptic use on the effectiveness of buprenorphine. Results showed that there was no meaningful effect.

22.8 Fentanyl for neuropathic pain. Systematic review Derry 2016

Methods
Systematic review/Meta-analysis: Fentanyl for neuropathic pain in adults. (50)
<u>Inclusion criteria:</u> <ul style="list-style-type: none">• Double-blind RCT's; ≥2 weeks study duration• Any oral dose or formulation of buprenorphine• Patients ≥18 years with cancer-related neuropathy; central neuropathic pain; complex regional pain syndrome (CRPS) Type II; HIV neuropathy; painful diabetic neuropathy; phantom limb pain; postherpetic neuralgia; postoperative or traumatic neuropathic pain; spinal cord injury; and trigeminal neuralgia.
<u>Search strategy:</u> The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE from inception to June 2016, together with reference lists of retrieved articles, and two online study registries.
<u>Assessment of quality of included trials:</u> yes
<u>Other methodological remarks:</u> /
Remarks
The authors of this meta-analysis found one study comparing transdermal fentanyl (1-day patch) with placebo that met their inclusion criteria. We did not include this study in our analysis since a one-day fentanyl patch is currently not available in Belgium.
Author's conclusions
"There is insufficient evidence to support or refute the suggestion that fentanyl works in any neuropathic pain condition." (50)

22.9 Hydromorphone for neuropathic pain. Systematic review Stannard 2016

Methods
<p>Systematic review/Meta-analysis: Hydromorphone for neuropathic pain in adults. (51)</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none">• Double-blind RCT's; ≥2 weeks study duration• Any dose/route of administration or any formulation of hydromorphone• Patients ≥18 years with cancer-related neuropathy; central neuropathic pain; complex regional pain syndrome (CRPS) Type II; HIV neuropathy; painful diabetic neuropathy; phantom limb pain; postherpetic neuralgia; postoperative or traumatic neuropathic pain; spinal cord injury; and trigeminal neuralgia. <p><u>Search strategy:</u> The Cochrane Central Register of Controlled Trials (CENTRAL) via the CRSO, MEDLINE via Ovid, and EMBASE via Ovid from inception to 17 November 2015, together with reference lists of retrieved papers and reviews, and two online study registries.</p> <p><u>Assessment of quality of included trials:</u> yes</p> <p><u>Other methodological remarks:</u> /</p>
Remarks
<p>This Cochrane review included one study in patients with chronic low back pain. In this study, results for participants with a definite or probable neuropathic pain component were reported separately from participants with nonneuropathic or nociceptive pain in a post hoc analysis. This study did not meet our inclusion criterion for study design (no post hoc analyses). However, the original study (35) on which this post-hoc analysis was based on is included in another section of this document.</p>
Author's conclusions
<p>"There was insufficient evidence to support or refute the suggestion that hydromorphone has any efficacy in any neuropathic pain condition." (51)</p>

22.10 Methadone for neuropathic pain. Systematic review McNicol Ewan 2017

Methods
<p>Systematic review/Meta-analysis: Methadone for neuropathic pain in adults. (2)</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none">• Double-blind RCT's; ≥2 weeks study duration• Any dose/route of administration or any formulation of hydromorphone• Patients ≥18 years with cancer-related neuropathy; central neuropathic pain; complex regional pain syndrome (CRPS) Type II; HIV neuropathy; painful diabetic neuropathy; phantom limb pain; postherpetic neuralgia; postoperative or traumatic neuropathic pain; spinal cord injury; and trigeminal neuralgia. <p><u>Search strategy:</u> The Cochrane Central Register of Controlled Trials (CENTRAL) (CRSO), MEDLINE (Ovid), and EMBASE (Ovid) and two clinical trial registries. Reference lists of retrieved articles were also searched. The date of the most recent search was 30 November 2016</p> <p><u>Assessment of quality of included trials:</u> yes <u>Other methodological remarks:</u> /</p>
Remarks
<p>This Cochrane review included three cross-over studies with heterogeneous designs. No meta-analysis could be performed and the three studies were reported separately. The included studies did not meet our inclusion criteria for several reasons including sample size (<40 patients per study-arm).</p>
Author's conclusions
<p>"The three studies provide very limited, very low quality evidence of the efficacy and safety of methadone for chronic neuropathic pain, and there were too few data for pooled analysis of efficacy or harm, or to have confidence in the results of the individual studies. No conclusions can be made regarding differences in efficacy or safety between methadone and placebo, other opioids, or other treatments." (2)</p>

22.11 Morphine for neuropathic pain. Systematic review Cooper Tess 2017

Methods

Systematic review/Meta-analysis:

Morphine for chronic neuropathic pain in adults (review)(52)

Inclusion criteria:

- Double-blind RCT's; ≥ 2 weeks study duration
- Morphine at any dose/route of administration
- Patients ≥ 18 years with cancer-related neuropathy; central neuropathic pain; complex regional pain syndrome (CRPS) Type II; HIV neuropathy; painful diabetic neuropathy; phantom limb pain; postherpetic neuralgia; postoperative or traumatic neuropathic pain; spinal cord injury; and trigeminal neuralgia.

Search strategy:

The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE were searched from inception to February 2017. The reference lists of retrieved studies and reviews, and online clinical trial registries were also searched.

Assessment of quality of included trials: yes

Other methodological remarks: /

Remarks

This Cochrane review included 5 cross-over studies with treatment periods of 4 to 7 weeks. The included studies did not meet our inclusion criteria for sample size (>40 patients per study-arm) and study duration (≥ 12 weeks). (52)

Author's conclusions

"There was insufficient evidence to support or refute the suggestion that morphine has any efficacy in any neuropathic pain condition." (52)

22.12 Oxycodone +/- naloxone for neuropathic pain. Systematic review Gaskell 2016

Methods
<p>Systematic review/Meta-analysis: Oxycodone for neuropathic pain in adults (Review). (53)</p> <p><u>Inclusion criteria:</u></p> <ul style="list-style-type: none">• Double-blind RCT's; ≥ 2 weeks study duration• Morphine at any dose/route of administration• Patients ≥ 18 years with cancer-related neuropathy; central neuropathic pain; complex regional pain syndrome (CRPS) Type II; HIV neuropathy; painful diabetic neuropathy; phantom limb pain; postherpetic neuralgia; postoperative or traumatic neuropathic pain; spinal cord injury; and trigeminal neuralgia. <p><u>Search strategy:</u> The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE were searched from inception to February 2017. The reference lists of retrieved studies and reviews, and online clinical trial registries were also searched.</p> <p><u>Assessment of quality of included trials:</u> yes</p> <p><u>Other methodological remarks:</u> /</p>
Remarks
<p>This Cochrane review included 5 studies. Three studies did not meet our inclusion criteria due to study duration (≥ 12 weeks) and sample size (>40 patients per study arm). Therefore, we only report on the 2 studies that met our inclusion criteria and do not report any pooled results presented in the Cochrane review. We also did not report any pooled results for these 2 studies, which are available for safety outcomes, because one study compared oxycodone with placebo while the other included study compared oxycodone/naloxone with placebo.</p>

Characteristics and results of included studies						
Ref + design	n	Population	Duration	Comparison	Results	Methodology
(43) Multicentre, randomised, double-blind, placebo-controlled, parallel group. Add-on design	n = 338 (randomised), 328 (efficacy), 335 (safety) Oxycodone, n = 163 Placebo, n = 165 (full analysis population)	Painful diabetic neuropathy (≥3months). Stable maximum tolerated dose of gabapentin (≥ 1 month), but pain intensity ≥ 5/10. HbA1c ≤ 11% Exclusions: long-acting opioid in previous month or previous treatment with oxycodone + gabapentin All participants were treated with stable doses of gabapentin	12 weeks	Gabapentin + Oxycodone prolonged release vs Gabapentin + placebo	At least moderate (30%) pain relief 72/163 (44.2%) vs 51/165 (30.9%) RR 1.43 (95%CI: 1.07-1.90) SS, in favour of oxycodone 27/16	ALLOCATION CONC: Low risk RANDO: Low risk BLINDING : Participants/personnel/assessors Unclear risk FOLLOW-UP: ITT: "The full analysis population included all randomised patients who received at least one dose of study medication, and had at least one primary efficacy measurement post randomization" FUNDING: Mundipharma Research Limited
					Adverse event withdrawals 27/163 (16.6%) vs 9/165 (5.5%) RR 3.04 (95%CI: 1.47,6.26) SS, in favour of placebo	
					Lack of efficacy withdrawals 6/163 (3.7%) vs 20/165 (12.1%) RR 0.30 (95%CI: 0.13-0.74)	
					Any adverse event 147/168 (87.5%) vs 119/167 (71.3%) RR 1.23 (95%CI: 1.10-1.37)	
NCT00944697 (unpublished data only – as	N=98 Oxycodone +	Painful diabetic polyneuropathy (pain intensity ≥ 5/10), opioid naive, aged _	12 weeks	Pregabalin + [Oxycodone prolonged release +	Short Form McGill Pain Score (0 to 150; high worse pain) at 12 weeks	ALLOCATION CONC: Unclear RANDO: Unclear

reported by Cochrane Gaskell)	naloxone (dose not specified), n = 48 Placebo, n = 50	18 years Exclusions: impaired liver/kidney function, significant structural abnormality of the gastrointestinal tract, pregnancy or breastfeeding All participants were treated with stable doses of pregabalin		naloxone] vs Pregabalin + placebo	Oxycodone MR: 48/150 (SD 30) Placebo: 50/150 (SD 30) Results indicate no benefit from adding oxycodone MR.	BLINDING : Participants/personnel/assessors Unclear FOLLOW-UP: ITT: unclear FUNDING: Mundipharma Research GmbH & Co KG Note: phase II study
					Adverse event withdrawals 3/48 vs 0/50 RR 7.29 (95%CI: 0.39,137.42) NS	
					Lack of efficacy withdrawals 0/48 vs 0/50 Not estimable	
					Any adverse event 40/48 (83.3%) vs 22/50 (44.0%) RR 1.89 (95%CI: 1.35-2.65) SS, in favour of placebo	
					Serious adverse events 4/48 vs 0/50 RR 9.37 (95%CI: 0.52-169.45) NS	

Author's conclusions

"There was only very low quality evidence that oxycodone (as oxycodone MR) is of value in the treatment of painful diabetic neuropathy or postherpetic neuralgia. There was no evidence for other neuropathic pain conditions. Adverse events typical of opioids appeared to be common." (53)

22.13 Tapentadol for diabetic peripheral neuropathy. Systematic review Dy 2017

Methods

Systematic review/Meta-analysis:

Preventing complications and treating symptoms of diabetic peripheral neuropathy. (46)

Inclusion criteria:

For the treatment of diabetic peripheral neuropathy symptoms, the authors included a systematic review of primary parallel or crossover randomized controlled trials that were blinded for interventions where blinding was possible.

Search strategy:

PubMed and the Cochrane Database of Systematic Reviews for systematic reviews was searched from January 1, 2011, to October 12, 2015. For questions for which high-quality relevant systematic reviews were identified, primary studies using PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to May 24, 2016. ClinicalTrials.gov was searched for pharmacologic treatment of diabetic peripheral neuropathy symptoms.

Assessment of quality of included trials: yes

Other methodological remarks: /

Remarks

A meta-analysis was conducted for “atypical opioids (tramadol and tapentadol)” vs placebo. Five studies were identified: 2 with tramadol and 3 with tapentadol. The Standardized mean difference for the full meta-analysis was -0.68 (95% CI: -.80 to -0.56).

Standardized mean difference (SMD) ranged from -7.0 to -0.36 (**from -1.43 to -0.46 for tapentadol** and from -7.0 to -0.36 for tramadol).

From the 3 studies with tapentadol, 1 study did not meet our inclusion criteria for study duration (≥ 12 weeks) and sample size (>40 patients per study arm). The studies that did meet our inclusion criteria (54) (55) had a SMD of -0.46 (95%CI: -0.68, -0.23) and -0.79 (-1.00, -0.59). However, after examining the individual studies, we excluded an additional study (55) because a new formulation (with a polyethylene oxide matrix) was used that is currently not available in Belgium.

