

Osteoarthritis: assessment and management (update)

[I1] Evidence reviews for the clinical and cost-effectiveness of oral, topical and transdermal medicines for the management of osteoarthritis

NICE guideline

Evidence reviews underpinning recommendations 1.4.1 to 1.4.9 and research recommendations in the NICE guideline

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Draft for Consultation

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1 Oral, topical and transdermal medicines for osteoarthritis

1.1 Review question

What is the clinical and cost-effectiveness of oral, topical and transdermal medicines for the management of osteoarthritis?

1.1.1 Introduction

A range of pharmacological interventions have been reported to reduce joint pain and improve function for people with osteoarthritis and this type of treatment approach is commonly used. However, these interventions are not used consistently and there is increasing concern regarding long term use of medications such as opioids. It is now recognised that if opioids are not helpful in managing pain then simply increasing the strength of the opioid may not result in any better pain relief but increases the harms of this medication. Osteoarthritis commonly co-exists with other conditions such as high blood pressure, heart or kidney disease which make using anti-inflammatories less favourable. Further, the pain in osteoarthritis fluctuates from day-to-day and from person-to-person over time. Some people may only require pain relief for short periods of flares, others need it daily for the long term. Current practice for people with osteoarthritis is to treat with the least harmful preparation first and review and change medication depending on the patient's response and co-existing conditions. Whereas previously the analgesic ladder had been followed for pain relief for osteoarthritis, there is an increasing perception that this ladder may not be directly applicable to chronic pain conditions such as osteoarthritis and that there are times where no effective pain killing medication can be identified for patients. To adequately discuss and weight up management options, it is important that healthcare professionals and patients are aware of the limitations and harms of medications and balance these against the likely benefit.

This review aims to evaluate the clinical and cost-effectiveness of oral, topical and transdermal pharmacological interventions in the management of osteoarthritis.

1.1.2 Summary of the protocol

Table 1: PICO characteristics of review question

Population	<p>Inclusion:</p> <ul style="list-style-type: none">Adults (age ≥16 years) with osteoarthritis affecting any joint <p>Stratify by site of osteoarthritis for topical (local) interventions only:</p> <ul style="list-style-type: none">HipKneeAnkleFootToeShoulderElbowWristHandThumbFinger
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	<ul style="list-style-type: none"> • Temporomandibular joint (TMJ) • Multisite <p>To note that where evidence for other rare forms of osteoarthritis is identified the committee will stratify into a group they are most similar to.</p> <p>Exclusion:</p> <ul style="list-style-type: none"> • Children (age <16 years) • People with conditions that may make them susceptible to osteoarthritis or often occur alongside osteoarthritis (including: crystal arthritis, inflammatory arthritis, septic arthritis, diseases of childhood that may predispose to osteoarthritis, medical conditions presenting with joint inflammation and malignancy). • Studies in people with meniscal injury without osteoarthritis • Studies with an unclear population (e.g, type of arthritis, proportion of participants with osteoarthritis) • Spinal osteoarthritis
Interventions	<p>Oral medicines:</p> <ul style="list-style-type: none"> • Paracetamol • Non-steroidal anti-inflammatory drugs • Non-steroidal anti-inflammatory drugs with gastroprotection • Weak opioids (including: codeine, dihydrocodeine) • Strong opioids (including: morphine, tramadol, oxycodone, hydromorphone, tapentadol) • Anti-epileptic drugs (including: gabapentin, pregabalin) • Antidepressants (including SSRIs, SNRIs, tricyclic antidepressants) • Glucosamine (doses above 1176mg/day) <p>Topical (local) medicines:</p> <ul style="list-style-type: none"> • Capsaicin • Non-steroidal anti-inflammatory drug (including: ibuprofen, diclofenac) • Rubefacients • Local anaesthetic <p>Topical (systemic, including transdermal) medicines:</p> <ul style="list-style-type: none"> • Opioids (buprenorphine, fentanyl ect.)
Comparisons	<ul style="list-style-type: none"> • Compared to each other • Placebo
Outcomes	<p>Primary outcomes:</p> <ul style="list-style-type: none"> • Health-related quality of life [validated patient-reported outcomes, continuous data prioritised] at ≤3 months and >3 months • Pain [validated patient-reported outcomes, continuous data prioritised] at ≤3 months and >3 months • Physical function [validated patient-reported outcomes, continuous data prioritised] at ≤3 months and >3 months <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Psychological distress [validated patient-reported outcomes, continuous data prioritised] at ≤3 months and >3 months • Osteoarthritis flare-ups [validated patient-reported outcomes, continuous data prioritised] at ≤3 months and >3 months • Serious adverse events 1A: Gastrointestinal (bleeding and perforation) adverse events [dichotomous] at ≤3 months and >3 months • Serious adverse events 1B: Gastrointestinal (non-bleeding and perforation) adverse events [dichotomous] at ≤3 months and >3 months

	<ul style="list-style-type: none">• Serious adverse events 2: Cardiovascular adverse events [dichotomous] at ≤ 3 months and >3 months• Serious adverse events 3: Hepatorenal adverse events [dichotomous] at ≤ 3 months and >3 months• Serious adverse events 4: Central nervous system adverse events [dichotomous] at ≤ 3 months and >3 months
Study design	RCTs or systematic reviews of RCTs

1 For full details see the review protocol in [Evidence review I OTT - appendices A-D](#).

2 **1.1.3 Methods and process**

3 This evidence review was developed using the methods and process described in
4 [Developing NICE guidelines: the manual](#). Methods specific to this review question are
5 described in the review protocol in appendix A and the methods document.

6 Declarations of interest were recorded according to [NICE's conflicts of interest policy](#).

7

1 **1.1.4 Effectiveness evidence**

2 **1.1.4.1 Included studies**

3 One-hundred and eighty one (two-hundred and eleven papers) RCT studies were included in
4 the review;^{1-23, 25, 27, 29-33, 37-41, 44-46, 48-51, 53-55, 59, 60, 62-71, 73-76, 78-80, 82-96, 98-101, 103-105, 108-112, 114-116, 120,}
5 ^{122-125, 127-143, 146, 147, 149, 151-159, 161-164, 166-170, 172, 173, 176-183, 185-190, 192-198, 202-206, 209-220, 222, 224-226} these
6 are summarised in Tables 2-26 below. Evidence from these studies is summarised in the
7 clinical evidence summaries (Tables 31-53) and the summary matrices below (Tables 27-
8 30).