Details of the individual studies that met our inclusion criteria

Ref + design	n	Population	Duration	Comparison	Results	Methodology
(54) Enriched enrollment randomized-withdrawal design	n = 588 Randomised: tapentadol: n= 199 placebo: n= 196	<p>Pts with painful diabetic peripheral neuropathy (DPN)</p> <p>At least 3-month history of opioid and/or non-opioid analgesic use for DPN, dissatisfaction with current treatment, average pain score $\geq 5/10$</p> <p>Prior to the open-label titration period, patients eligible for study participation entered a washout period for discontinuation of all analgesic medications followed by a 3-day pain intensity evaluation period. Patients with a pre-titration average pain intensity of $\geq 5/10$ entered the open-label titration period.</p> <p>Neuroleptics, SNRIs, anticonvulsants, and antiparkinsonian drugs were prohibited during the study. Use of SSRI was allowed if patients were on a stable dose for at least 30 days prior to screening.</p> <p>The use of any analgesic except the study drug or permitted rescue medication</p>	<p>open-label titration phase: 3 weeks</p> <p>double-blind maintenance phase: 12 weeks</p>	<p>Tapentadol extended release 100-250 mg BID</p> <p>Vs</p> <p>placebo</p>	<p>Change in average pain intensity (NRS: range:0-10) (PO):</p> <p>Least-squares mean difference of -1.3 (95%CI: -1.70, -0.92); $p < 0.001$ SS, in favour of tapentadol</p> <p>‘very much’ or ‘much’ improved patient’s global impression of change (PGIC) at week 12:</p> <p>116/180 (64.4%) vs 68/177 (38.4%); $p < 0.001$ SS, in favour of tapentadol</p>	<p>ALLOCATION CONC: Low risk</p> <p>RANDO: Low risk</p> <p>BLINDING : Participants/personnel/assessors low risk</p> <p>FOLLOW-UP: <u>Open label phase</u> -Received study drug: n=588 -Discontinued from study: n=196 (33.3%) Reasons -Adverse event: 100 pts (51.0%) -Patient choice: 24 pts (12.2%) -Lack of efficacy: 23 pts (11.7%)</p> <p><u>Double-blind phase</u> Discontinuation: 63/196 (32.1%) vs 62/193 (32.1%) Reasons: -adverse event: 29/63 (63.0%) vs 15/62 (24.2%) -lack of efficacy: 8/63 (12.7%) vs 29/62 (46.8%)</p> <p>Dealing with missing values: The primary efficacy analysis (PO) used the last observation carried forward (LOCF) to impute missing pain intensity values after discontinuation and was repeated using the following methods:</p>

		<p>(acetaminophen during the open-label phase except last 4 days), including NSAID, topical capsaicin, topical anesthetics, and opioids, was prohibited throughout the study.</p> <p>Previous opioid use: Tapentadol arm: 34.7% Placebo arm: 34.2%</p> <p>Patients with at least a 1–point improvement in average pain intensity from the pre-titration pain intensity evaluation period to the last 3 days of titration (baseline pain) were eligible for double-blind treatment.</p>				<p>baseline observation carried forward (BOCF); worst observation carried forward; placebo mean imputation (mean of all available pain intensity scores for all patients who received placebo and completed treatment for a given day).</p> <p>ITT: “all randomized patients who took ≥1 dose of study medication during the double-blind maintenance period.”</p> <p>FUNDING: Johnson & Johnson Pharmaceutical Research & Development, L.L.C., and Global Development, Grünenthal GmbH, Aachen, Germany.</p>
					<p>Any adverse events during double-blind treatment period: 139/196 (70.9%) vs 100/193 (51.8%) NT</p>	

Author’s conclusions of the meta-analysis

“Overall, based on the available data, atypical opioids are more effective than placebo for reducing pain. We considered the strength of evidence low for atypical opioids overall due to precise but inconsistent findings across the studies, as well as concerns about study methodology. There were particular concerns for the tapentadol studies as they were inconsistent with standards for pain trials, including using nonstandard primary pain outcomes and withdrawal study methodology (of concern for studies of opioids, where withdrawal causes additional symptoms). For individual drugs, we considered the strength of evidence low for use of tapentadol to reduce pain due to these issues, and low for tramadol due to inconsistency across the studies and unclear risk of bias.” (46)

General conclusion for the treatment of diabetic neuropathy symptoms:

“For reducing pain, the only class with moderate strength of evidence was serotonin-noradrenaline reuptake inhibitors; pregabalin and oxcarbazepine, atypical opioids, botulinum toxin, alpha-lipoic acid and spinal cord stimulation are more effective than placebo but with low SOE. However, studies were generally short term with unclear risk of bias, we could not draw conclusions for quality of life, all oral drugs had significant side effects, opioids have significant long-term risks including abuse, and spinal cord stimulation has risks of serious complications.” (46)

23 Appendix. Evidence tables. Opioids for cancer pain

23.1 Opioids for cancer pain. Overview of Cochrane reviews Wiffen 2017

Methods
<p>Systematic review/Meta-analysis: “Opioids for cancer pain - an overview of Cochrane reviews” (56)</p> <p><u>Inclusion criteria:</u> Study type: Cochrane systematic reviews of RCTs Population: Adults with cancer pain Intervention: Opioid drugs, compared with placebo or a different active treatment. Outcomes: Pain on treatment by day 14, Patient Global Impression of Change, withdrawals due to adverse events or lack of efficacy, Adverse events.</p> <p><u>Search strategy:</u></p> <p>The Cochrane Database of Systematic Reviews was searched on 4 May 2017.</p> <p><u>Assessment of quality of included trials:</u> yes, AMSTAR tool</p>
Remarks
<p>9 systematic reviews, containing 152 RCTs (some of which were overlapping), were found.</p> <p>All 9 systematic reviews are discussed below. One SR on oxycodone was updated since the last search date of this Cochrane overview of reviews; we have evaluated the updated version.</p>

23.2 Morphine, fentanyl oxycodone or codeine for cancer pain: adverse events. Overview of Cochrane reviews Wiffen Philip 2014

Methods
Systematic review/Meta-analysis: “Impact of morphine, fentanyl, oxycodone or codeine on patient consciousness, appetite and thirst when used to treat cancer pain”(66)
<u>Inclusion criteria:</u> Study type: RCTs reported in four Cochrane reviews (on morphine, fentanyl, oxycodone and codeine). Population: Adults with cancer pain requiring treatment with opioids. Intervention: morphine, fentanyl, oxycodone or codeine preparations versus placebo, an alternative formulation of morphine or an active control. Outcomes: Numbers of patients experiencing adverse events of level of consciousness or inability to eat or drink .
<u>Search strategy:</u> Studies included in the four Cochrane reviews were considered.
<u>Assessment of quality of included trials:</u> yes, Risk of Bias tool.
Remarks
77 RCTs were found. However, none met our inclusion criteria.
Author’s conclusions
“We found no direct evidence that opioids affected patient consciousness, appetite or thirst when used to treat cancer pain. However, somnolence, dry mouth, and anorexia were common adverse events in people with cancer pain treated with morphine, fentanyl, oxycodone, or codeine. We are aware that there is an important literature concerning the problems that exist with adverse event measurement, reporting, and attribution. Together with the known complications concerning concomitant medication, data collection and reporting, and nomenclature, this means that these adverse events cannot always be attributed unequivocally to the use of opioids, and so they provide only a broad picture of adverse events with opioids in cancer pain. The research agenda includes developing definitions for adverse events that have a spectrum of severity or importance, and the development of appropriate measurement tools for recording such events to aid clinical practice and clinical research.”

23.3 Tramadol +/- paracetamol for cancer pain. Cochrane systematic review Wiffen 2017

Methods
Systematic review/Meta-analysis: "Tramadol with or without paracetamol (acetaminophen) for cancer pain" (57) <u>Inclusion criteria:</u> Study type: RCTs Population: Adults or children with cancer-related pain. Intervention: tramadol with or without paracetamol versus placebo or any active comparator. Outcomes: Pain, QoL, rescue medication, participant preference, adverse events, attrition <u>Search strategy:</u> CENTRAL, MEDLINE, Embase and LILACS were searched from inception to November 2016. <u>Assessment of quality of included trials:</u> yes, Cochrane Risk of Bias tool.
Remarks
10 RCTs were found. However, none met our inclusion criteria as all but one study had a treatment duration of < 3 months, and the remaining study was unblinded.

23.4 Codeine +/- paracetamol for cancer pain. Cochrane systematic review Straube 2014

Methods
<p>Systematic review/Meta-analysis: "Codeine, alone and with paracetamol (acetaminophen), for cancer pain" (58)</p> <p><u>Inclusion criteria:</u> Study type: RCTs Population: children or adults with cancer pain. Intervention: codeine, alone or in combination with paracetamol (in any formulation, dose, route) versus placebo or another active treatment. Outcomes: Pain, Functioning, Adverse events, Withdrawals, Death.</p> <p><u>Search strategy:</u></p> <p>CENTRAL, MEDLINE and Embase were searched from inception to March 2014.</p> <p><u>Assessment of quality of included trials:</u> yes, Risk of Bias tool and Oxford Quality Scale.</p>
Remarks
<p>15 RCTs were found. None met our inclusion criteria, as treatment durations were < 3 months in all fifteen studies.</p>

23.5 Hydromorphone for cancer pain. Cochrane systematic review Bao Yan 2016

Methods
Systematic review/Meta-analysis: "Hydromorphone for cancer pain" (59) <u>Inclusion criteria:</u> Study type: RCTs Population: adults and children with moderate to severe cancer pain who were clinically assessed as requiring treatment with opioid analgesia Interventions: hydromorphone (any dose and route of administration) versus placebo, other opioids or another active control. Outcomes: Pain intensity and pain relief; Impact on consciousness, appetite and thirst. <u>Search strategy:</u> CENTRAL, MEDLINE and Embase were search from inception to April 2016. <u>Assessment of quality of included trials:</u> yes, Cochrane Risk of Bias tool. <u>Other methodological remarks:</u>
Remarks
4 RCTs were found. None met our inclusion criteria, as treatment durations were < 3 months in all four studies.

23.6 Transdermal fentanyl for cancer pain. Cochrane systematic review Hadley 2013

Methods
<p>Systematic review/Meta-analysis: “Transdermal fentanyl for cancer pain” (60)</p> <p><u>Inclusion criteria:</u> Study type: RCTs Population: patients of any age with moderate to severe chronic pain, due to malignant disease Intervention: Transdermal fentanyl versus placebo or active controls Outcomes: pain, QoL, use of rescue medication, patient satisfaction or preference, adverse events, attrition</p> <p><u>Search strategy:</u> CENTRAL, MEDLINE, EMBASE were searched from inception to May 2013. CANCERLIT (PubMed) was searched up to November 2012.</p> <p><u>Assessment of quality of included trials:</u> yes, Jadad score.</p>
Remarks
<p>9 RCTs were found. However, none met our inclusion criteria as all nine studies had a treatment duration of < 3 months or a sample size of < 40 participants per study arm.</p>

23.7 Methadone for cancer pain. Cochrane systematic review Nicholson Alexander 2017

Methods
<p>Systematic review/Meta-analysis: "Methadone for cancer pain" (61)</p> <p><u>Inclusion criteria:</u> Study type: RCTs Population: Patients of any age with cancer pain of at least moderate intensity Intervention: methadone given specifically for relief of cancer-related pain (any dose, any route), versus placebo or any other active comparison Outcomes: pain, adverse events</p> <p><u>Search strategy:</u></p> <ul style="list-style-type: none">• CENTRAL: May 2016• MEDLINE: from January 2006 to May 2016.• Embase: from January 2006 to May 2016.• CINAHL: to May 2016.• clinicaltrials.gov to May 2016. <p><u>Assessment of quality of included trials:</u> yes, Risk of Bias tool.</p>
Remarks
<p>6 RCTs were found. However, none met our inclusion criteria as all six studies had a treatment duration of < 3 months or a sample size of < 40 participants per study arm.</p>

23.8 Oxycodone for cancer pain. Cochrane systematic review Schmidt-Hansen 2017

Methods
<p>Systematic review/Meta-analysis: “Oxycodone for cancer-related pain” (62)</p> <p><u>Inclusion criteria:</u> Study type: RCTs Population: adults (age ≥ 18 years old) with cancer pain Intervention: oxycodone (any formulation and route) versus placebo or an active drug (including oxycodone) Outcomes: Pain, adverse events, QoL, participant preference</p> <p><u>Search strategy:</u> CENTRAL, MEDLINE, Embase, Science Citation Index, Conference Proceedings Citation Index, BIOSIS, PsycINFO were searched from inception to November 2016.</p> <p><u>Assessment of quality of included trials:</u> yes, Cochrane Risk of Bias tool.</p>
Remarks
<p>23 RCTs were found. However, none met our inclusion criteria as all but one study had a treatment duration of < 3 months, and the remaining study was unblinded.</p>

23.9 Buprenorphine for cancer pain. Cochrane systematic review Schmidt-Hansen 2014

Methods
<p>Systematic review/Meta-analysis: “Buprenorphine for treating cancer pain” (63)</p> <p><u>Inclusion criteria:</u> Study type: RCTs Population: Adults and children with cancer pain. Intervention: Buprenorphine (any dose, formulation or route) versus placebo, another active drug, or buprenorphine. Outcome: Pain, adverse events, QoL, patient preference.</p> <p><u>Search strategy:</u> CENTRAL, MEDLINE, Embase, Web of Science, BIOSIS were searched from inception to January 2015.</p> <p><u>Assessment of quality of included trials:</u> yes, Cochrane Risk of Bias tool.</p>
Remarks
<p>19 RCTs were found. However, none met our inclusion criteria as all but one study had a treatment duration of < 3 months, and the remaining study was unblinded.</p>

23.10 Oral Tapentadol for cancer pain. Cochrane systematic review Wiffen 2015

Methods
<p>Systematic review/Meta-analysis: "Oral tapentadol for cancer pain" (64)</p> <p><u>Inclusion criteria:</u> Study type: RCTs Population: Adults (≥ 18 years old) with cancer pain of moderate to severe intensity. Intervention: Oral tapentadol versus placebo or active controls Outcomes: Pain, QoL, rescue medication, participant preference, adverse events, attrition</p> <p><u>Search strategy:</u> CENTRAL, MEDLINE and Embase were searched from 2005 to July 2015.</p> <p><u>Assessment of quality of included trials:</u> yes, Cochrane Risk of Bias tool.</p>
Remarks
<p>4 RCTs were found. None met our inclusion criteria, as treatment durations were < 3 months in all four studies.</p>

23.11 Oral morphine for cancer pain. Cochrane systematic review Wiffen 2016

Methods
<p>Systematic review/Meta-analysis: "Oral morphine for cancer pain" (65)</p> <p><u>Inclusion criteria:</u> Study type: RCTs Population: Adults and children with cancer pain requiring treatment with opioids. Intervention: Oral morphine preparations versus placebo, an alternative presentation of morphine, or an active control. Outcomes: Pain, rescue medication, discontinuation of treatment, adverse events.</p> <p><u>Search strategy:</u> CENTRAL, MEDLINE and Embase were searched from inception to October 2015.</p> <p><u>Assessment of quality of included trials:</u> yes, Risk of Bias tool and Oxford Quality Scale.</p>
Remarks
<p>62 RCTs were found. None met our inclusion criteria, as treatment durations were < 3 months in all 62 studies.</p>

23.12 Opioids in cancer survivors

Methods
<p>Systematic review prepared for clinical guideline: “Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline” (14)</p> <p><u>Inclusion criteria:</u> Study type: Published, English-language systematic reviews, meta-analyses, RCTs or comparative observational studies. Population: Adult cancer survivors at risk of or with chronic pain; although literature on chronic pain in other adult populations was also considered because of the paucity of evidence in cancer survivors. Intervention: Pharmacologic or non-pharmacologic interventions for pain management. Outcomes: Symptom relief, pain, QoL, functional outcomes, caregiver end points, adverse events</p> <p><u>Search strategy:</u></p> <p>Pubmed was searched from 1996 to 2015.</p> <p><u>Assessment of quality of included trials:</u> yes, Risk of Bias tool and Oxford Quality Scale.</p>

Remarks
<p>35 systematic reviews, 9 RCTs and 19 observational studies were found.</p> <p>Only one RCT concerned opioids, and it did not meet our inclusion criteria for duration.</p>

24 Appendix: Opioid rotation

24.1 Opioid rotation vs no opioid rotation in chronic non-cancer pain. Systematic review Busse 2017

Methods
<p>Systematic review/Meta-analysis (9)</p> <p><u>Inclusion criteria:</u></p> <p>chronic pain (any painful condition that persists for ≥3 months that is not associated with a diagnosis of cancer), opioid therapy (not cancer, opioid use disorder, pain <3m, pain in end-of-life)</p> <ul style="list-style-type: none">• values and preferences• benefits and harms• dosing and risk mitigation• systematic reviews, RCTs, observational studies<ul style="list-style-type: none">○ opioids versus optimisation of non-opioids in chronic pain○ if optimal non-opioid therapy and persistent pain: opioids versus non-opioids (placebo)○ opioid rotation versus no opioid rotation○ tapering vs no tapering if persistent pain using opioids <p><u>Search strategy:</u></p> <p>AMED, CINAHL, Cochrane Library, Embase, MEDLINE, PsycINFO, and PubMed through October 2016, including randomized trials and observational studies (excluding case reports).Bibliographies of all retrieved articles, to april 2016</p> <p><u>Assessment of quality of included trials:</u> yes, GRADE</p> <p><u>Other methodological remarks:</u></p> <p>This is a systematic review that was performed as an evidence base for a Canadian Guideline on opioid therapy in chronic noncancer pain</p>

Remarks
<p>This systematic review searched for studies comparing rotation to other opioids to no change in opioid therapy in chronic noncancer pain with persistent problematic pain and/or problematic side effects.</p> <p>For the outcome pain, 5 observational studies were found, ranging between 2 weeks and 8 months.</p> <p>For the outcome physical function, 2 observational studies were found, ranging between 2 and 3 months.</p> <p>For the outcome success of opioid rotation, 4 observational studies were found, ranging from 2 to 34 months.</p> <p>For the outcome gastro-intestinal adverse events, 6 observational studies were found, ranging from 2 to 3 months.</p> <p>For the outcome opioid use disorder, 2 observational studies were found, ranging from 2 to 9 months.</p> <p>No RCTs evaluating opioid rotation versus no change in opioid therapy were found.</p>

24.2 Opioid switching. Cochrane systematic review Quigley 2013

The 2013 Cochrane Systematic Review “Opioid switching to improve pain relief and drug tolerability” (67) has been retracted.

24.3 Opioid rotation in cancer pain. Meta-analysis Schuster 2018

Methods

Systematic review/Meta-analysis: "Opioid Rotation in Cancer Pain Treatment" (68)

Inclusion criteria:

- Study types: systematic reviews, RCTs and prospective observational studies
- Population: adults (≥ 18 years old) with chronic cancer-related pain and regular oral or transdermal administration of WHO level III opioids
- Intervention: opioid rotation between WHO level III opioids owing to insufficient analgesia and/or intolerable adverse drug reactions
- Endpoints: Pain intensity, adverse events, additional analgesics required for breakthrough pain, patient preference/satisfaction, QoL, rotation ratio of dosages (conversion ratio), efficacy of rotation

Search strategy:

This systematic review performed a search in DARE and MEDLINE for aggregated evidence (systematic reviews) published from January 2003 to January 2017, after the final search date of the Cochrane Systematic review by Quigley, which was published in 2004. This search yielded a systematic review by Dale (2011), with a search date 2003-2010. Based on the search strategy in Dale, the databases MEDLINE and CENTRAL were searched for primary literature from January 2010 to January 2017.

- Systematic review Quigley 2004: search date 1960 -2003 (searched for rotation studies in cancer and non-cancer pain)
- Systematic review Dale 2011: search date 2003 -2010 (searched for rotation studies in cancer pain)
- Systematic review Schuster 2018: search date 2010 -2017

Assessment of quality of included trials: yes, SRs were evaluated with the AMSTAR tool, RCTs were evaluated with the Cochrane Risk of Bias tool

Remarks

- Systematic review Quigley 2004: search date 1960 -2003: found no RCTs
- Systematic review Dale 2011: search date 2003 -2010: found no RCTs
- Systematic review Schuster 2018: found 5 RCTs. Four were open-label RCTs, one was a post-hoc analysis. None met our inclusion criteria. No meta-analysis was performed. Schuster also searched for and included observational studies.

25 Appendix: Tapering

25.1 Tapering for opioid induced hypogonadism in chronic non-cancer pain. Systematic review AminiLari 2018

Methods
Systematic review/Meta-analysis: “Hormone Replacement Therapy and Opioid Tapering for Opioid-Induced Hypogonadism Among Patients with Chronic Noncancer Pain: A Systematic Review” (69)
<u>Inclusion criteria:</u> <ul style="list-style-type: none">• RCTs or observational studies• n ≥10 patients• follow-up ≥ 14 days• population: patients with chronic noncancer pain and opioid-induced hypogonadism• reporting effect of testosterone replacement therapy or opioid tapering
<u>Search strategy:</u> MEDLINE, CINAHL, EMBASE, and PsycINFO were searched from inception to August 2017
<u>Assessment of quality of included trials:</u> yes; a modified Cochrane risk of bias instrument was used
Remarks
No RCTs evaluating opioid tapering for patients with chronic noncancer pain and opioid-induced hypogonadism were found.

25.2 Tapering vs no tapering in chronic non-cancer pain. Systematic review Buse 2017

Methods
<p>Systematic review/Meta-analysis:</p> <p><u>Inclusion criteria:</u></p> <p>chronic pain (any painful condition that persists for ≥ 3 months that is not associated with a diagnosis of cancer), opioid therapy (not cancer, opioid use disorder, pain < 3m, pain in end-of-life)</p> <ul style="list-style-type: none">• values and preferences• benefits and harms• dosing and risk mitigation• systematic reviews, RCTs, observational studies<ul style="list-style-type: none">○ opioids versus optimisation of non-opioids in chronic pain○ if optimal non-opioid therapy and persistent pain: opioids versus non-opioids (placebo)○ opioid rotation versus no opioid rotation○ tapering vs no tapering if persistent pain using opioids <p><u>Search strategy:</u></p> <p>AMED, CINAHL, Cochrane Library, Embase, MEDLINE, PsycINFO, and PubMed through October 2016, including randomized trials and observational studies (excluding case reports).Bibliographies of all retrieved articles, to april 2016</p> <p><u>Assessment of quality of included trials:</u> yes, GRADE</p> <p><u>Other methodological remarks:</u></p> <p>This is a systematic review that was performed as an evidence base for a Canadian Guideline on opioid therapy in chronic noncancer pain</p>
Remarks
<p>This systematic review searched for studies comparing tapering of opioids to keeping the dose of opioid the same in chronic noncancer pain with persistent problematic pain.</p> <p>For the outcome pain, 2 observational studies were found, with a maximum follow-up of 1 year.</p> <p>For the outcome success of tapering, 2 observational studies were found, with a maximum follow-up of 1 year.</p> <p>No RCTs evaluating opioid tapering versus no change in opioid dose were found.</p>

25.3 Dose reduction or discontinuation of long-term opioid therapy for chronic pain. Systematic review Frank 2017

Methods
Systematic review/Meta-analysis: “Patient Outcomes in Dose Reduction or Discontinuation of Long-Term Opioid Therapy” (70)
<u>Inclusion criteria:</u> RCTs and observational studies published in English population: adults (aged ≥ 18) who were prescribed long-term opioid therapy for chronic pain addressing: <ul style="list-style-type: none">• the effectiveness of strategies to reduce or discontinue LTOT• the effect of dose reduction or discontinuation of LTOT on prespecified patient outcomes of pain severity, pain-related function, quality of life, opioid withdrawal symptoms, substance use, or adverse events. <u>Search strategy:</u> MEDLINE, EMBASE, PsycINFO, CINAHL, and the Cochrane Library were searched from inception to April 2017 <u>Assessment of quality of included trials:</u> yes, GRADE. <u>Other methodological remarks:</u>
Remarks
40 studies were found that assessed the effect of dose reduction or discontinuation of long-term opioid therapy. 35 of these were observational studies. 5 RCTs of poor quality (as assessed by the authors of the systematic review) were found that assessed the effect of dose reduction or discontinuation of long-term opioid therapy on patient outcomes (such as pain, function, quality of life). All five RCTs included less than 40 patients per study arm and were thus excluded from our literature overview. The authors did not perform a meta-analysis due to heterogeneity across studies and methodological limitations of the studies.
Author’s conclusion
Very low quality evidence suggests that several types of interventions may be effective to reduce or discontinue LTOT and that pain, function, and quality of life may improve with opioid dose reduction.

26 Appendix. Agree scores of guidelines

26.1 Agree scores. Summary

Rigour of development item	7	8	9	10	11	12	13	14	Total	Domain score
NPC_Canada 2017	7	6	6	6	6	6	5	5	47	0,84
WOREL 2017	4	2	3	3	5	5	5	5	32	0,57
CDC 2016	7	7	6	5	6	6	5	4	46	0,82
NHG 2018	7	4	5	5	6	7	6	3	43	0,77
NICE 2017	7	6	6	6	6	6	6	7	50	0,89
ASCO 2016	7	6	6	5	6	6	5	7	48	0,86
DOH_Ireland 2015	5	4	6	6	6	6	7	7	47	0,84
KCE 2013	7	7	7	5	6	7	7	5	51	0,91
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.										

26.2 Agree scores. Details

NPC_Canada 2017	Item	Rating	Comment
Systematic methods were used to search for evidence	7	7	uitgebreid in supplement, search strategy was peer reviewed
The criteria for selecting the evidence are clearly described	8	6	in Main document + PICO voor elke zoekvraag + in het supplement
The strengths and limitations of the body of evidence are clearly described	9	6	ok, geen taalcriterium bij inclusie criteria?
The methods for formulating the recommendations are clearly described	10	6	goed beschreven, 2-day meeting, voting, via grade, 80% agreement was nodig, ...
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	6	"benefits and harms" na elke aanbeveling; geselecteerde outcomes,...
There is an explicit link between the recommendations and the supporting evidence.	12	6	na elke aanbeveling,
The guideline has been externally reviewed by experts prior to its publication	13	5	zie "external review" p13. via een externe evaluatie committee. "any dificits identified were addressed before finalization...": geen details gevonden
A procedure for updating the guideline is provided	14	5	zie "update of the guideline". Ongoing update indien funding, ander binnen 5 jaar
Worel 2017	Item	Rating	Comment
Systematic methods were used to search for evidence	7	4	adapte procedure werd gebruikt voor 4 RL (sign, cdc, cancada doen normaal wel een goede search). Daarnaast hebben ze zelf een search gedaan in de cochrane DB naar "SR" en "ivm ons onderwerp", verder niets: dus geen exacte zoektermen vermeld wel start/stop datum
The criteria for selecting the evidence are clearly described	8	2	methodologie pagina is maar 1 pagina - geen apendices. In de inleiding word ook wel nog iets gezegd over de beoogde patiëntenpopulatie
The strengths and limitations of the body of evidence are clearly described	9	3	geen evidence tables (wat heeft de extra search in cochrane opgeleverd?); enige (niet gedetailleerd) uitleg in elke "basis voor de aanbeveling"; er wordt verwezen naar de originele RL. Vereenvoudigde grade werd gebruikt maar geen tabel met info over risk of bias