9 Studies included the following comparisons for oral medicines (some studies reported
10 multiple comparisons):

- 11 • Paracetamol
 - 12 ○ Paracetamol compared to placebo (n=8)^{4, 41, 90, 96, 140, 156, 158, 163}
- 13 • Non-steroidal anti-inflammatory drugs (NSAIDs)
 - 14 ○ NSAIDs compared to paracetamol (n=13)^{17, 31, 32, 41, 64, 84, 90, 135, 156, 183, 196, 210, 219}
 - 15 ○ NSAIDs compared to placebo (n=87)^{6-9, 12, 13, 19-21, 23, 25, 27, 40, 41, 51, 53-55, 60, 63, 65, 67-71, 74, 76, 85-}
16 ^{88, 90, 92, 93, 95, 99, 103, 104, 108-111, 116, 122-125, 127, 128, 130-133, 137, 138, 141, 151, 156, 161, 168, 172, 173, 176, 177, 179-}
17 ^{182, 185, 186, 188-190, 192, 194, 195, 203, 204, 214-218, 220, 222, 226}
- 18 • NSAIDs and gastroprotection
 - 19 ○ NSAIDs and gastroprotection compared to paracetamol (n=1)¹⁵⁷
 - 20 ○ NSAIDs and gastroprotection compared to NSAIDs (n=6)^{27, 29, 44, 55, 91, 139}
 - 21 ○ NSAIDs and gastroprotection compared to placebo (n=2)^{27, 55}
- 22 • Weak opioids (for example: codeine, dihydrocodeine)
 - 23 ○ Weak opioids compared to placebo (n=1)¹⁵⁴
- 24 • Strong opioids (for example: morphine, oxycodone, hydromorphone, tapentadol and
25 tramadol. It was decided to include tramadol as a strong opioid to be consistent with the
26 BNF¹⁴⁴).
 - 27 ○ Strong opioids compared to NSAIDs (n=4)^{14, 18, 60, 153}
 - 28 ○ Strong opioids compared to placebo (n=16)^{2, 10, 37, 39, 48, 60, 73, 75, 82, 83, 134, 136, 187, 197, 211, 224}
- 29 • Anti-epileptic drugs
 - 30 ○ Anti-epileptic drugs compared to paracetamol (n=1)⁶⁶
 - 31 ○ Anti-epileptic drugs compared to antidepressant drugs (n=1)¹⁹³
 - 32 ○ Anti-epileptic drugs compared to placebo (n=1)¹⁹³
- 33 • Antidepressant drugs
 - 34 ○ Antidepressant drugs compared to paracetamol (n=1)⁶⁶
 - 35 ○ Antidepressant drugs compared to placebo (n=8)^{1, 45, 46, 78, 100, 193, 206, 213}
- 36 • Glucosamine
 - 37 ○ Glucosamine compared to paracetamol (n=1)⁹⁶
 - 38 ○ Glucosamine compared to NSAIDs (n=6)^{49, 51, 129, 142, 149, 162}
 - 39 ○ Glucosamine compared to placebo (n=17)^{5, 38, 50, 51, 79, 80, 89, 96, 98, 101, 115, 147, 152, 159, 164, 170,}
40 ²²⁵

42 Studies included the following comparisons for topical (local) medicines:

- 43 • Knee osteoarthritis
 - 44 ○ Topical capsaicin compared to placebo (n=1)¹¹⁴
 - 45 ○ Topical NSAIDs compared to oral NSAIDs (n=7)^{53, 62, 168, 190, 198, 205, 209}

- 1 o Topical NSAIDs compared to topical capsaicin (n=1)¹⁵⁵
- 2 o Topical NSAIDs compared to placebo (n=17)^{11, 15, 16, 22, 30, 53, 59, 94, 112, 146, 166-169, 190, 202, 212}
- 3 • Hand osteoarthritis:
- 4 o Topical capsaicin compared to placebo (n=1)¹⁷⁸
- 5 o Topical NSAIDs compared to placebo (n=1)³

6

7 No relevant clinical studies comparing either intervention for people with other joint sites of
8 osteoarthritis were identified.

9

10 Studies included the following comparisons for topical (systemic) medicines:

- 11 • Transdermal opioids compared to oral strong opioids (n=1)¹⁰⁵
- 12 • Transdermal opioids compared to placebo (n=3)^{33, 120, 143}

13 No relevant clinical studies comparing the following interventions to placebo were identified:

- 14 • Rubefacients (topical local)
- 15 • Local anaesthetics (topical local)

16 This review includes enrichment trials (including 'flare trials'), where the inclusion criteria may
17 lead to the inclusion of participants that may have a different response to a medicine than the
18 general population of people with osteoarthritis. This effect has been examined for trials of
19 non-steroidal anti-inflammatory drugs in two previous systematic reviews^{191, 201}, which
20 showed different results. To investigate whether this influences the results of the meta-
21 analyses, a sensitivity analysis was conducted (see methods section). Information about the
22 study sensitivity analysis categories can be seen in the clinical evidence summaries below
23 (Tables 2-26).

24 A network meta-analysis was not completed for this review. This was decided as the
25 populations included in the studies were heterogenous, as would be appropriate for clinical
26 practice (for example: paracetamol may be considered for people with milder symptoms from
27 osteoarthritis than strong opioids). As the populations were not comparable and the clinical
28 indications for the medicines are different, it was decided that a network meta-analysis would
29 not provide an appropriate comparison to aid recommendations.

30 See also the study selection flow chart in [Evidence review I OTT - appendices A-D](#), study
31 evidence tables in [Evidence review I OTT - appendices A-D](#), forest plots in [Evidence review I
32 OTT - appendices E-L](#) and GRADE tables in [Evidence review I OTT - appendices E-L](#).

33 **1.1.4.2 Excluded studies**

34 Fourteen Cochrane reviews were identified but could not be included. Ten were excluded
35 due to the PICO not matching that specified in the protocol^{56, 57, 61, 72, 126, 148, 160, 199, 200, 223}, three
36 were excluded due to including different interventions to those included in the protocol^{58, 102,}
37 ²²¹, one was excluded as it included different definitions of outcomes (such as adverse
38 events outcomes)⁴³. The references of these reviews were cross-checked for inclusion with
39 any studies being included in the review if relevant to the protocol.

40 See the excluded studies list in [Evidence review I OTT - appendices E-L](#).

41

1 **1.1.5 Summary of studies included in the effectiveness evidence**

2 **1.1.5.1 Oral**

3 **1.1.5.1.1 Paracetamol compared to placebo**

4 **Table 2: Summary of studies included in the evidence review for paracetamol compared to placebo**

Study	Intervention and comparison	Population	Outcomes	Comments
Altman 2007 ⁴	<p>Paracetamol (n=318) Paracetamol ER 1950/day or 3900mg/day in three divided doses for 16 weeks</p> <p>Placebo (n=165)</p> <p>Concomitant therapy: Self-administered non-pharmacological therapies and propoxyphene HCl (maximum dose 390mg/day for no more than 3 days in any 7 day period) were permitted</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 62.2 (10.8) years N = 483</p> <p>Definition: Symptomatic idiopathic osteoarthritis of the hip or knee with radiographic features</p> <p>Severity: Equivalent to Kellgren Lawrence grade 2-3 Duration of symptoms: At least 6 months Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months Serious adverse events 3: hepatorenal adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	Study design classification: 1) Including only responders
Case 2003 ⁴¹	<p>Paracetamol (n=29) Paracetamol 1000mg four times daily with matching placebo twice daily for 12 weeks</p> <p>Oral non-steroidal anti-inflammatory drugs (n=25)</p>	<p>Knee osteoarthritis Mean age (SD): 62.2 (9.6) years N = 82</p> <p>Definition: Unilateral symptomatic osteoarthritis of</p>	<p>Pain at ≤3 months Physical function at ≤3 months</p>	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Diclofenac sodium 75mg twice daily with matching placebo two tablets four times a day for 12 weeks</p> <p>Placebo (n=28)</p> <p>Concomitant therapy: Use of nonstudy pain medications during the trial was prohibited</p>	<p>the knee based on clinical and radiological criteria</p> <p>Severity: Kellgren Lawrence grade 2</p> <p>Duration of symptoms: Not stated</p> <p>Presence of multimorbidities: Not stated/unclear</p>		
Golden 2004 ⁹⁰	<p>Paracetamol (n=148) Paracetamol 1000mg four times daily for 7 days</p> <p>Non-steroidal anti-inflammatory drugs (n=162) Naproxen 220mg three times a day (if the person was age 65 years or over they were to take it two times a day only) for 7 days</p> <p>Placebo (n=155)</p> <p>Concomitant therapy: Paracetamol could be taken during the washout period but could not be used in the study</p>	<p>Knee osteoarthritis</p> <p>Mean age (SD): 60.57 (12.78) years N = 465</p> <p>Definition: Radiographic knee osteoarthritis</p> <p>Severity: Functional class I-III Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 6) No response criteria</p> <p>Pooled analysis of 2 trials</p>
Herrero-beaumont 2007 ⁹⁶	<p>Paracetamol (n=108) Paracetamol 1 gram three times a day and matching placebo for 26 weeks</p>	<p>Knee osteoarthritis</p> <p>Mean age (SD): 63.9 (7.0) years N = 318</p>	<p>Pain at >3 months</p> <p>Physical function at >3 months</p>	<p>Study design classification: 6) No response criteria</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Glucosamine (n=106) Glucosamine 1500mg oral powder for solution per day and matching placebo for 26 weeks</p> <p>Glucosamine purity: Purity not stated</p> <p>Placebo (n=104)</p> <p>Concomitant therapy: Ibuprofen 400mg was permitted for rescue medication</p>	<p>Definition: Primary symptomatic knee osteoarthritis according to the clinical and radiographic American College of Rheumatology criteria</p> <p>Severity: Kellgren Lawrence grade 2-3</p> <p>Duration of symptoms (mean [SD]): 7.0 (5.7) years</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 2: cardiovascular adverse events at >3 months</p> <p>Serious adverse events 3: hepatorenal adverse events at >3 months</p>	
Miceli-richard 2004 ¹⁴⁰	<p>Paracetamol (n=405) Paracetamol 1 gram four times a day for 6 weeks</p> <p>Placebo (n=374)</p> <p>Concomitant therapy: Concomitant treatments, such as long acting osteoarthritis drugs, psychotropic or myorelaxing drugs, vitamins or minerals, had to be given at stable doses for at least 3 weeks before inclusion and during the study. Rescue drugs for osteoarthritis, such as oral or injectable analgesics (including paracetamol), NSAIDs and intra-articular drugs were prohibited</p>	<p>Knee osteoarthritis</p> <p>Mean age (SD): 70 (11) years N = 779</p> <p>Definition: Symptomatic osteoarthritis of the knee for at least 3 months</p> <p>Severity: Kellgren Lawrence grade 2-4</p> <p>Duration of symptoms (mean [SD]): 46 (47) months</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months</p> <p>Physical function at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	Study design classification: 4) Unclear

Study	Intervention and comparison	Population	Outcomes	Comments
Pincus 2004 ¹⁵⁶ (PACES trial)	<p>Paracetamol (n=631) Paracetamol 1000mg four times a day for 6 weeks</p> <p>Non-steroidal anti-inflammatory drugs (n=723) Celecoxib 200mg/day for 6 weeks</p> <p>Placebo (n=562)</p> <p>Concomitant therapy: Propoxyphene 65mg up to four times a day was given as rescue treatment; codeine 60mg or tramadol 100mg up to four times per day were provided as alternatives to fewer than 5% of people if propoxyphene was poorly tolerated or ineffective</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 63.45 (10.03) years N = 1916</p> <p>Definition: Radiographic and clinical osteoarthritis</p> <p>Severity: Kellgren Lawrence mean grade 2-3 Duration of symptoms (mean [SD]): 9.36 (8.99) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 4) Unclear</p> <p>Pooled analysis of two trials</p> <p>Crossover trial</p>
Prior 2014 ¹⁵⁸	<p>Paracetamol (n=267) Paracetamol extended release 1300mg 3 times a day for 12 weeks</p> <p>Placebo (n=275)</p> <p>Concomitant therapy: People were instructed that the study medication could have contained 1300mg paracetamol per dose and that they should not exceed a maximum daily dose of 4000mg of paracetamol.</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 61.7 (10.1) years N = 542</p> <p>Definition: Clinical and radiographic osteoarthritis</p> <p>Severity: Kellgren Lawrence grades 2-3. ACR class 1-3. Duration of symptoms: At least 6 months</p>	<p>Quality of life at ≤3 months Pain at ≤3 months Physical function at ≤3 months Serious adverse events 2: cardiovascular adverse events at ≤3 months Serious adverse events 3: hepatorenal adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	A prescription of propoxyphene HCl 65mg was given as rescue medications.	Presence of multimorbidities: Not stated/unclear		
Reed 2018 ¹⁶³	<p>Paracetamol (n=471) Sustained release paracetamol 2000mg twice a day or extended release paracetamol 1330mg three times a day for 12 weeks</p> <p>Placebo (n=237)</p> <p>Concomitant therapy: People were permitted to take oral ibuprofen 2x200mg as rescue medication.</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 60.8 (8.4) years N = 708</p> <p>Definition: Clinical and radiographic diagnosis of osteoarthritis</p> <p>Severity: Kellgren Lawrence grade 2-4 Duration of symptoms: More than 6 months Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Physical function at ≤3 months Serious adverse events 2: cardiovascular adverse events at ≤3 months Serious adverse events 3: hepatorenal adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	Study design classification: 4) Unclear

1 **1.1.5.1.2 Oral non-steroidal anti-inflammatory drugs compared to paracetamol**

2 **Table 3: Summary of studies included in the evidence review for oral non-steroidal anti-inflammatory drugs compared to paracetamol**

Study	Intervention and comparison	Population	Outcomes	Comments
Battle-gualda 2007 ¹⁷	<p>Non-steroidal anti-inflammatory drugs (n=82) Aceclofenac 100mg twice a day with matching placebo for 6 weeks</p> <p>Paracetamol (n=86)</p>	<p>Knee osteoarthritis Mean age (SD): 62.4 (6.8) years N = 168</p> <p>Definition: Primary knee osteoarthritis diagnosed with radiographic and clinical features</p>	<p>Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months Serious adverse events 3: hepatorenal adverse events at ≤3 months</p>	Study design classification: 2) Excluding non-responders