The methods for formulating the recommendations are clearly described	10	3	consensus onder de auteurs; aanpassen na expertmeeting, geen voting bv. vermeld of hoe de finale beslissing werd bekomen
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	5	globaal wel, zit ook voor een stuk in de aanbevelingen; maar niet zo duidelijk beschreven
There is an explicit link between the recommendations and the supporting evidence.	12	5	telkens in "basis voor de aanbeveling"
The guideline has been externally reviewed by experts prior to its publication	13	5	gevalideerd door CEBAM, is herzien geweest op basis van deze review. Maar geen methodologie hier rond; expertopmerkingen en eventuele aanpassingen zijn wel opvraagbaar.
A procedure for updating the guideline is provided	14	5	Om de 5 jaar is een herziening van deze richtlijn voorzien. Geen methodologie beschreven
CDC 2016	Item	Rating	Comment
Systematic methods were used to search for evidence	7	7	goed beschreven; ze verwijzen naar en gebruikten dezelfde zoekstrategie als AHRQ 2014 die wel de exacte zoektermen vermeldt
The criteria for selecting the evidence are clearly described	8	7	zie appendix "clinical evidence review..." bij study selection
The strengths and limitations of the body of evidence are clearly described	9	6	in tekst en zie ook appendix "clinical evidence review..."
The methods for formulating the recommendations are clearly described	10	5	duidelijk beschreven. De experts scoorden de aanbevelingen op een aantal punten voor de meeting. Geen voting, enkel comments (2x), geen methode op basis van consensus maar CDC maakte zelf de finale beslissingen. Er werd wel advies ingewonnen van publiek en bepaalde instanties
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	6	er is een aparte sectie "benefits and harms of opioid therapy". Zie ook appendices "clinical evidence review..." and "contextual evidence review..."
There is an explicit link between the recommendations and the supporting evidence.	12	6	Zie ook appendices "clinical evidence review..." and "contextual evidence review..."
The guideline has been externally reviewed by experts prior to its publication	13	5	zie sectie "peer review"
A procedure for updating the guideline is provided	14	4	"CDC will revisit this guideline as new evidence becomes available to determine when evidence gaps have been sufficiently closed to warrant an update of the guideline"

NHG 2018	Item	Rating	Comment
Systematic methods were used to search for evidence	7	7	full search in bijlage, methodologie beschreven in handleiding
The criteria for selecting the evidence are clearly described	8	4	Handleiding beschrijft opstellen van selectiecriteria afhankelijk van richtlijn, maar geen specifieke criteria voor deze richtlijn terug te vinden, buiten de populatie
The strengths and limitations of the body of evidence are clearly described	9	5	Handleiding beschrijft beoordeling van evidentie volgens AMSTAR (voor SRs), maken van evidentietabellen, toepassen GRADE; maar geen verslag voor specifieke richtlijn te vinden; soms wel beschrijving van kwaliteit van evidentie in noten
The methods for formulating the recommendations are clearly described	10	5	beschrijving in totstandkoming; focusgroep/commentaarrondes
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	6	In handleiding beschreven; ook in noten meestal gestaafd
There is an explicit link between the recommendations and the supporting evidence.	12	7	Noten; duidelijke beschrijving
The guideline has been externally reviewed by experts prior to its publication	13	6	In handleiding wordt dit beschreven, verschillende verenigingen, ook patiënten; ook in specifieke richtlijn, maar niet alle namen gekend
A procedure for updating the guideline is provided	14	3	Niet beschreven, richtlijnen lijken wel regelmatig te worden bijgewerkt
NICE 2017	Item	Rating	Comment
Systematic methods were used to search for evidence	7	7	in tekst and appendix D
The criteria for selecting the evidence are clearly described	8	6	in tekst and appendix D
The strengths and limitations of the body of evidence are clearly described	9	6	
The methods for formulating the recommendations are clearly described	10	6	ook in online NICE manual
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	6	zie "trade-off between benefits and harms" onder 3.1.4. evidence to recommendations
There is an explicit link between the recommendations and the supporting evidence.	12	6	zie 3.1.4. evidence to recommendations

The guideline has been externally reviewed by experts prior to its publication	13	6	zie manual website punt 9 en 10
A procedure for updating the guideline is provided	14	7	staat uitgebreid in de online NICE manual
ASCO 2016	Item	Rating	Comment
Systematic methods were used to search for evidence	7	7	zie data supplement 2: chronic pain pubmed search strategy strings and dates
The criteria for selecting the evidence are clearly described	8	6	Ik vind niet onmiddellijk naar welke "comparisons" exact werd gezocht. Wel beschreven in tabel 2, maar dit zijn de vergelijkingen van de gevonden studies
The strengths and limitations of the body of evidence are clearly described	9	6	zie "study quality assessment"; fig 1 in de methodologie supplement; ratings available for overall potential risk of bias; zie ook onder elke aanbeveling
The methods for formulating the recommendations are clearly described	10	5	in methodologie en data supplement; volgens "GuideLines Into Decision Support methodology"
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	6	risks zitten in de aanbevelingen, ook telkens een uitspraak over afweging risico/baten na elke aanbeveling
There is an explicit link between the recommendations and the supporting evidence.	12	6	zie fig 1 in de methodologie supplement en "Literature review, analysis, and clinical interpretation" en data supplement met evidence tabellen.
The guideline has been externally reviewed by experts prior to its publication	13	5	zie "external review". peer review voor publicatie (JCO)
A procedure for updating the guideline is provided	14	7	jaarlijkse evaluatie. Methodologie uitgebreid beschreven, zie onder "revisions" in de "methodology supplement"
DOH_Ireland 2015	Item	Rating	Comment
Systematic methods were used to search for evidence	7	5	adapte procedure van o.a. Sign RL, daarnaast een eigen search: niet zo gedetailleerd gerapporteerd (geen full search met search terms gerapporteerd) maar zijn ook 22 zoekvragen
The criteria for selecting the evidence are clearly described	8	4	appendix VII per pico, inclusie en exclusie criteria niet zo duidelijk: welke study design (enkel RCT's?), language restrictions in search?
The strengths and limitations of the body of evidence are clearly	9	6	uitgebreid bespreking met level of evidence voor elke aanbeveling in

described			"the following are responsible for implementation of recommendation x"
The methods for formulating the recommendations are clearly described	10	6	appendix II. Appendix IV as source for recommendations; zie ook 1.8.7 en 1.8.8
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	6	zit in de aanbevelingen
There is an explicit link between the recommendations and the supporting evidence.	12	6	na elke aanbeveling "the following are responsible for implementation of recommendation"
The guideline has been externally reviewed by experts prior to its publication	13	7	external review and amendments to guideline in appendix VIII
A procedure for updating the guideline is provided	14	7	zie 1.13 on page 22, met link naar methodologie van NICE (ref36)
KCE 2013	Item	Rating	Comment
Systematic methods were used to search for evidence	7	7	zie p18 en search syntax in appendix I
The criteria for selecting the evidence are clearly described	8	7	zie table 1 p19
The strengths and limitations of the body of evidence are clearly described	9	7	uitgebreide quality appraisal: amstar tool gebruikt voor SR, cochrane collaboration tool voor RCT's, tabel 18 p60 in supplement: risk of bias, zie ook evidence tabellen, zie ook 2.8.2.
The methods for formulating the recommendations are clearly described	10	5	zie 2.8. vanaf p23
The health benefits, side effects, and risks have been considered in formulating the recommendations.	11	6	
There is an explicit link between the recommendations and the supporting evidence.	12	7	
The guideline has been externally reviewed by experts prior to its publication	13	7	zie p25 en p26 (ook cebam), en appendix 4
A procedure for updating the guideline is provided	14	5	p13, methodologie niet zo uitgebreid

27 Appendix: Search strategy details

The following search string was used to search for RCTs and systematic reviews/meta-analyses of RCTs

```
(((((((((( "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] )) )))) AND ((("Analgesics, Opioid"[Mesh] OR "Analgesics,
Opioid"[Pharmacological Action] OR Opioid* [tiab] OR Codeine[tiab] OR "Codeine"[Mesh] OR
Tramadol[tiab] OR "Tramadol"[Mesh] OR Tilidine[tiab] OR "Tilidine"[Mesh] OR
Buprenorphine[tiab] OR "Buprenorphine"[Mesh] OR Fentanyl[tiab] OR "Fentanyl"[Mesh] OR
Hydromorphone[tiab] OR "Hydromorphone"[Mesh] OR Methadon*[tiab] OR "Methadone"[Mesh]
OR Morphine[tiab] OR "Morphine"[Mesh] OR Oxycodone[tiab] OR "Oxycodone"[Mesh] OR
Tapentadol[tiab] OR "tapentadol" [Supplementary Concept]))) AND ((randomized controlled trial
OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])))
AND ("2016/03/01"[Date - Publication] : "2018/06/01"[Date - Publication])))
OR
(((( Neuralg*[tiab] OR *neuropath*[tiab] OR "Peripheral Nervous System Diseases"[Mesh] OR
"cranial Nerve Diseases"[Mesh] OR "Somatosensory Disorders"[Mesh] )) AND (((("Analgesics,
Opioid"[Mesh] OR "Analgesics, Opioid"[Pharmacological Action] OR Opioid* [tiab] OR
Codeine[tiab] OR "Codeine"[Mesh] OR Tramadol[tiab] OR "Tramadol"[Mesh] OR Tilidine[tiab] OR
"Tilidine"[Mesh] OR Buprenorphine[tiab] OR "Buprenorphine"[Mesh] OR Fentanyl[tiab] OR
"Fentanyl"[Mesh] OR Hydromorphone[tiab] OR "Hydromorphone"[Mesh] OR Methadon*[tiab] OR
"Methadone"[Mesh] OR Morphine[tiab] OR "Morphine"[Mesh] OR Oxycodone[tiab] OR
"Oxycodone"[Mesh] OR Tapentadol[tiab] OR "tapentadol" [Supplementary Concept]))) AND
("2016/12/01"[Date - Publication] : "2018/06/01"[Date - Publication]))) OR (((Codeine[tiab] OR
"Codeine"[Mesh] OR Tilidine[tiab] OR "Tilidine"[Mesh] OR Methadon*[tiab]))) AND
("2016/03/01"[Date - Publication] : "2018/06/01"[Date - Publication]))) AND ((randomized
controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR
medline[TIAB])))
OR
((((("Cancer Pain"[Mesh] OR cancer pain[tiab] OR oncologic pain[tiab] OR cancer-related
pain[tiab]))) AND (((((((Fentanyl[tiab] OR "Fentanyl"[Mesh]))) AND ("2013/04/01"[Date -
Publication] : "2018/06/01"[Date - Publication]))) OR (((Codeine[tiab] OR "Codeine"[Mesh]))) AND
("2014/01/01"[Date - Publication] : "2018/06/01"[Date - Publication]))) OR ((Tilidine[tiab] OR
"Tilidine"[Mesh]))) OR (((("2014/12/01"[Date - Publication] : "2018/06/01"[Date - Publication]))
AND ((("Analgesics, Opioid"[Mesh] OR "Analgesics, Opioid"[Pharmacological Action] OR Opioid*
[tiab] OR Codeine[tiab] OR "Codeine"[Mesh] OR Tramadol[tiab] OR "Tramadol"[Mesh] OR
Tilidine[tiab] OR "Tilidine"[Mesh] OR Buprenorphine[tiab] OR "Buprenorphine"[Mesh] OR
Fentanyl[tiab] OR "Fentanyl"[Mesh] OR Hydromorphone[tiab] OR "Hydromorphone"[Mesh] OR
Methadon*[tiab] OR "Methadone"[Mesh] OR Morphine[tiab] OR "Morphine"[Mesh] OR
Oxycodone[tiab] OR "Oxycodone"[Mesh] OR Tapentadol[tiab] OR "tapentadol" [Supplementary
```

Concept]))) AND ((randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])))

OR

(((((("Neoplasms"[Mesh] OR cancer[tiab] OR neoplasm*[tiab]) AND ("Cancer Survivors"[Mesh] OR survivor*[tiab]))) AND (("Analgesics, Opioid"[Mesh] OR "Analgesics, Opioid"[Pharmacological Action] OR Opioid*[tiab] OR Codeine[tiab] OR "Codeine"[Mesh] OR Tramadol[tiab] OR "Tramadol"[Mesh] OR Tilidine[tiab] OR "Tilidine"[Mesh] OR Buprenorphine[tiab] OR "Buprenorphine"[Mesh] OR Fentanyl[tiab] OR "Fentanyl"[Mesh] OR Hydromorphone[tiab] OR "Hydromorphone"[Mesh] OR Methadon*[tiab] OR "Methadone"[Mesh] OR Morphine[tiab] OR "Morphine"[Mesh] OR Oxycodone[tiab] OR "Oxycodone"[Mesh] OR Tapentadol[tiab] OR "tapentadol" [Supplementary Concept]))) AND ((randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB]))) AND ("2014/10/01"[Date - Publication] : "2018/06/01"[Date - Publication])))

OR

((((((((rotat*[TIAB] OR switch*[TIAB] OR substitut*[TIAB])) OR ((taper*[tiab] OR withdraw*[tiab] OR wean*[tiab]))) AND (((("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]))) AND ((("Analgesics, Opioid"[Mesh] OR "Analgesics, Opioid"[Pharmacological Action] OR Opioid*[tiab] OR Codeine[tiab] OR "Codeine"[Mesh] OR Tramadol[tiab] OR "Tramadol"[Mesh] OR Tilidine[tiab] OR "Tilidine"[Mesh] OR Buprenorphine[tiab] OR "Buprenorphine"[Mesh] OR Fentanyl[tiab] OR "Fentanyl"[Mesh] OR Hydromorphone[tiab] OR "Hydromorphone"[Mesh] OR Methadon*[tiab] OR "Methadone"[Mesh] OR Morphine[tiab] OR "Morphine"[Mesh] OR Oxycodone[tiab] OR "Oxycodone"[Mesh] OR Tapentadol[tiab] OR "tapentadol" [Supplementary Concept]))) AND ((randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB]))) AND ("2015/03/01"[Date - Publication] : "2018/06/01"[Date - Publication]))

The following search string was used to search for observational studies

(((((("Analgesics, Opioid"[Mesh] OR "Analgesics, Opioid"[Pharmacological Action] OR Opioid*[tiab]) AND (((((((((hypogonadism[Title/Abstract]) OR testosterone[Title/Abstract]) OR oestrogen[Title/Abstract]) OR androgen[Title/Abstract]) OR endocrin*[Title/Abstract]) OR ((sexual[Title/Abstract]) OR erectile[Title/Abstract])) OR ((amenorr*[Title/Abstract]) OR infertility[Title/Abstract])) OR "Hypogonadism"[Mesh])) OR (((infection[Title/Abstract]) OR immunosuppress*[Title/Abstract])) OR ((cancer[Title/Abstract]) AND (((relapse[Title/Abstract]) OR recurrence[Title/Abstract]))))) 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])))) AND ("2015/01/01"[Date - Publication] : "2018/07/01"[Date - Publication]))

28 Appendix. List of excluded publications (after evaluation of full tekst)

1. Ahn JS, Lin J, Ogawa S, et al. Transdermal buprenorphine and fentanyl patches in cancer pain: a network systematic review. *J Pain Res* 2017;10:1963-72.**n. network meta-analysis. only studies comparing different opioids were included**
2. Aiyer R, Mehta N, Gungor S, et al. A Systematic Review of NMDA Receptor Antagonists for Treatment of Neuropathic Pain in Clinical Practice. *Clin J Pain* 2018;34:450-67.**n. Cochrane McNichol has better search strategy; no newer studies included.**
3. Alinejad S, Ghaemi K, Abdollahi M, et al. Nephrotoxicity of methadone: a systematic review. *Springerplus* 2016;5:2087.**n. not a research question**
4. Alviar MJ, Hale T, Dungca M. Pharmacologic interventions for treating phantom limb pain. *Cochrane Database Syst Rev* 2016;10:Cd006380.**n. trials with opioids did not meet inclusion criteria (duration and sample size)**
5. Arai T, Kashimoto Y, Ukyo Y, et al. Two placebo-controlled, randomized withdrawal studies to evaluate the fentanyl 1 day patch in opioid-naïve patients with chronic pain. *Curr Med Res Opin* 2015;31:2207-18.**n. this formulation (1-day patch) is not available in Belgium**
6. Bell KL, Shohat N, Goswami K, et al. Preoperative Opioids Increase the Risk of Periprosthetic Joint Infection After Total Joint Arthroplasty. *J Arthroplasty* 2018.**n. this observational study examines the link between preoperative opioids and subsequent periprosthetic joint infection. no information on duration of opioid use was provided.**
7. Binder A, Baron R. The Pharmacological Therapy of Chronic Neuropathic Pain. *Dtsch Arztebl Int* 2016;113:616-25.**n. not SR.**
8. Birthi P, Nagar VR, Nickerson R, et al. Hypogonadism associated with long-term opioid therapy: A systematic review. *J Opioid Manag* 2015;11:255-78.**n. search date is earlier than our source document. reference list screened, no eligible studies.**
9. Blagden M, Hafer J, Duerr H, et al. Long-term evaluation of combined prolonged-release oxycodone and naloxone in patients with moderate-to-severe chronic pain: pooled analysis of extension phases of two Phase III trials. *Neurogastroenterol Motil* 2014;26:1792-801.**n. comparison of opioid vs opioid**
10. Brant JM, Keller L, McLeod K, et al. Chronic and Refractory Pain: A Systematic Review of Pharmacologic Management in Oncology. *Clin J Oncol Nurs* 2017;21:31-53.**n. Incomplete search. References screened, no new relevant references found.**
11. Bredow J, Bloess K, Oppermann J, et al. [Conservative treatment of nonspecific, chronic low back pain : Evidence of the efficacy - a systematic literature review]. *Orthopade* 2016;45:573-8.**n. reference list screened; no new information**
12. CADTH. CADTH Rapid Response Reports. Long-acting Opioids for Chronic Non-cancer Pain: A Review of the Clinical Efficacy and Safety 2015.**n. compares opioid vs opioid**
13. Cakici N, Fakkal TM, van Neck JW, et al. Systematic review of treatments for diabetic peripheral neuropathy. *Diabet Med* 2016;33:1466-76.**n. Dy 2017 is more recent**
14. Carmona-Bayonas A, Jimenez Fonseca P, Virizuela Echaburu J. Tapentadol for Cancer Pain Management: A Narrative Review. *Pain Pract* 2017;17:1075-88.**n. includes the same trials as Cochrane Wiffen 2015**
15. Chaparro Luis E, Furlan Andrea D, Deshpande A, et al. Opioids compared to placebo or other treatments for chronic low-back pain. *Cochrane Database of Systematic Reviews* 2013.**n. We have a more recent SR for this research question (Abdel Shaheed 2016)**

16. Cho JH, Lee JH, Song KS, et al. Treatment Outcomes for Patients with Failed Back Surgery. *Pain Physician* 2017;20:E29-e43.**n. no included studies met our inclusion criteria**
17. Coluzzi F, Fornasari D, Pergolizzi J, et al. From acute to chronic pain: tapentadol in the progressive stages of this disease entity. *Eur Rev Med Pharmacol Sci* 2017;21:1672-83.**n. not SR**
18. Coluzzi F, Ruggeri M. Clinical and economic evaluation of tapentadol extended release and oxycodone/naloxone extended release in comparison with controlled release oxycodone in musculoskeletal pain. *Curr Med Res Opin* 2014;30:1139-51.**n. compares opioid vs opioid**
19. Connolly C, Buggy DJ. Opioids and tumour metastasis: does the choice of the anesthetic-analgesic technique influence outcome after cancer surgery? *Curr Opin Anaesthesiol* 2016;29:468-74.**n. is not SR. focusses on opioids used in perioperative period**
20. Corli O, Roberto A, Bennett MI, et al. Nonresponsiveness and Susceptibility of Opioid Side Effects Related to Cancer Patients' Clinical Characteristics: A Post-Hoc Analysis. *Pain Pract* 2017.**n. post hoc; duration 28 days.**
21. Cronin-Fenton D, Lash TL, Ahern TP, et al. Concurrent new drug prescriptions and prognosis of early breast cancer: studies using the Danish Breast Cancer Group clinical database. *Acta Oncol* 2018;57:120-8.**n. we include the original publication to which this review refers. See Cronin-Fenton 2015**
22. Deyo RA, Smith DH, Johnson ES, et al. Prescription opioids for back pain and use of medications for erectile dysfunction. *Spine (Phila Pa 1976)* 2013;38:909-15.**n. this publication was found by CDC Dowell 2016. This is a cross-sectional design.**
23. Deyo RA, Von Korff M, Duhrkoop D. Opioids for low back pain. *Bmj* 2015;350:g6380.**n. incomplete search.**
24. Dieckmann G, Goyal S, Hamrah P. Neuropathic Corneal Pain: Approaches for Management. *Ophthalmology* 2017;124:S34-s47.**n. not a research question**
25. Dosenovic S, Jelacic Kadic A, Miljanovic M, et al. Interventions for Neuropathic Pain: An Overview of Systematic Reviews. *Anesth Analg* 2017;125:643-52.**n. we have all the included SRs**
26. Dupoirson D, Stachowiak A, Loewenstein O, et al. Long-term efficacy and safety of oxycodone-naloxone prolonged-release formulation (up to 180/90 mg daily) - results of the open-label extension phase of a phase III multicenter, multiple-dose, randomized, controlled study. *Eur J Pain* 2017;21:1485-94.**n. comparison of opioid vs opioid**
27. Ferreira ML, McLachlan A. The Challenges of Treating Sciatica Pain in Older Adults. *Drugs Aging* 2016;33:779-85.**n. not a specific research question**
28. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol* 2015;14:162-73.**n. not used as a meta-analysis. included studies screened. extracted 1 RCT.**
29. Gilron I, Tu D, Holden RR, et al. Combination of morphine with nortriptyline for neuropathic pain. *Pain* 2015;156:1440-8.**n. six week treatment period only**
30. Gimbel J, Spierings EL, Katz N, et al. Efficacy and tolerability of buccal buprenorphine in opioid-experienced patients with moderate to severe chronic low back pain: results of a phase 3, enriched enrollment, randomized withdrawal study. *Pain* 2016;157:2517-26.**n. this formulation (buccal film) is not available in Belgium**
31. Grandhi RK, Lee S, Abd-Elseyed A. Does Opioid Use Cause Angiogenesis and Metastasis? *Pain Med* 2017;18:140-51.**n. researches in vitro studies**
32. Griebeler ML, Morey-Vargas OL, Brito JP, et al. Pharmacologic interventions for painful diabetic neuropathy: An umbrella systematic review and comparative effectiveness network meta-analysis. *Ann Intern Med* 2014;161:639-49.**n. Dy 2017 is more recent and incorporates these results**
33. Hadley GR, Gayle JA, Ripoll J, et al. Post-herpetic Neuralgia: a Review. *Curr Pain Headache Rep* 2016;20:17.**n. not SR**
34. Hayes CJ, Painter JT. A comprehensive clinical review of opioid-induced allodynia: Discussion of the current evidence and clinical implications. *J Opioid Manag* 2017;13:95-103.**n. not a research question**

35. Higgins C, Smith BH, Matthews K. Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: a systematic review and meta-analysis. *Br J Anaesth* 2018;120:1335-44.**n. no RCTs included**
36. Hofmann JF, Lal A, Steffens M, et al. Patient-relevant outcomes and health-related quality of life in patients with chronic, severe, noncancer pain treated with tapentadol prolonged release-Using criteria of health technology assessment. *J Opioid Manag* 2016;12:323-31.**n. opioid vs opioid comparison. not a research question**
37. Imanaka K, Tominaga Y, Etropolski M, et al. Ready conversion of patients with well-controlled, moderate to severe, chronic malignant tumor-related pain on other opioids to tapentadol extended release. *Clin Drug Investig* 2014;34:501-11.**n. this is not a trial about indication for rotation (population with adequate control on opioids). this trial evaluates conversion (dose).**
38. Kim HJ, Kim YS, Park SH. Opioid rotation versus combination for cancer patients with chronic uncontrolled pain: a randomized study. *BMC Palliat Care* 2015;14:41.**n. study type**
39. Kim PY, Johnson CE. Chemotherapy-induced peripheral neuropathy: a review of recent findings. *Curr Opin Anaesthesiol* 2017;30:570-6.**n. not full SR.**
40. Kim SY, Kim NK, Baik SH, et al. Effects of Postoperative Pain Management on Immune Function After Laparoscopic Resection of Colorectal Cancer: A Randomized Study. *Medicine (Baltimore)* 2016;95:e3602.**n. perioperative opioid use. sample size**
41. 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. no systematic search.**
42. Koopmans G, Simpson K, De Andres J, et al. Fixed ratio (2:1) prolonged-release oxycodone/naloxone combination improves bowel function in patients with moderate-to-severe pain and opioid-induced constipation refractory to at least two classes of laxatives. *Curr Med Res Opin* 2014;30:2389-96.**n. sample size, no systematic search**
43. Krebs EE, Jensen AC, Nugent S, et al. Design, recruitment outcomes, and sample characteristics of the Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) trial. *Contemp Clin Trials* 2017;62:130-9.**n. is description of SPACE trial (included). no additional info in this article.**
44. Kress HG, Koch ED, Kosturski H, et al. Direct conversion from tramadol to tapentadol prolonged release for moderate to severe, chronic malignant tumour-related pain. *Eur J Pain* 2016;20:1513-8.**n. study type**
45. Kurita GP, Hojsted J, Sjogren P. Tapering off long-term opioid therapy in chronic non-cancer pain patients: A randomized clinical trial. *Eur J Pain* 2018.**n. sample size.**
46. Lamb YN, Garnock-Jones KP, Keam SJ. Oxycodone DETERx((R)) ER Capsules: A Review in Severe, Chronic Pain. *Drugs* 2016;76:1759-69.**n. this is not the original publication. this formulation (deterX) is not available in Belgium**
47. Lange B, von Zabern D, Elling C, et al. Efficacy and safety of tapentadol prolonged release for moderate-to-severe chronic osteoarthritis knee pain: a pooled analysis of two double-blind, randomized, placebo- and oxycodone controlled release-controlled studies. *Curr Med Res Opin* 2017;33:1413-22.**n. pooled analysis, not based on systematic search. We have all included RCT's through other publications**
48. Lucchesi M, Lanzetta G, Antonuzzo A, et al. Developing drugs in cancer-related bone pain. *Crit Rev Oncol Hematol* 2017;119:66-74.**n. not full SR. no studies met our inclusion criteria.**
49. Ma H, Liu Y, Huang L, et al. The Adverse Events of Oxycodone in Cancer-Related Pain: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Medicine (Baltimore)* 2016;95:e3341.**n. only includes oxy vs other opioids.**
50. Majithia N, Loprinzi CL, Smith TJ. New Practical Approaches to Chemotherapy-Induced Neuropathic Pain: Prevention, Assessment, and Treatment. *Oncology (Williston Park)* 2016;30:1020-9.**n. unclear search strategy. no studies on opioids included.**