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Paracetamol 1000mg three times a day with matching placebo for 6 weeks</p> <p>Concomitant therapy: Antacid, anti-histamine-2 receptor antagonists, and proton pump inhibitors were allowed</p>	<p>Severity: ACR functional class 1-3. Kellgren Lawrence grade 2-3.</p> <p>Duration of symptoms (mean [SD]): 8.5 (6.5) years</p> <p>Presence of multimorbidities: Not stated/unclear</p>		
Boureau 2004 ³¹ IPSO trial	<p>Non-steroidal anti-inflammatory drugs (n=111) Ibuprofen 400mg three times daily for 14 days</p> <p>Paracetamol (n=111) Paracetamol 2000mg three times daily for 14 days</p> <p>Concomitant therapy: No additional information</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 66.5 (9.3) years N = 222</p> <p>Definition: Lower limb osteoarthritis diagnosed according to clinical and radiographic criteria from the American College of Rheumatology</p> <p>Severity: Not stated Duration of symptoms (mean [SD]): 4.7 (5.5) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Physical function at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p> <p>Serious adverse events 3: hepatorenal adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 2) Excluding non-responders</p>
Bradley 1991 ³²	<p>Non-steroidal anti-inflammatory drugs (n=123) Ibuprofen 1200mg/day or 2400mg/day for 4 weeks</p> <p>Paracetamol (n=61) Paracetamol 4000mg/day for 4 weeks</p>	<p>Knee osteoarthritis Mean age (SD): 56.5 (12.3) years N = 184</p> <p>Definition: Knee pain and evidence of radiographic osteoarthritis</p>	<p>Pain at ≤3 months Physical function at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p>	<p>Study design classification: 2) Excluding non-responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Concomitant therapy: Propoxyphene napsylate was permitted as rescue medication during the washout period (100mg up to four times daily) only.</p>	<p>Severity: Radiographic grade 2-3 Duration of symptoms (mean [SD]): 9.2 (9.4) years Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 2: cardiovascular adverse events at ≤3 months Serious adverse events 3: hepatorenal adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	
Case 2003 ⁴¹	<p>Paracetamol (n=29) Paracetamol 1000mg four times daily with matching placebo twice daily for 12 weeks</p> <p>Oral non-steroidal anti-inflammatory drugs (n=25) Diclofenac sodium 75mg twice daily with matching placebo two tablets four times a day for 12 weeks</p> <p>Placebo (n=28)</p> <p>Concomitant therapy: Use of nonstudy pain medications during the trial was prohibited</p>	<p>Knee osteoarthritis Mean age (SD): 62.2 (9.6) years N = 82</p> <p>Definition: Unilateral symptomatic osteoarthritis of the knee based on clinical and radiological criteria</p> <p>Severity: Kellgren Lawrence grade 2 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Physical function at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p>
Doherty 2011 ⁶⁴	<p>Non-steroidal anti-inflammatory drugs (n=224) Ibuprofen 200mg three times a day for 13 weeks</p> <p>Paracetamol (n=222)</p>	<p>Knee osteoarthritis Mean age (range): 60.6 (40-84) years N = 892</p> <p>Definition: Knee pain with changes on imaging</p>	<p>Pain at ≤3 months Physical function at ≤3 months</p>	<p>Study design classification: 2) Excluding non-responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Paracetamol 1000mg three times a day for 13 weeks</p> <p>A third group (n=446) was reported which was not included in the analysis as it was excluded in the protocol (combination paracetamol and NSAID treatment).</p> <p>Concomitant therapy: Concomitant medication was allowed apart from anticoagulants (except ≤ 325mg aspirin/day).</p>	<p>Severity: Functional classification 1-3</p> <p>Duration of symptoms: Not stated</p> <p>Presence of multimorbidities: Not stated/unclear</p>		
Geba 2002 ⁸⁴	<p>Non-steroidal anti-inflammatory drugs (n=97) Celecoxib 200mg per day for 6 weeks</p> <p>Paracetamol (n=94) Paracetamol 1000mg four times a day for 6 weeks</p> <p>A third group (n=191) was not included in the analysis due to the medication not being licensed for use in the UK (rofecoxib).</p> <p>Concomitant therapy: NSAID users were allowed to take paracetamol during the washout phase (restricted to</p>	<p>Knee osteoarthritis Mean age (SD): 62.6 (10.81) years N = 382</p> <p>Definition: Symptomatic osteoarthritis of the knee fulfilling the American College of Rheumatology clinical criteria</p> <p>Severity: Functional class 1-3 Duration of symptoms: At least 6 months Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤ 3 months Physical function at ≤ 3 months</p>	<p>Study design classification: 1) Including only responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	2600mg per day). No other rescue medication was permitted during the study.			
Golden 2004 ⁹⁰	<p>Paracetamol (n=148) Paracetamol 1000mg four times daily for 7 days</p> <p>Non-steroidal anti-inflammatory drugs (n=162) Naproxen 220mg three times a day (if the person was age 65 years or over they were to take it two times a day only) for 7 days</p> <p>Placebo (n=155)</p> <p>Concomitant therapy: Paracetamol could be taken during the washout period but could not be used in the study</p>	<p>Knee osteoarthritis Mean age (SD): 60.57 (12.78) years N = 465</p> <p>Definition: Radiographic knee osteoarthritis</p> <p>Severity: Functional class I-III Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 6) No response criteria</p> <p>Pooled analysis of 2 trials</p>
March 1993 ¹³⁵	<p>Non-steroidal anti-inflammatory drugs (n=25) Diclofenac 50mg twice daily for 2 weeks</p> <p>Paracetamol (n=25) Paracetamol 1 gram twice daily for 2 weeks</p> <p>Concomitant therapy:</p>	<p>Osteoarthritis (site unclear) Median age (range): 64 (38-85) years N = 50</p> <p>Definition: Osteoarthritis with daily pain</p> <p>Severity: Not stated Duration of symptoms: Not stated</p>	Pain at ≤3 months	<p>Study design classification: 4) Unclear</p> <p>N of 1 trials Crossover study</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	Paracetamol was available as an escape analgesic up to a maximum of 2 grams/day	Presence of multimorbidities: Not stated/unclear		
Pincus 2004 ¹⁵⁶ (PACES trial)	<p>Paracetamol (n=631) Paracetamol 1000mg four times a day for 6 weeks</p> <p>Non-steroidal anti-inflammatory drugs (n=723) Celecoxib 200mg/day for 6 weeks</p> <p>Placebo (n=562)</p> <p>Concomitant therapy: Propoxyphene 65mg up to four times a day was given as rescue treatment; codeine 60mg or tramadol 100mg up to four times per day were provided as alternatives to fewer than 5% of people if propoxyphene was poorly tolerated or ineffective</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 63.45 (10.03) years N = 1916</p> <p>Definition: Radiographic and clinical osteoarthritis</p> <p>Severity: Kellgren Lawrence mean grade 2-3 Duration of symptoms (mean [SD]): 9.36 (8.99) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 4) Unclear</p> <p>Pooled analysis of two trials</p> <p>Crossover trial</p>
Schnitzer 2005 ¹⁸³ VACT trial	<p>Non-steroidal anti-inflammatory drugs (n=523) Celecoxib 200mg/day for 6 weeks</p> <p>Paracetamol (n=269) Paracetamol 1000mg four times a day for 6 weeks</p> <p>A third group (n=786) was not included in the analysis due to</p>	<p>Knee osteoarthritis Mean age (SD): 62.1 (10.34) years N = 1578</p> <p>Definition: Symptomatic osteoarthritis of the knee defined by clinical diagnosis</p> <p>Severity: Functional class 1-3</p>	<p>Pain at ≤3 months Physical function at ≤3 months Serious adverse events 2: cardiovascular adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p> <p>Pooled analysis of 2 trials. One trial was Geba 2002⁸⁴, which is analysed separately.</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>the medication not being licensed for use in the UK (rofecoxib).</p> <p>Concomitant therapy: No rescue medication was permitted</p>	<p>Duration of symptoms: Not stated/unclear</p> <p>Presence of multimorbidities: Not stated/unclear</p>		
Temple 2006 ¹⁹⁶	<p>Non-steroidal anti-inflammatory drugs (n=291) Naproxen 750mg/day for 12 months</p> <p>Paracetamol (n=290) Paracetamol 4 grams/day for 12 months</p> <p>Concomitant therapy: No additional information</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 59.3 (8.6) years N = 581</p> <p>Definition: Symptomatic osteoarthritis based on clinical and radiographic criteria</p> <p>Severity: Kellgren Lawrence grade 2-3. Functional class 1-3.</p> <p>Duration of symptoms: At least 3 months</p> <p>Presence of multimorbidities: Not stated/unclear</p>	Serious adverse events 2: cardiovascular adverse events at ≤3 months	Study design classification: 1) Including only responders
Verkleij 2015 ²¹⁰	<p>Non-steroidal anti-inflammatory drugs (n=52) Diclofenac 50mg three times a day maximum for 2 weeks, and if required an additional 2 weeks</p> <p>Paracetamol (n=52) Paracetamol 1000mg three times a day maximum for 2</p>	<p>Knee osteoarthritis Mean age (SD): 64.0 (9.1) years N = 104</p> <p>Definition: Fulfilling the clinical criteria of the American College of Rheumatology</p>	<p>Quality of life at ≤3 months</p> <p>Pain at ≤3 months</p> <p>Physical function at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p>	Study design classification: 5) All drug naïve

Study	Intervention and comparison	Population	Outcomes	Comments
	weeks and, if required, an additional 2 weeks Concomitant therapy: Usual care was provided by the GP to all patients (not defined further)	Severity: Kellgren Lawrence grades 0-4 (most 0-1) Duration of symptoms (mean [SD]): Majority greater than 3 months (some less than 3 weeks) Presence of multimorbidities: Not stated/unclear	Serious adverse events 2: cardiovascular adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months	
Williams 1993 ²¹⁹	Non-steroidal anti-inflammatory drugs (n=90) Naproxen 375mg twice daily for 2 years Paracetamol (n=88) Paracetamol 325mg four times a day for 2 years Concomitant therapy: Concurrent treatment with corticosteroids or any other experimental drug was not permitted	Knee osteoarthritis Mean age (SD): 59.5 (10.8) years N = 178 Definition: Clinical and radiographic diagnosis of osteoarthritis Severity (mean radiographic severity [SD]): 2.2 (0.94) Duration of symptoms (mean [SD]): 79.8 (74.4) months Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months at >3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at >3 months Serious adverse events 2: cardiovascular adverse events at >3 months Serious adverse events 3: hepatorenal adverse events at >3 months Serious adverse events 4: central nervous system adverse events at >3 months	Study design classification: 3) selection of specific population

1 **1.1.5.1.3 Oral non-steroidal anti-inflammatory drugs compared to placebo**

2 **Table 4: Summary of studies included in the evidence review for oral non-steroidal anti-inflammatory drugs compared to placebo**

Study	Intervention and comparison	Population	Outcomes	Comments
Amundsen 1983 ⁶	Non-steroidal anti-inflammatory drugs (n=104) Naproxen 250mg twice a day (n=52) or diclofenac 50mg twice	Knee osteoarthritis Mean age (range): 61 (34-78) years N = 52	Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months	Study design classification: 4) Unclear Crossover trial

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>a day (n=52) for 10 days (for each drug)</p> <p>Placebo (n=52)</p> <p>Concomitant therapy: Paracetamol up to 1 gram four times a day was allowed as rescue medication</p>	<p>Definition: Osteoarthritis with active synovitis</p> <p>Severity: Not stated</p> <p>Duration of symptoms (mean [range]): 10 (1-38) years</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	
Andelman 1983 ⁷	<p>Non-steroidal anti-inflammatory drugs (n=20) Aspirin 2400-4800mg/day for 12 weeks or Etodolac 100-400mg/day for 12 weeks</p> <p>Placebo (n=10)</p> <p>Concomitant therapy: Paracetamol (650mg, up to four times daily as needed) was permitted only during the washout period</p>	<p>Mixed osteoarthritis (knee or hip)</p> <p>Mean age (range): 61.3 (44-70) years N = 30</p> <p>Definition: Roentgenological and clinical criteria for the diagnosis of degenerative joint disease of the knee or hip</p> <p>Severity: Not stated</p> <p>Duration of symptoms (mean): 7.9 years</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p>
Anonymous 1983 ⁸	<p>Non-steroidal anti-inflammatory drugs (n=306) Piroxicam 20mg once daily for 2 weeks</p> <p>Placebo (n=306)</p>	<p>Osteoarthritis (unclear site)</p> <p>Mean age (range): 62.9 (24-84) years N = 306</p>	<p>Pain at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 4) Unclear</p> <p>Crossover trial</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: No additional information	Definition: Osteoarthritis with a typical history and physical findings Severity: Not stated Duration of symptoms (mean): 8.1 years Presence of multimorbidities: Not stated/unclear		
Asmus 2014 ⁹	Non-steroidal anti-inflammatory drugs (n=385) Celecoxib 200mg once daily for 6 weeks Placebo (n=383) Concomitant therapy: No additional information	Knee osteoarthritis Mean age (SD): 59.4 (10.1) years N = 768 Definition: Symptomatic osteoarthritis of the knee in a flare state Severity: Functional class 1-3 Duration of symptoms (mean [range]): 7.9 (0.0-64.2) years Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months	Study design classification: 6) No response criteria Pooled analysis of 2 trials. Results for studies are reported separately so are integrated into the review separately.
Baerwald 2010 ¹²	Non-steroidal anti-inflammatory drugs (n=156) Naproxen 500mg twice daily for 13 weeks Placebo (n=331) A third group (n=323) was not included in the analysis due to the medication not being	Hip osteoarthritis Mean age (SD): 63.02 (9.424) years N = 810 Definition: Primary osteoarthritis confirmed with radiography Severity: Functional class 1-3	Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months Serious adverse events 2: cardiovascular adverse events at ≤3 months	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>licensed for use in the UK (naproxinod).</p> <p>Concomitant therapy: Paracetamol was allowed as rescue medication during the study (up to 3000mg/day, not to be used within 24 hours prior to each study visit).</p>	<p>Duration of symptoms: Not stated</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	
Bakshi 1991 ¹³	<p>Non-steroidal anti-inflammatory drugs (n=208) Diclofenac 50mg three times a day for 4 weeks</p> <p>Placebo (n=106)</p> <p>Concomitant therapy: Paracetamol (up to a maximum of 4g/day) was permitted as rescue analgesic for both treatment groups</p>	<p>Mixed osteoarthritis (knee, hip or hand) Mean age (range): 68.9 (60-80) years N = 314</p> <p>Definition: Clinical evidence of osteoarthritis requiring therapy with anti-inflammatory drugs</p> <p>Severity: Not stated Duration of symptoms (mean): 6.4 years Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 4) Unclear</p>
Bensen 1999 ¹⁹	<p>Non-steroidal anti-inflammatory drugs (n=800) Naproxen 500mg twice a day or Celecoxib 50mg, 100mg or 200mg twice a day for 12 weeks</p> <p>Placebo (n=203)</p>	<p>Knee osteoarthritis Mean age (range): 62 (21-87) years N = 1003</p> <p>Definition: Primary osteoarthritis of the knee fulfilling the American College</p>	<p>Pain at ≤3 months</p> <p>Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding</p>	<p>Study design classification: 1) Including only responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Concomitant therapy: Stable doses of aspirin, 325mg/d or less, and paracetamol, up to 2g/d, taken for no longer than 3 consecutive days, except during the 48-hour period prior to assessment, were allowed</p>	<p>of Rheumatology clinical criteria</p> <p>Severity: Functional class 1-3</p> <p>Duration of symptoms (mean [SD]): 10 (8) years</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	
Berry 1982 ²⁰	<p>Non-steroidal anti-inflammatory drugs (n=30) Diclofenac 50mg three times daily or piroxicam 20mg once daily for 4 weeks</p> <p>Placebo (n=30)</p> <p>Concomitant therapy: People were withdrawn from all anti-inflammatory/analgesic preparations on the first day of the study period</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (range): 67.3 (51-82) years N = 30</p> <p>Definition: Clinical evidence of osteoarthritis</p> <p>Severity: Not stated</p> <p>Duration of symptoms (mean): 7 years</p> <p>Presence of multimorbidities: Not stated/unclear</p>	Pain at ≤3 months	<p>Study design classification: 4) Unclear</p> <p>Crossover trial</p>
Berry 1983 ²¹	<p>Non-steroidal anti-inflammatory drugs (n=24) Naproxen 750mg per day (250mg in the morning, 500mg at night) for 2 weeks</p> <p>Placebo (n=24)</p> <p>A third group (n=24) was not included in the analysis due to the medication not being</p>	<p>Knee osteoarthritis Mean age (SD): 62.3 (1.8) years N = 24</p> <p>Definition: Osteoarthritis confirmed by radiography</p> <p>Severity: Not stated</p>	Pain at ≤3 months	<p>Study design classification: 4) Unclear</p> <p>Crossover trial</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>licensed for use in the UK (antrafenine).</p> <p>Concomitant therapy: Throughout the study people were allowed paracetamol, up to 4g/day as a 'rescue' analgesic. No other anti-inflammatory or analgesic drug therapy was permitted.</p>	<p>Duration of symptoms: Not stated</p> <p>Presence of multimorbidities: Not stated/unclear</p>		
Bingham 2007 ²³	<p>Non-steroidal anti-inflammatory drugs (n=963) Etoricoxib 30mg or celecoxib 200mg once a day for 12 weeks</p> <p>Placebo (n=244)</p> <p>Concomitant therapy: Low dose aspirin (325mg or less, once daily) was allowed for cardio-protective benefit. People could continue with existing physical therapy, but were not permitted to initiate physical therapy during the study period.</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 62.1 (9.6) years N =</p> <p>Definition: A diagnosis of osteoarthritis for at least 6 months</p> <p>Severity: Functional class 1-3 Duration of symptoms: At least 6 months Presence of multimorbidities: People with multimorbidities excluded</p>	<p>Pain at ≤3 months Physical function at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p> <p>Pooled analysis of 2 trials</p>
Birbara 2006 ²⁵	<p>Non-steroidal anti-inflammatory drugs (n=326) Celecoxib 200mg once a day for 6 weeks</p> <p>Placebo (n=163)</p>	<p>Knee osteoarthritis Mean age (SD): 60.7 (10.6) years N = 808</p> <p>Definition: A clinical diagnosis for at least 6 months</p>	<p>Pain at ≤3 months Physical function at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p> <p>Pooled analysis of 2 trials</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>A third group (n=319) was not included in the analysis due to the medication not being licensed for use in the UK (rofecoxib).</p> <p>Concomitant therapy: People were allowed to take paracetamol (maximum dose 2600mg/day) as rescue therapy for osteoarthritis pain if the study medication did not provide adequate pain control and were instructed to discontinue use 12 hours before study visits. People who used low-dose aspirin (81mg or less daily) for cardioprotective effects were permitted to continue low-dose aspirin use during the studies. Glucosamine and chondroitin sulfate, if taken for longer than 6 months, were also permitted if taken at the same stable dose for the duration of the studies.</p>	<p>Severity: Functional class 1-3 Duration of symptoms: At least 6 months Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p>	
Bocanegra 1998 ²⁷	<p>Non-steroidal anti-inflammatory drugs (n=154) Diclofenac 75mg twice a day for 6 weeks</p> <p>Non-steroidal anti-inflammatory drugs and gastroprotection (n=327) Diclofenac 50mg with misoprostol 200 microgram</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 62.5 (10.4) years N = 572</p> <p>Definition: Symptomatic osteoarthritis with a functional classification of 1-3</p>	<p>Pain at ≤3 months Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months Serious adverse events 3: hepatorenal adverse events at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>three times a day or diclofenac 75mg with misoprostol 200 microgram two times a day for 6 weeks</p> <p>Placebo (n=91)</p> <p>Concomitant therapy: No additional information - all antiinflammatory drugs were not permitted (with the exception of aspirin \leq325mg/day).</p>	<p>Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 11.2 (8.7) years Presence of multimorbidities: Not stated/unclear</p>		
Caroit 1976 ⁴⁰	<p>Non-steroidal anti-inflammatory drugs (n=9) Ketoprofen 50mg three times a day for 2 weeks</p> <p>Placebo (n=9)</p> <p>Concomitant therapy: Analgesics were withdrawn except for aspirin in so far as it had been used before and provided that the treatment was continued at the same dosage during the two treatment periods</p>	<p>Hip osteoarthritis Mean age (range): 63 (54-72) years N = 9</p> <p>Definition: Osteoarthritis based on classical criteria associated with presence of radiological signs</p> <p>Severity: Not stated Duration of symptoms (mean): 9 years Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 3: hepatorenal adverse events at \leq3 months</p>	<p>Study design classification: 1) Including only responders</p> <p>Crossover trial</p>