51. Makris UE, Abrams RC, Gurland B, et al. Management of persistent pain in the older patient: A clinical review. *JAMA* 2014;312:825-37.**n. not a specific research question**
52. McNicol Ewan D, Strassels S, Goudas L, et al. NSAIDs or paracetamol, alone or combined with opioids, for cancer pain. *Cochrane Database of Systematic Reviews* 2015.**n. retracted publication. included studies did not meet our inclusion criteria**
53. Meng Z, Yu J, Acuff M, et al. Tolerability of Opioid Analgesia for Chronic Pain: A Network Meta-Analysis. *Sci Rep* 2017;7:1995.**n. network meta-analysis. includes only opioid - opioid comparisons**
54. Mercadante S, Bruera E. Methadone as a First-Line Opioid in Cancer Pain Management: A Systematic Review. *J Pain Symptom Manage* 2018;55:998-1003.**n. none of the included trials met our inclusion criteria (duration, comparison to other opioids only)**
55. Meske DS, Lawal OD, Elder H, et al. Efficacy of opioids versus placebo in chronic pain: a systematic review and meta-analysis of enriched enrollment randomized withdrawal trials. *J Pain Res* 2018;11:923-34.**n. This is not a research question. References checked for relevant RCTs**
56. Nagar VR, Birthi P, Salles S, et al. Opioid Use in Chronic Pain Patients with Chronic Kidney Disease: A Systematic Review. *Pain Med* 2017;18:1416-49.**n. not a specific research question**
57. Odonkor CA, Kim G, Erdek M. Global cancer pain management: a systematic review comparing trials in Africa, Europe and North America. *Pain Manag* 2017;7:299-310.**n. not a research question**
58. Oosten AW, Oldenmenger WH, Mathijssen RH, et al. A Systematic Review of Prospective Studies Reporting Adverse Events of Commonly Used Opioids for Cancer-Related Pain: A Call for the Use of Standardized Outcome Measures. *J Pain* 2015;16:935-46.**n. none of the included RCTs fulfilled our criteria for inclusion. This publication was used in the chapter 'Critical reflection'.**
59. O'Rourke TK, Jr., Wosnitzer MS. Opioid-Induced Androgen Deficiency (OPIAD): Diagnosis, Management, and Literature Review. *Curr Urol Rep* 2016;17:76.**n. reviews studies about treatment of opioid induced androgen deficiency**
60. Pampati S, Manchikanti L. What Is the Prevalence of Symptomatic Obstructive Sleep Apnea Syndrome in Chronic Spinal Pain Patients? An Assessment of the Correlation of OSAS with Chronic Opioid Therapy, Obesity, and Smoking. *Pain Physician* 2016;19:E569-79.**n. not a specific research question**
61. Pergolizzi JV, Jr., Raffa RB, Fleischer C, et al. Management of moderate to severe chronic low back pain with buprenorphine buccal film using novel bioerodible mucoadhesive technology. *J Pain Res* 2016;9:909-16.**n. this formulation (buccal film) is not available in Belgium**
62. Pergolizzi JV, Raffa RB, Marcum Z, et al. Safety of buprenorphine transdermal system in the management of pain in older adults. *Postgrad Med* 2017;129:92-101.**n. not a research question. no systematic search.**
63. Pinto RZ, Verwoerd AJH, Koes BW. Which pain medications are effective for sciatica (radicular leg pain)? *Bmj* 2017;359:j4248.**n. not SR; 1 study opioids vs placebo: does fulfill our inclusion criteria**
64. Plein LM, Rittner HL. Opioids and the immune system - friend or foe. *Br J Pharmacol* 2017.**n. not SR**
65. Rauck RL, Hale ME, Bass A, et al. A randomized double-blind, placebo-controlled efficacy and safety study of ALO-02 (extended-release oxycodone surrounding sequestered naltrexone) for moderate-to-severe chronic low back pain treatment. *Pain* 2015;156:1660-9.**n. this combination (oxycodone + naltrexone) is not available in Belgium.**
66. Rauck RL, Potts J, Xiang Q, et al. Efficacy and tolerability of buccal buprenorphine in opioid-naïve patients with moderate to severe chronic low back pain. *Postgrad Med* 2016;128:1-11.**n. this formulation (buccal film) is not available in Belgium**
67. Reinecke H, Weber C, Lange K, et al. Analgesic efficacy of opioids in chronic pain: recent meta-analyses. *Br J Pharmacol* 2015;172:324-33.**n. Searched until 2009. We have more recent publications**
68. Richardson C, Kulkarni J. A review of the management of phantom limb pain: challenges and solutions. *J Pain Res* 2017;10:1861-70.**n. none of the included RCTs met our inclusion criteria.**

69. Rubinstein A, Carpenter DM. Elucidating risk factors for androgen deficiency associated with daily opioid use. *Am J Med* 2014;127:1195-201.**n. this publication was found by CDC Dowell 2016. This is a cross-sectional design.**
70. Schmidt-Hansen M, Bennett MI, Arnold S, et al. Efficacy, tolerability and acceptability of oxycodone for cancer-related pain in adults: an updated Cochrane systematic review. *BMJ Support Palliat Care* 2018;8:117-28.**n. Is double publication, identical with Cochrane Schmidt Hansen**
71. Schmidt-Hansen M, Taubert M, Bromham N, et al. The effectiveness of buprenorphine for treating cancer pain: an abridged Cochrane review. *BMJ Support Palliat Care* 2016;6:292-306.**n. double publication. we included the original cochrane review.**
72. Serinken M, Eken C, Gungor F, et al. Comparison of Intravenous Morphine Versus Paracetamol in Sciatica: A Randomized Placebo Controlled Trial. *Acad Emerg Med* 2016;23:674-8.**n. duration**
73. Snedecor SJ, Sudharshan L, Cappelleri JC, et al. Systematic review and meta-analysis of pharmacological therapies for pain associated with postherpetic neuralgia and less common neuropathic conditions. *Int J Clin Pract* 2014;68:900-18.**n. None of the included RCTs met our inclusion criteria**
74. Snedecor SJ, Sudharshan L, Cappelleri JC, et al. Systematic review and comparison of pharmacologic therapies for neuropathic pain associated with spinal cord injury. *J Pain Res* 2013;6:539-47.**n. none of the included RCTs met our inclusion criteria**
75. Song D, He A, Xu R, et al. Efficacy of Pain Relief in Different Postherpetic Neuralgia Therapies: A Network Meta-Analysis. *Pain Physician* 2018;21:19-32.**n. none of the included RCTs met our inclusion criteria**
76. Sullivan MD, Turner JA, DiLodovico C, et al. Prescription Opioid Taper Support for Outpatients With Chronic Pain: A Randomized Controlled Trial. *J Pain* 2017;18:308-18.**n. sample size.**
77. Ueberall MA, Mueller-Schwefe GH. Efficacy and tolerability balance of oxycodone/naloxone and tapentadol in chronic low back pain with a neuropathic component: a blinded end point analysis of randomly selected routine data from 12-week prospective open-label observations. *J Pain Res* 2016;9:1001-20.**n. study type/sample size**
78. Varma A, Sapra M, Iranmanesh A. Impact of opioid therapy on gonadal hormones: focus on buprenorphine. *Horm Mol Biol Clin Investig* 2018.**n. incomplete search. includes only small observational studies (n<200)**
79. Voon P, Karamouzian M, Kerr T. Chronic pain and opioid misuse: a review of reviews. *Subst Abuse Treat Prev Policy* 2017;12:36.**n. not a research question**
80. Waldfogel JM, Nesbit SA, Dy SM, et al. Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life: A systematic review. *Neurology* 2017;88:1958-67.**n. has the same information as Dy 2017**
81. Wang D. Opioid Medications in the Management of Chronic Abdominal Pain. *Curr Pain Headache Rep* 2017;21:40.**n. none of the included trials met our inclusion criteria**
82. Wang DD, Ma TT, Zhu HD, et al. Transdermal fentanyl for cancer pain: Trial sequential analysis of 3406 patients from 35 randomized controlled trials. *J Cancer Res Ther* 2018;14:S14-s21.**n. compares fentanyl only to morphine.**
83. Webster L, Gruener D, Kirby T, et al. Evaluation of the Tolerability of Switching Patients on Chronic Full mu-Opioid Agonist Therapy to Buccal Buprenorphine. *Pain Med* 2016.**n. sample size. formulation not available in Belgium**
84. Weil AJ, Masters ET, Barsdorf AI, et al. Patient-reported health-related quality of life, work productivity, and activity impairment during treatment with ALO-02 (extended-release oxycodone and sequestered naltrexone) for moderate-to-severe chronic low back pain. *Health Qual Life Outcomes* 2017;15:202.**n. this combination (oxycodone + naltrexone) is not available in belgium**
85. Welsch P, Sommer C, Schiltenswolf M, et al. [Opioids in chronic noncancer pain-are opioids superior to nonopioid analgesics? A systematic review and meta-analysis of efficacy, tolerability and safety in randomized

List of excluded publications

head-to-head comparisons of opioids versus nonopioid analgesics of at least four week's duration]. Schmerz 2015;29:85-95.n. we have more recent systematic reviews. reference list screened for relevant articles.

86. Wiese AD, Griffin MR, Stein CM, et al. Opioid Analgesics and the Risk of Serious Infections Among Patients With Rheumatoid Arthritis: A Self-Controlled Case Series Study. *Arthritis Rheumatol* 2016;68:323-31.**n. This population was excluded from our literature search.**

87. Wylde V, Dennis J, Beswick AD, et al. Systematic review of management of chronic pain after surgery. *Br J Surg* 2017;104:1293-306.**n. none of the included trials met our inclusion criteria**

88. Zylla D, Steele G, Gupta P. A systematic review of the impact of pain on overall survival in patients with cancer. *Support Care Cancer* 2017;25:1687-98.**n. does not examine opioids and immunosuppression**

29 References

1. Dowell D, Haegerich T, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States. MMWR Recomm Rep 2016;65: 1-49.
2. McNicol Ewan D, Ferguson McKenzie C, Schumann R. Methadone for neuropathic pain in adults. Cochrane Database of Systematic Reviews 2017.
3. Steiner DJ, Sitar S, Wen W, Sawyerr G, Munera C, Ripa SR, et al. Efficacy and safety of the seven-day buprenorphine transdermal system in opioid-naïve patients with moderate to severe chronic low back pain: an enriched, randomized, double-blind, placebo-controlled study. Journal of pain and symptom management 2011;42: 903-17.
4. Furlan AD, Chaparro LE, Irvin E, Mailis-Gagnon A. A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. Pain Research & Management : The Journal of the Canadian Pain Society 2011;16: 337-51.
5. Chevalier P. RCT met 'enriched enrollment'. Het risico van bias en beperkte veralgemeenbaarheid. Minerva 2012;11: 103.
6. Yamato TP, Maher CG, Saragiotto BT, Shaheed CA, Moseley AM, Lin CC, et al. Comparison of effect sizes between enriched and nonenriched trials of analgesics for chronic musculoskeletal pain: a systematic review. British journal of clinical pharmacology 2017;83: 2347-55.
7. Abdel Shaheed C, Maher CG, Williams KA, Day R, McLachlan AJ. Efficacy, Tolerability, and Dose-Dependent Effects of Opioid Analgesics for Low Back Pain: A Systematic Review and Meta-analysis. JAMA internal medicine 2016;176: 958-68.
8. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction- GRADE evidence profiles and summary of findings tables. Journal of clinical epidemiology 2011;64: 383-94.
9. Busse JW, Craigie S, Juurlink DN, Buckley DN, Wang L, Couban RJ, et al. Guideline for opioid therapy and chronic noncancer pain. Canadian Medical Association Journal 2017;189: E659-E66.
10. 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.
11. Henrard G, Cordyn S, Chaspierre A, kessels T, Mingels S, Vanhalewyn M. 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.
12. De Jong L, Jansen P, Keizer D, Köke A, Schiere S, Van Bommel M, et al. NHG-Standaard Pijn. Huisarts en Wetenschap 2015 (herziening 2016): <https://www.nhg.org/standaarden/volledig/nhg-standaard-pijn>.
13. 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. Paice JA, Portenoy R, Lacchetti C, Campbell T, Cheville A, Citron M, et al. Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. Journal of Clinical Oncology 2016;34: 3325-45.
15. Department of Health. Pharmacological management of cancer pain in adults: national clinical guideline no 9. 2015.