Case 2003 ⁴¹	<p>Paracetamol (n=29) Paracetamol 1000mg four times daily with matching placebo twice daily for 12 weeks</p>	<p>Knee osteoarthritis Mean age (SD): 62.2 (9.6) years N = 82</p>	<p>Pain at \leq3 months Physical function at \leq3 months</p>	<p>Study design classification: 1) Including only responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Oral non-steroidal anti-inflammatory drugs (n=25) Diclofenac sodium 75mg twice daily with matching placebo two tablets four times a day for 12 weeks</p> <p>Placebo (n=28)</p> <p>Concomitant therapy: Use of nonstudy pain medications during the trial was prohibited</p>	<p>Definition: Unilateral symptomatic osteoarthritis of the knee based on clinical and radiological criteria</p> <p>Severity: Kellgren Lawrence grade 2</p> <p>Duration of symptoms: Not stated</p> <p>Presence of multimorbidities: Not stated/unclear</p>		
<p>Clegg 2006⁵¹ GAIT trial Subsidiary papers: Hochberg 2008⁹⁷ Sawitzke 2008¹⁷⁴ Sawitzke 2010¹⁷⁵</p>	<p>Non-steroidal anti-inflammatory drugs (n=318) Celecoxib 200mg daily for 24 weeks</p> <p>Glucosamine (n=317) Glucosamine hydrochloride 500mg three times daily for 24 weeks</p> <p>Placebo (n=313)</p> <p>A forth and fifth group (n=635) was reported which was not included in the analysis as it was excluded in the protocol (combination glucosamine and chondroitin sulfate, or chondroitin sulfate alone).</p>	<p>Knee osteoarthritis Mean age (SD): 58.6 (10.4) years N = 1583</p> <p>Definition: Clinical and radiographic evidence of osteoarthritis</p> <p>Severity: Kellgren Lawrence grade 2-3. Functional class 1-3.</p> <p>Duration of symptoms (mean [SD]): 10.0 (9.8) years</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at >3 months Physical function at >3 months Serious adverse events 2: cardiovascular adverse events at >3 months</p>	<p>Study design classification: 6) No response criteria</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Glucosamine purity: Statement regarding purity</p> <p>Concomitant therapy: People were allowed to take paracetamol up to 4000mg per day, except during the 24 hours before a clinical evaluation for joint pain.</p>			
Conaghan 2013 ⁵³	<p>Oral non-steroidal anti-inflammatory drugs (n=235) Celecoxib 100mg twice a day for 12 weeks</p> <p>Topical non-steroidal anti-inflammatory drugs (n=463) Ketoprofen gel either 50mg or 100mg in 2.2 or 4.4 grams respectively applied twice a day for 12 weeks</p> <p>Oral placebo (n=228)</p> <p>Topical placebo (n=473) Ketoprofen gel vehicle without the ketoprofen</p> <p>Concomitant therapy: Paracetamol 500mg up to four times a day was permitted for intermittent pain treatment, although not within 24 hours of the next study visit or between the baseline visits. People</p>	<p>Knee osteoarthritis Mean age (range): 61.2 (24-90) years N = 1399</p> <p>Definition: Primary diagnosis meeting the American College of Rheumatology clinical classification. People aged 18-45 were permitted if they had radiological confirmation of osteoarthritis</p> <p>Severity: Functional class 1-3 Duration of symptoms (mean [SD]): Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 2) Excluding non-responders</p> <p>When comparing to placebo, one the placebo of the same formulation was used (for example: oral non-steroidal anti-inflammatory drugs compared to oral placebo).</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	requiring ≥2 grams of paracetamol or other analgesic medication for longer than 3 consecutive days were considered treatment failures and withdrawn from the study.			
Couto 2018 ⁵⁴	<p>Non-steroidal anti-inflammatory drugs (n=428) Naproxen 220mg two to three times per day for 1 week</p> <p>Placebo (n=419)</p> <p>Concomitant therapy: Use of aspirin ≤325mg/day was permitted</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 60.7 (12.9) years N = 847</p> <p>Definition: Radiographic evidence of osteoarthritis</p> <p>Severity: Kellgren Lawrence grade 1-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p> <p>Serious adverse events 3: hepatorenal adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 4) Unclear</p> <p>Pooled analysis of 4 studies</p>
Cryer 2011 ⁵⁵	<p>Non-steroidal anti-inflammatory drugs (n=494) Celecoxib 200mg once daily for 12 weeks</p> <p>Non-steroidal anti-inflammatory drugs with gastroprotection (n=492) Naproxen 500mg and esomeprazole 20mg twice daily for 12 weeks</p> <p>Placebo (n=248)</p>	<p>Knee osteoarthritis Mean age (range): 61.9 (49-90) years N = 1234</p> <p>Definition: Symptomatic, clinically diagnosed osteoarthritis</p> <p>Severity: Functional class I-III Duration of symptoms: Not stated</p>	<p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p> <p>Pooled analysis of 2 trials</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Concomitant therapy: Incidental use of rescue antacid (≤ 6 tablets per day) and supplemental use of rescue paracetamol (≤ 3g/day) were allowed during the study. Concomitant use of oral prednisone (≤ 7.5mg/day), low dose aspirin (≤ 325mg/day) and antiplatelet agents (non-concomitant with aspirin) were allowed.</p>	<p>Presence of multimorbidities: Not stated/unclear</p>		
Delemos 2011 ⁶⁰	<p>Non-steroidal anti-inflammatory drugs (n=203) Celecoxib 200mg once a day for 12 weeks</p> <p>Strong opioids (n=606) Tramadol 100mg once to three times a day for 12 weeks</p> <p>Placebo (n=202)</p> <p>Concomitant therapy: Aspirin up to 325mg/day for cardiovascular prophylaxis was allowed as was paracetamol up to 2g/day for up to 3 consecutive days for reasons other than osteoarthritis or chronic pain if absolutely necessary.</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 59.92 (10.96) years N = 1011</p> <p>Definition: Radiologically confirmed osteoarthritis</p> <p>Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 8.1 (7.9) years Presence of multimorbidities: Not stated/unclear</p>	<p>Quality of life at ≤ 3 months Pain at ≤ 3 months Physical function at ≤ 3 months Psychological distress at ≤ 3 months</p>	<p>Study design classification: 1) Including only responders</p>
Dieppe 1993 ⁶³	<p>Non-steroidal anti-inflammatory drugs (n=45)</p>	<p>Knee osteoarthritis</p>	<p>Serious adverse events 1B: gastrointestinal (non-bleeding)</p>	<p>Study design classification: 4) Unclear</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Diclofenac 100mg/day (slow release formulation) for 2 years</p> <p>Placebo (n=44)</p> <p>Concomitant therapy: Tablets of 500mg paracetamol were provided as escape analgesia and people were instructed to take up to a maximum of eight tablets in 24 hours if necessary for pain relief.</p>	<p>Mean age (range): 63.1 (40-82) years N = 89</p> <p>Definition: Symptomatic knee osteoarthritis with radiological confirmation</p> <p>Severity: Kellgren Lawrence grades 1-4 Duration of symptoms (mean): 9.8 years Presence of multimorbidities: Not stated/unclear</p>	<p>and perforation) adverse events at >3 months</p> <p>Serious adverse events 3: hepatorenal adverse events at >3 months</p>	
Dore 1995 ⁶⁵	<p>Non-steroidal anti-inflammatory drugs (n=168) Naproxen 500mg twice daily or Etodolac 400mg twice daily for 4 weeks</p> <p>Placebo (n=86)</p> <p>Concomitant therapy: Maintenance of low-dose aspirin (maximum of 325mg/day) as antithrombosis prophylaxis and occasional use of non-anti-inflammatory analgesics for nonarthritic pain was permitted</p>	<p>Knee osteoarthritis Mean age: 63.7 years N = 254</p> <p>Definition: Symptomatic, radiologically confirmed osteoarthritis of the knee that required NSAID treatment</p> <p>Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 2) Excluding non-responders</p>
Esselinckx 1990 ⁶⁷	<p>Non-steroidal anti-inflammatory drugs (n=258) Diclofenac retard 100mg or tenoxicam 20mg or 40mg once a day for 4 weeks</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 62.5 (10.1) years N = 347</p>	<p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p>	<p>Study design classification: 3) Selection of specific population</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Placebo (n=89)</p> <p>Concomitant therapy: No additional information</p>	<p>Definition: Painful osteoarthritis with radiological confirmation</p> <p>Severity: Not stated Duration of symptoms: median between 1 and 5 years Presence of multimorbidities: Not stated/unclear</p>		
Essex 2012 ⁶⁹	<p>Non-steroidal anti-inflammatory drugs (n=255) Naproxen 500mg twice a day or celecoxib 200mg once daily for 6 weeks</p> <p>Placebo (n=67)</p> <p>Concomitant therapy: Paracetamol no more than 2g/day for no more than 3 consecutive days and not within 24 hours before any arthritis assessment was allowed during the study. People taking aspirin no more than 325mg/day were allowed to continue for the duration of the study if they had been taking a stable dose for at least 30 days before the first dose of study medication.</p>	<p>Knee osteoarthritis Mean age (SD): 58.0 (8.5) years N = 322</p> <p>Definition: Osteoarthritis in a flare state according to the American College of Rheumatology guidelines</p> <p>Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 5.4 (5.8) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months</p>	Study design classification: 1) Including only responders
Essex 2014 ⁶⁸	<p>Non-steroidal anti-inflammatory drugs (n=256)</p>	<p>Knee osteoarthritis</p>	<p>Pain at ≤3 months</p>	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Naproxen 500mg twice a day or celecoxib 200mg once a day for 6 weeks</p> <p>Placebo (n=62)</p> <p>Concomitant therapy: No additional information</p>	<p>Mean age (SD): 60.4 (10.6) years N = 318</p> <p>Definition: Osteoarthritis of the knee in a flare state diagnosed according to the American College of Rheumatology criteria</p> <p>Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 6.0 (6.3) years Presence of multimorbidities: Not stated/unclear</p>	<p>Physical function at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months</p>	
Essex 2016 ⁷⁰	<p>Non-steroidal anti-inflammatory drugs (n=289) Naproxen 500mg twice daily or celecoxib 200mg once daily for 6 weeks</p> <p>Placebo (n=78)</p> <p>Concomitant therapy: Paracetamol (up to 2g/day) was permitted as a rescue analgesia for the treatment of arthritis symptoms during the pretreatment screening period only.</p>	<p>Knee osteoarthritis Mean age (SD): 64.8 (11.3) years N = 367</p> <p>Definition: Altman criteria for defining osteoarthritis of the knee according to the American Rheumatism Association</p> <p>Severity: Not stated Duration of symptoms (mean [SD]): 4.6 (4.7) years Presence of multimorbidities: Not stated/unclear</p>	Pain at ≤3 months	Study design classification: 1) Including only responders
Famaey 1976 ⁷¹	<p>Non-steroidal anti-inflammatory drugs (n=23)</p>	<p>Hip osteoarthritis Mean age: 66 years</p>	Serious adverse events 1B: gastrointestinal (non-bleeding)	Study design classification: 4) Unclear

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Ketoprofen 50mg three times a day for 2 weeks</p> <p>Placebo (n=23)</p> <p>Concomitant therapy: No additional information</p>	<p>N = 23</p> <p>Definition: Osteoarthritis diagnosed clinical and radiologically</p> <p>Severity: "6 were early cases and 17 were seriously affected by the disease"</p> <p>Duration of symptoms: Not stated</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p>	Crossover trial
Fleischmann 1997 ⁷⁶	<p>Non-steroidal anti-inflammatory drugs (n=185) Naproxen 1000mg per day or nabumetone 1500mg per day for 4 weeks</p> <p>Placebo (n=94)</p> <p>Concomitant therapy: The established use of low-dose aspirin (maximum dose of 325mg) as antithrombotic prophylaxis and the occasional use of a pure analgesic at low doses for nonarthritic pain was permitted</p>	<p>Knee osteoarthritis Mean age (SD): 62.3 (10.4) years N = 279</p> <p>Definition: Radiologically confirmed symptomatic osteoarthritis of the knee</p> <p>Severity: Not stated Duration of symptoms: At least 3 months Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	Study design classification: 2) Excluding non-responders
Fleischmann 2006 ⁷⁴	<p>Non-steroidal anti-inflammatory drugs (n=446) Celecoxib 200mg once a day for 13 weeks</p>	<p>Knee osteoarthritis Mean age (SD): 61.1 (11.3) years N = 1608</p>	<p>Pain at ≤3 months</p> <p>Physical function at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding</p>	Study design classification: 2) Excluding non-responders