16. KCE - Belgian Healthcare Knowledge Centre. Supportive treatment for cancer – Part 3: Treatment of pain: most common practices. 2013.
17. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Annals of internal medicine* 2015;162: 276-86.
18. Chou R, Deyo RA, Devine B, Hansen R, Sullivan S, Jarvik J, et al. The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain. . Evidence Report/Technology Assessment No 218 (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No 290-2012-00014-I) AHRQ Publication No 14-E005-EF Rockville, MD: Agency for Healthcare Research and Quality September 2014.
19. Noble M, Treadwell Jonathan R, Tregear Stephen J, Coates Vivian H, Wiffen Philip J, Akafofomo C, et al. Long-term opioid management for chronic noncancer pain. *Cochrane Database of Systematic Reviews* 2010.
20. Els C, Jackson Tanya D, Hagtvedt R, Kunyk D, Sonnenberg B, Lappi Vernon G, et al. High-dose opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database of Systematic Reviews* 2017.
21. DeLemos BP, Xiang J, Benson C, Gana TJ, Pascual ML, Rosanna R, et al. Tramadol hydrochloride extended-release once-daily in the treatment of osteoarthritis of the knee and/or hip: a double-blind, randomized, dose-ranging trial. *American journal of therapeutics* 2011;18: 216-26.
22. Krebs EE, Gravely A, Nugent S, Jensen AC, DeRonne B, Goldsmith ES, et al. Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial. *Jama* 2018;319: 872-82.
23. Els C, Jackson Tanya D, Kunyk D, Lappi Vernon G, Sonnenberg B, Hagtvedt R, et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. *Cochrane Database of Systematic Reviews* 2017.
24. Thornton JD, Goyat R, Dwibedi N, Kelley GA. Health-related quality of life in patients receiving long-term opioid therapy: a systematic review with meta-analysis. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 2017;26: 1955-67.
25. Kraemer HC, Kupfer DJ. Size of treatment effects and their importance to clinical research and practice. *Biological psychiatry* 2006;59: 990-6.
26. da Costa Bruno R, Nüesch E, Kasteler R, Husni E, Welch V, Rutjes Anne WS, et al. Oral or transdermal opioids for osteoarthritis of the knee or hip. *Cochrane Database of Systematic Reviews* 2014.
27. Cepeda MS, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis. *Cochrane Database of Systematic Reviews* 2006.
28. Chaparro LE, Furlan Andrea D, Deshpande A, Mailis-Gagnon A, Atlas S, Turk Dennis C. Opioids compared to placebo or other treatments for chronic low-back pain. *Cochrane Database of Systematic Reviews* 2013.
29. Chou R, Deyo R, Friedly J, Skelly A, Hashimoto R, Weimer M FR, et al. Noninvasive Treatments for Low Back Pain. Comparative Effectiveness Review No. 169. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2012-00014-I.) AHRQ Publication No. 16-EHC004-EF. Februari 2016.
30. Chou R, Deyo R, Friedly J, Skelly A, Weimer M, Fu R, et al. Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. *Annals of internal medicine* 2017;166: 480-92.
31. Gana TJ, Pascual MLG, Fleming RRB, Schein JR, Janagap CC, Xiang J, et al. Extended-release tramadol in the treatment of osteoarthritis:a multicenter, randomized, double-blind, placebo-controlled clinical trial. *Current medical research and opinion* 2006;22: 1391-401.

32. Burch F, Fishman R, Messina N, Corser B, Radulescu F, Sarbu A, et al. A Comparison of the Analgesic Efficacy of Tramadol Contramid OAD Versus Placebo in Patients with Pain Due to Osteoarthritis. *Journal of pain and symptom management* 2007;34: 328-38.
33. Haroutounian S, McNicol Ewan D, Lipman Arthur G. Methadone for chronic non-cancer pain in adults. *Cochrane Database of Systematic Reviews* 2012.
34. Quigley C. Hydromorphone for acute and chronic pain. *Cochrane Database of Systematic Reviews* 2013.
35. Hale M, Khan A, Kutch M, Li S. Once-daily OROS hydromorphone ER compared with placebo in opioid-tolerant patients with chronic low back pain. *Current medical research and opinion* 2010;26: 1505-18.
36. Vojtassak J, Jacobs A, Rynn L, Waechter S, Richarz U. A Phase IIIb, Multicentre, Randomised, Parallel-Group, Placebo-Controlled, Double-Blind Study to Investigate the Efficacy and Safety of OROS Hydromorphone in Subjects with Moderate-to-Severe Chronic Pain Induced by Osteoarthritis of the Hip or the Knee. *Pain Research and Treatment* 2011;2011: 9.
37. Rauck R, Rapoport R, Thippawong J. Results of a Double-blind, Placebo-controlled, Fixed-dose Assessment of Once-daily OROS® Hydromorphone ER in Patients with Moderate to Severe Pain Associated with Chronic Osteoarthritis. *Pain Practice* 2013;13: 18-29.
38. Webster LR, Butera PG, Moran LV, Wu N, Burns LH, Friedmann N. Oxytrex minimizes physical dependence while providing effective analgesia: a randomized controlled trial in low back pain. *The journal of pain : official journal of the American Pain Society* 2006;7: 937-46.
39. Buynak R, Shapiro DY, Okamoto A, Van Hove I, Rauschkolb C, Steup A, et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study. *Expert opinion on pharmacotherapy* 2010;11: 1787-804.
40. Vondrackova D, Leyendecker P, Meissner W, Hopp M, Szombati I, Hermanns K, et al. Analgesic Efficacy and Safety of Oxycodone in Combination With Naloxone as Prolonged Release Tablets in Patients With Moderate to Severe Chronic Pain. *The Journal of Pain* 2008;9: 1144-54.
41. Santos J, Alarcão J, Fareleira F, Vaz-Carneiro A, Costa J. Tapentadol for chronic musculoskeletal pain in adults. *Cochrane Database of Systematic Reviews* 2015.
42. McNicol Ewan D, Midbari A, Eisenberg E. Opioids for neuropathic pain. *Cochrane Database of Systematic Reviews* 2013.
43. Hanna M, O'Brien C, Wilson MC. Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients. *European Journal of Pain* 2008;12: 804-13.
44. Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2012.
45. Wiffen PJ, Knaggs R, Derry S, Cole P, Phillips T, Moore RA. Paracetamol (acetaminophen) with or without codeine or dihydrocodeine for neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2016.
46. Dy SM, Bennett WL, Sharma R, Zhang A, Waldfogel JM, Nesbit SA, et al. AHRQ Comparative Effectiveness Reviews. Preventing Complications and Treating Symptoms of Diabetic Peripheral Neuropathy 2017.
47. Duehmke Rudolf M, Derry S, Wiffen Philip J, Bell Rae F, Aldington D, Moore RA. Tramadol for neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2017.
48. Simpson RW, Wlodarczyk JH. Transdermal Buprenorphine Relieves Neuropathic Pain: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial in Diabetic Peripheral Neuropathic Pain. *Diabetes care* 2016;39: 1493-500.
49. Wiffen PJ, Derry S, Moore RA, Stannard C, Aldington D, Cole P, et al. Buprenorphine for neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2015.

50. Derry S, Stannard C, Cole P, Wiffen Philip J, Knaggs R, Aldington D, et al. Fentanyl for neuropathic pain in adults. Cochrane Database of Systematic Reviews 2016.
51. Stannard C, Gaskell H, Derry S, Aldington D, Cole P, Cooper Tess E, et al. Hydromorphone for neuropathic pain in adults. Cochrane Database of Systematic Reviews 2016.
52. Cooper Tess E, Chen J, Wiffen Philip J, Derry S, Carr Daniel B, Aldington D, et al. Morphine for chronic neuropathic pain in adults. Cochrane Database of Systematic Reviews 2017.
53. Gaskell H, Derry S, Stannard C, Moore RA. Oxycodone for neuropathic pain in adults. Cochrane Database of Systematic Reviews 2016.
54. Schwartz S, Etropolski M, Shapiro DY, Okamoto A, Lange R, Haeussler J, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. *Current medical research and opinion* 2011;27: 151-62.
55. Vinik AI, Shapiro DY, Rauschkolb C, Lange B, Karcher K, Pennett D, et al. A randomized withdrawal, placebo-controlled study evaluating the efficacy and tolerability of tapentadol extended release in patients with chronic painful diabetic peripheral neuropathy. *Diabetes care* 2014;37: 2302-9.
56. Wiffen PJ, Wee B, Derry S, Bell Rae F, Moore RA. Opioids for cancer pain - an overview of Cochrane reviews. Cochrane Database of Systematic Reviews 2017.
57. Wiffen PJ, Derry S, Moore RA. Tramadol with or without paracetamol (acetaminophen) for cancer pain. Cochrane Database of Systematic Reviews 2017.
58. Straube C, Derry S, Jackson Kenneth C, Wiffen Philip J, Bell Rae F, Strassels S, et al. Codeine, alone and with paracetamol (acetaminophen), for cancer pain. Cochrane Database of Systematic Reviews 2014.
59. Bao Yan J, Hou W, Kong Xiang Y, Yang L, Xia J, Hua Bao J, et al. Hydromorphone for cancer pain. Cochrane Database of Systematic Reviews 2016.
60. Hadley G, Derry S, Moore RA, Wiffen Philip J. Transdermal fentanyl for cancer pain. Cochrane Database of Systematic Reviews 2013.
61. Nicholson Alexander B, Watson Graeme R, Derry S, Wiffen Philip J. Methadone for cancer pain. Cochrane Database of Systematic Reviews 2017.
62. Schmidt-Hansen M, Bennett Michael I, Arnold S, Bromham N, Hilgart Jennifer S. Oxycodone for cancer-related pain. Cochrane Database of Systematic Reviews 2017.
63. Schmidt-Hansen M, Bromham N, Taubert M, Arnold S, Hilgart Jennifer S. Buprenorphine for treating cancer pain. Cochrane Database of Systematic Reviews 2015.
64. Wiffen PJ, Derry S, Naessens K, Bell Rae F. Oral tapentadol for cancer pain. Cochrane Database of Systematic Reviews 2015.
65. Wiffen PJ, Wee B, Moore RA. Oral morphine for cancer pain. Cochrane Database of Systematic Reviews 2016.
66. Wiffen PJ, Derry S, Moore RA. Impact of morphine, fentanyl, oxycodone or codeine on patient consciousness, appetite and thirst when used to treat cancer pain. Cochrane Database of Systematic Reviews 2014.
67. Quigley C. Opioid switching to improve pain relief and drug tolerability. Cochrane Database of Systematic Reviews 2013.
68. Schuster M, Bayer O, Heid F, Laufenberg-Feldmann R. Opioid Rotation in Cancer Pain Treatment. *Deutsches Arzteblatt international* 2018;115: 135-42.
69. AminiLari M, Manjoo P, Craigie S, Couban R, Wang L, Busse JW. Hormone Replacement Therapy and Opioid Tapering for Opioid-Induced Hypogonadism Among Patients with Chronic Noncancer Pain: A Systematic Review. *Pain medicine (Malden, Mass)* 2018.
70. Frank JW, Lovejoy TI, Becker WC, Morasco BJ, Koenig CJ, Hoffecker L, et al. Patient Outcomes in Dose Reduction or Discontinuation of Long-Term Opioid Therapy: A Systematic Review. *Annals of internal medicine* 2017;167: 181-91.

71. Ali K, Raphael J, Khan S, Labib M, Duarte R. The effects of opioids on the endocrine system: an overview. *Postgraduate medical journal* 2016.
72. Wersocki E, Bedson J, Chen Y, LeResche L, Dunn KM. Comprehensive systematic review of long-term opioids in women with chronic noncancer pain and associated reproductive dysfunction (hypothalamic-pituitary-gonadal axis disruption). *Pain* 2017;158: 8-16.
73. Richardson E, Bedson J, Chen Y, Lacey R, Dunn KM. Increased risk of reproductive dysfunction in women prescribed long-term opioids for musculoskeletal pain: A matched cohort study in the Clinical Practice Research Datalink. *European journal of pain* (London, England) 2018.
74. Zhao S, Deng T, Luo L, Wang J, Li E, Liu L, et al. Association Between Opioid Use and Risk of Erectile Dysfunction: A Systematic Review and Meta-Analysis. *The journal of sexual medicine* 2017;14: 1209-19.
75. Bawor M, Bami H, Dennis BB, Plater C, Worster A, Varenbut M, et al. Testosterone suppression in opioid users: a systematic review and meta-analysis. *Drug and alcohol dependence* 2015;149: 1-9.
76. Cronin-Fenton DP, Heide-Jorgensen U, Ahern TP, Lash TL, Christiansen PM, Ejlersen B, et al. Opioids and breast cancer recurrence: A Danish population-based cohort study. *Cancer* 2015;121: 3507-14.
77. BCFI. Opioïden bij de behandeling van chronische niet-kankerpijn. *Folia Pharmacotherapeutica* 2016.
78. BCFI. Gecommentarieerd Geneesmiddelenrepertorium 2018. Gecommentarieerd Geneesmiddelenrepertorium 2018.
79. Brayfield A. *Martindale: The Complete Drug Reference*: Pharmaceutical Press; 2017.
80. BCFI. Hyponatriëmie van medicamenteuze oorsprong. *Folia Pharmacotherapeutica* 2016.
81. BCFI. Beperking van het gebruik van codeïne als analgeticum bij kinderen. *Folia Pharmacotherapeutica* 2013.
82. Afilalo M, Etropolski MS, Kuperwasser B, Kelly K, Okamoto A, Van Hove I, et al. Efficacy and safety of Tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. *Clinical drug investigation* 2010;30: 489-505.
83. Bennett RM, Kamin M, Karim R, Rosenthal N. Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study. *The American journal of medicine* 2003;114: 537-45.
84. Boureau F, Legallicier P, Kabir-Ahmadi M. Tramadol in post-herpetic neuralgia: a randomized, double-blind, placebo-controlled trial. *Pain* 2003;104: 323-31.
85. Breivik H, Ljosaa TM, Stengaard-Pedersen K, Persson J, Aro H, Villumsen J, et al. A 6-months, randomised, placebo-controlled evaluation of efficacy and tolerability of a low-dose 7-day buprenorphine transdermal patch in osteoarthritis patients naive to potent opioids. *Scandinavian journal of pain* 2010;1: 122-41.
86. Caldwell JR, Rapoport RJ, Davis JC, Offenbergh HL, Marker HW, Roth SH, et al. Efficacy and Safety of a Once-Daily Morphine Formulation in Chronic, Moderate-to-Severe Osteoarthritis Pain. *Journal of pain and symptom management* 2002;23: 278-91.
87. Chu LF, D'Arcy N, Brady C, Zamora AK, Young CA, Kim JE, et al. Analgesic tolerance without demonstrable opioid-induced hyperalgesia: a double-blinded, randomized, placebo-controlled trial of sustained-release morphine for treatment of chronic nonradicular low-back pain. *Pain* 2012;153: 1583-92.
88. Cloutier C, Taliano J, O'Mahony W, Csanadi M, Cohen G, Sutton I, et al. Controlled-release oxycodone and naloxone in the treatment of chronic low back pain: a placebo-controlled, randomized study. *Pain research & management* 2013;18: 75-82.

89. Emkey R, Rosenthal N, Wu SC, Jordan D, Kamin M. Efficacy and safety of tramadol/acetaminophen tablets (Ultracet) as add-on therapy for osteoarthritis pain in subjects receiving a COX-2 nonsteroidal antiinflammatory drug: a multicenter, randomized, double-blind, placebo-controlled trial. *The Journal of rheumatology* 2004;31: 150-6.
90. Fleischmann RM, Caldwell JR, Roth SH, Tesser JRP, Olson W, Kamin M. Tramadol for the treatment of joint pain associated with osteoarthritis: a randomized, double-blind, placebo-controlled trial. *Current Therapeutic Research* 2001;62: 113-28.
91. Freeman R, Raskin P, Hewitt DJ, Vorsanger GJ, Jordan DM, Xiang J, et al. Randomized study of tramadol/acetaminophen versus placebo in painful diabetic peripheral neuropathy. *Current medical research and opinion* 2007;23: 147-61.
92. Friedmann N, Klutzaritz V, Webster L. Efficacy and safety of an extended-release oxycodone (Remoxy) formulation in patients with moderate to severe osteoarthritic pain. *Journal of opioid management* 2011;7: 193-202.
93. Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy. A randomized controlled trial 2003;60: 927-34.
94. Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, Gabapentin, or Their Combination for Neuropathic Pain. *New England Journal of Medicine* 2005;352: 1324-34.
95. Gordon A, Callaghan D, Spink D, Cloutier C, Dzongowski P, O'Mahony W, et al. Buprenorphine transdermal system in adults with chronic low back pain: A randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase. *Clinical therapeutics* 2010;32: 844-60.
96. Gordon A, Rashiq S, Moulin DE, Clark AJ, Beaulieu AD, Eisenhoffer J, et al. Buprenorphine transdermal system for opioid therapy in patients with chronic low back pain. *Pain research & management* 2010;15: 169-78.
97. Meske DS, Lawal OD, Elder H, Langberg V, Paillard F, Katz N. Efficacy of opioids versus placebo in chronic pain: a systematic review and meta-analysis of enriched enrollment randomized withdrawal trials. *Journal of pain research* 2018;11: 923-34.
98. Hale ME, Laudadio C, Yang R, Narayana A, Malamut R. Efficacy and tolerability of a hydrocodone extended-release tablet formulated with abuse-deterrence technology for the treatment of moderate-to-severe chronic pain in patients with osteoarthritis or low back pain. *Journal of pain research* 2015;8: 623-36.
99. Katz N, Kopecky EA, O'Connor M, Brown RH, Fleming AB. A phase 3, multicenter, randomized, double-blind, placebo-controlled, safety, tolerability, and efficacy study of Xtampza ER in patients with moderate-to-severe chronic low back pain. *Pain* 2015;156: 2458-67.
100. Katz N, Hale M, Morris D, Stauffer J. Morphine sulfate and naltrexone hydrochloride extended release capsules in patients with chronic osteoarthritis pain. *Postgraduate medicine* 2010;122: 112-28.
101. Langford R, McKenna F, Ratcliffe S, Vojtassak J, Richarz U. Transdermal fentanyl for improvement of pain and functioning in osteoarthritis: a randomized, placebo-controlled trial. *Arthritis and rheumatism* 2006;54: 1829-37.
102. MANGEL AW, BORNSTEIN JD, HAMM LR, BUDA J, WANG J, IRISH W, et al. Clinical trial: asimadoline in the treatment of patients with irritable bowel syndrome. *Alimentary Pharmacology & Therapeutics* 2008;28: 239-49.
103. Hyup Lee J, Lee C-S. A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of the Extended-Release Tramadol Hydrochloride/Acetaminophen Fixed-Dose Combination Tablet for the Treatment of Chronic Low Back Pain. *Clinical therapeutics* 2013;35: 1830-40.
104. Ma K, Jiang W, Zhou Q, Du D-P. The efficacy of oxycodone for management of acute pain episodes in chronic neck pain patients. *International journal of clinical practice* 2008;62: 241-7.

105. Matsumoto AK, Babul N, Ahdieh H. Oxymorphone extended-release tablets relieve moderate to severe pain and improve physical function in osteoarthritis: results of a randomized, double-blind, placebo- and active-controlled phase III trial. *Pain medicine (Malden, Mass)* 2005;6: 357-66.
106. Munera C, Drehabl M, Sessler NE, Landau C. A randomized, placebo-controlled, double-blinded, parallel-group, 5-week study of buprenorphine transdermal system in adults with osteoarthritis. *Journal of opioid management* 2010;6: 193-202.
107. Norrbrink C, Lundeberg T. Tramadol in Neuropathic Pain After Spinal Cord Injury: A Randomized, Double-blind, Placebo-controlled Trial. *The Clinical journal of pain* 2009;25: 177-84.
108. Peloso PM, Fortin L, Beaulieu A, Kamin M, Rosenthal N. Analgesic efficacy and safety of tramadol/ acetaminophen combination tablets (Ultracet) in treatment of chronic low back pain: a multicenter, outpatient, randomized, double blind, placebo controlled trial. *The Journal of rheumatology* 2004;31: 2454-63.
109. Rauck RL, Hale ME, Bass A, Bramson C, Pixton G, Wilson JG, et al. A randomized double-blind, placebo-controlled efficacy and safety study of ALO-02 (extended-release oxycodone surrounding sequestered naltrexone) for moderate-to-severe chronic low back pain treatment. *Pain* 2015;156: 1660-9.
110. Rauck RL, Nalamachu S, Wild JE, Walker GS, Robinson CY, Davis CS, et al. Single-Entity Hydrocodone Extended-Release Capsules in Opioid-Tolerant Subjects with Moderate-to-Severe Chronic Low Back Pain: A Randomized Double-Blind, Placebo-Controlled Study. *Pain Medicine* 2014;15: 975-85.
111. Rauck RL, Potts J, Xiang Q, Tzanis E, Finn A. Efficacy and tolerability of buccal buprenorphine in opioid-naïve patients with moderate to severe chronic low back pain. *Postgraduate medicine* 2016;128: 1-11.
112. Ruoff GE, Rosenthal N, Jordan D, Karim R, Kamin M. Tramadol/acetaminophen combination tablets for the treatment of chronic lower back pain: a multicenter, randomized, double-blind, placebo-controlled outpatient study. *Clinical therapeutics* 2003;25: 1123-41.
113. Trenkwalder C, Chaudhuri KR, Martinez-Martin P, Rascol O, Ehret R, Vališ M, et al. Prolonged-release oxycodone–naloxone for treatment of severe pain in patients with Parkinson's disease (PANDA): a double-blind, randomised, placebo-controlled trial. *The Lancet Neurology* 2015;14: 1161-70.
114. Thorne C, Beaulieu AD, Callaghan DJ, O'Mahony WF, Bartlett JM, Knight R, et al. A randomized, double-blind, crossover comparison of the efficacy and safety of oral controlled-release tramadol and placebo in patients with painful osteoarthritis. *Pain research & management* 2008;13: 93-102.
115. Vorsanger GJ, Xiang J, Gana TJ, Pascual ML, Fleming RR. Extended-release tramadol (tramadol ER) in the treatment of chronic low back pain. *Journal of opioid management* 2008;4: 87-97.
116. Wen W, Sitar S, Lynch SY, He E, Ripa SR. A multicenter, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of single-entity, once-daily hydrocodone tablets in patients with uncontrolled moderate to severe chronic low back pain. *Expert opinion on pharmacotherapy* 2015;16: 1593-606.
117. Zin CS, Nissen LM, O'Callaghan JP, Duffull SB, Smith MT, Moore BJ. A Randomized, Controlled Trial of Oxycodone Versus Placebo in Patients With PostHerpetic Neuralgia and Painful Diabetic Neuropathy Treated With Pregabalin. *The Journal of Pain* 2010;11: 462-71.
118. Afilalo M, Morlion B. Efficacy of tapentadol ER for managing moderate to severe chronic pain. *Pain physician* 2013;16: 27-40.
119. Serrie A, Lange B, Steup A. Tapentadol prolonged-release for moderate-to-severe chronic osteoarthritis knee pain: a double-blind, randomized, placebo- and oxycodone controlled release-controlled study. *Current medical research and opinion* 2017;33: 1423-32.
120. Chindalore VL, Craven RA, Yu KP, Butera PG, Burns LH, Friedmann N. Adding ultralow-dose naltrexone to oxycodone enhances and prolongs analgesia: a randomized, controlled trial of Oxytrex. *The journal of pain : official journal of the American Pain Society* 2005;6: 392-9.

121. Etropolski M, Kelly K, Okamoto A, Rauschkolb C. Comparable efficacy and superior gastrointestinal tolerability (nausea, vomiting, constipation) of tapentadol compared with oxycodone hydrochloride. *Advances in therapy* 2011;28: 401-17.
122. Fidelholtz J, Tark M, Spierings E, Wolfram G, Annis K, Smith M. A phase 3 placebo- and oxycodone controlled study of tanezumab in adults with osteoarthritis. *Proceedings of the ACR/ARHP Scientific Meeting* 2011;Nov 9-11; Chicago.
123. Hartrick C, Van Hove I, Stegmann JU, Oh C, Upmalis D. Efficacy and tolerability of tapentadol immediate release and oxycodone HCl immediate release in patients awaiting primary joint replacement surgery for end-stage joint disease: a 10-day, phase III, randomized, double-blind, active- and placebo-controlled study. *Clinical therapeutics* 2009;31: 260-71.
124. Kivitz A, Ma C, Ahdieh H, Galer BS. A 2-week, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, phase III trial comparing the efficacy of oxymorphone extended release and placebo in adults with pain associated with osteoarthritis of the hip or knee. *Clinical therapeutics* 2006;28: 352-64.
125. Kjaersgaard-Andersen P, Nafei A, Skov O, Madsen F, Andersen HM, Kroner K, et al. Codeine plus paracetamol versus paracetamol in longer-term treatment of chronic pain due to osteoarthritis of the hip. A randomised, double-blind, multi-centre study. *Pain* 1990;43: 309-18.
126. Markenson JA, Croft J, Zhang PG, Richards P. Treatment of persistent pain associated with osteoarthritis with controlled-release oxycodone tablets in a randomized controlled clinical trial. *The Clinical journal of pain* 2005;21: 524-35.
127. Peloso PM, Bellamy N, Bensen W, Thomson GT, Harsanyi Z, Babul N, et al. Double blind randomized placebo control trial of controlled release codeine in the treatment of osteoarthritis of the hip or knee. *The Journal of rheumatology* 2000;27: 764-71.
128. Quiding H, Grimstad J, Rusten K, Stubhaug A, Bremnes J, Breivik H. Ibuprofen plus codeine, ibuprofen, and placebo in a single- and multidose cross-over comparison for coxarthrosis pain. *Pain* 1992;50: 303-7.
129. Shannon MJ, Kivitz AJ, Landau CJ, Sessler NE, Xia Y, Ripa SR. Buprenorphine transdermal system in chronic pain due to osteoarthritis. Poster 154. *Archives of physical medicine and rehabilitation* 2005;86: e32.
130. Zautra AJ, Smith BW. Impact of controlled-release oxycodone on efficacy beliefs and coping efforts among osteoarthritis patients with moderate to severe pain. *The Clinical journal of pain* 2005;21: 471-7.
131. Katz N, Rauck R, Ahdieh H, Ma T, Gerritsen van der Hoop R, Kerwin R, et al. A 12-week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid-naïve patients with chronic low back pain. *Current medical research and opinion* 2007;23: 117-28.
132. Babul N, Noveck R, Chipman H, Roth SH, Gana T, Albert K. Efficacy and safety of extended-release, once-daily tramadol in chronic pain: a randomized 12-week clinical trial in osteoarthritis of the knee. *Journal of pain and symptom management* 2004;28: 59-71.
133. Bianchi M, Broggin M, Balzarini P, Baratelli E, Ferrario P, Panerai AE, et al. Effects of tramadol on synovial fluid concentrations of substance P and interleukin-6 in patients with knee osteoarthritis: comparison with paracetamol. *International immunopharmacology* 2003;3: 1901-8.
134. Malonne H, Coffiner M, Sonet B, Sereno A, Vanderbist F. Efficacy and tolerability of sustained-release tramadol in the treatment of symptomatic osteoarthritis of the hip or knee: a multicenter, randomized, double-blind, placebo-controlled study. *Clinical therapeutics* 2004;26: 1774-82.
135. Schnitzer TJ, Kamin M, Olson WH. Tramadol allows reduction of naproxen dose among patients with naproxen-responsive osteoarthritis pain: a randomized, double-blind, placebo-controlled study. *Arthritis and rheumatism* 1999;42: 1370-7.

136. Silverfield JC, Kamin M, Wu SC, Rosenthal N. Tramadol/acetaminophen combination tablets for the treatment of osteoarthritis flare pain: a multicenter, outpatient, randomized, double-blind, placebo-controlled, parallel-group, add-on study. *Clinical therapeutics* 2002;24: 282-97.
137. Aiyer R, Gulati A, Gungor S, Bhatia A, Mehta N. Treatment of Chronic Pain With Various Buprenorphine Formulations: A Systematic Review of Clinical Studies. *Anesthesia and analgesia* 2017.
138. Quigley C. Hydromorphone for acute and chronic pain. *Cochrane Database of Systematic Reviews* 2002.