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Placebo (n=232)</p> <p>A third group (n=930) was not included in the analysis due to the medication not being licensed for use in the UK (lumiracoxib).</p> <p>Concomitant therapy: Paracetamol (≤ 2 gram/day) was permitted as rescue medication during the screening and treatment periods. Concomitant therapy with any other NSAIDs (with the exception of low dose aspirin ≤ 325 mg/day for a cardiovascular indication) was prohibited. Other prohibited concomitant therapies included histamine-2 receptor blockers, proton pump inhibitors, misoprostol, sucralfate (antacids were permitted up to twice a week), intra-articular/peri-articular injections and corticosteroids (ocular, topical, nasal or inhaled corticosteroids were allowed if the dosage was stable at study entry and throughout the study period)</p>	<p>Definition: Primary osteoarthritis of the knee with symptoms for at least 3 months</p> <p>Severity: Not stated Duration of symptoms (mean [SD]): 6.4 (7.4) years Presence of multimorbidities: Not stated/unclear</p>	<p>and perforation) adverse events at ≤ 3 months</p>	
Ghosh 2007 ⁸⁵	<p>Non-steroidal anti-inflammatory drugs (n=304)</p>	<p>Knee osteoarthritis Mean age (range): 54.9 (40-64) years N = 427</p>	<p>Pain at ≤ 3 months Serious adverse events 1A: gastrointestinal (bleeding and</p>	<p>Study design classification: 1) Including only responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Diclofenac 75mg once a day or etoricoxib 90mg once a day for 4 weeks</p> <p>Placebo (n=123)</p> <p>Concomitant therapy: Paracetamol (up to 2g/day for a maximum of 3 days but not before assessment of arthritis) was permitted</p>	<p>Definition: Osteoarthritis with symptoms for at least 6 months and radiological evidence</p> <p>Severity: Functional class 1-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>perforation) adverse events at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	
Giansiracusa 1977 ⁸⁶	<p>Non-steroidal anti-inflammatory drugs (n=437) Ibuprofen 150mg four times daily or aspirin 300mg four times daily</p> <p>Placebo (n=437)</p> <p>Concomitant therapy: They supplied propoxyphene, which has no known anti-inflammatory activity, as an adjunctive analgesic for people whose pain was not adequately controlled by the study medication</p>	<p>Mixed osteoarthritis (knee, hip or shoulder) Mean age: 64.4 years N = 437</p> <p>Definition: Clinical diagnosis with roentgenograms confirming the diagnosis in most cases</p> <p>Severity: Not stated Duration of symptoms (mean): 11.6 years Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months</p>	<p>Study design classification: 4) Unclear</p> <p>Crossover trial</p>
Gibofsky 2003 ⁸⁸	<p>Non-steroidal anti-inflammatory drugs (n=189) Celecoxib 200mg once a day</p> <p>Placebo (n=96)</p>	<p>Knee osteoarthritis Mean age (SD): 62.9 (10.3) years N = 475</p> <p>Definition: Osteoarthritis in a flare state diagnosed</p>	<p>Pain at ≤3 months Physical function at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>A third group (n=190) was not included in the analysis due to the medication not being licensed for use in the UK (rofecoxib).</p> <p>Concomitant therapy: Use of low-dose aspirin (≤ 325mg/day) for cardiovascular prophylaxis was allowed, as was occasional use of paracetamol (use of paracetamol had to be discontinued for 48 hours prior to the arthritis assessments) or antacids</p>	<p>according to the American College of Rheumatology criteria</p> <p>Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 8.6 (8.1) years Presence of multimorbidities: Not stated/unclear</p>		
Gibofsky 2014 ⁸⁷	<p>Non-steroidal anti-inflammatory drugs (n=292) Low dose submicron diclofenac 35mg twice or three times a day for 12 weeks</p> <p>Placebo (n=103)</p> <p>Concomitant therapy: Paracetamol (up to 500mg) every 4 to 6 hours as required was permitted as rescue analgesia (to not exceed 3000mg daily)</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 61.6 (8.9) years N = 395</p> <p>Definition: Clinically and radiographically confirmed osteoarthritis</p> <p>Severity: Kellgren-Lawrence grade 2-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤ 3 months Physical function at ≤ 3 months</p>	<p>Study design classification: 1) Including only responders</p>
Golden 2004 ⁹⁰	<p>Paracetamol (n=148) Paracetamol 1000mg four times daily for 7 days</p>	<p>Knee osteoarthritis Mean age (SD): 60.57 (12.78) years</p>	<p>Serious adverse events 1A: gastrointestinal (bleeding and</p>	<p>Study design classification: 4) Unclear</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Non-steroidal anti-inflammatory drugs (n=162) Naproxen 220mg three times a day (if the person was age 65 years or over they were to take it two times a day only) for 7 days</p> <p>Placebo (n=155)</p> <p>Concomitant therapy: Paracetamol could be taken during the washout period but could not be used in the study</p>	<p>N = 465</p> <p>Definition: Radiographic knee osteoarthritis</p> <p>Severity: Functional class I-III Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>perforation) adverse events at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	Pooled analysis of 2 trials
Gordo 2017 ⁹²	<p>Non-steroidal anti-inflammatory drugs (n=309) Ibuprofen 800mg three times daily for 6 weeks</p> <p>Placebo (n=79)</p> <p>Concomitant therapy: No additional information</p>	<p>Knee osteoarthritis Mean age (SD): 63.0 (6.7) years N = 388</p> <p>Definition: Clinical diagnosis and in a flare state according to the American College of Rheumatology guidelines</p> <p>Severity: Not stated Duration of symptoms (mean [SD]): 5.7 (5.9) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	Study design classification: 1) Including only responders
Gottesdiener 2002 ⁹³	<p>Non-steroidal anti-inflammatory drugs (n=557)</p>	<p>Knee osteoarthritis Mean age (range): 61.3 (40-87) years</p>	<p>Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months</p>	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Etoricoxib 5, 10, 30, 60 or 90mg once daily for 6 weeks</p> <p>Placebo (n=60)</p> <p>Concomitant therapy: After completing 2 weeks of treatment, people were provided open-label paracetamol, maximum daily dose of 2.6g, that could be taken for osteoarthritic pain that was not adequately controlled by the study medication</p>	<p>N = 617</p> <p>Definition: Clinical and radiographic evidence of osteoarthritis</p> <p>Severity: Functional class 1-3 Duration of symptoms (mean): 7.83 years Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 3: hepatorenal adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	
Haghighi 2005 ⁹⁵	<p>Non-steroidal anti-inflammatory drugs (n=40) Ibuprofen 400mg three times daily for 4 weeks</p> <p>Placebo (n=40)</p> <p>A third group (n=40) was reported which was not included in the analysis as it was excluded in the protocol (ginger extract).</p> <p>Concomitant therapy: Paracetamol was used as a rescue medication throughout the study (1 to 3 tablets daily).</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (range): 58.5 (52-64) years N = 120</p> <p>Definition: Clinical dysfunction and pain due to osteoarthritis with radiological verification</p> <p>Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	Pain at ≤3 months	Study design classification: 6) No response criteria
Hubault 1976 ⁹⁹	<p>Non-steroidal anti-inflammatory drugs (n=9)</p>	<p>Hip osteoarthritis Age not stated N = 9</p>	Serious adverse events 1B: gastrointestinal (non-bleeding)	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Ketoprofen 50mg three times a day for 2 weeks</p> <p>Placebo (n=9)</p> <p>Concomitant therapy: No additional information</p>	<p>Definition: Painful osteoarthritis with positive radiological signs</p> <p>Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 3: hepatorenal adverse events at ≤3 months</p>	Crossover trial
Kageyama 1973 ¹⁰³	<p>Non-steroidal anti-inflammatory drugs (n=74) Naproxen 500mg daily for 2 weeks</p> <p>Placebo (n=43)</p> <p>A third group (n=61) was not included in the analysis due to the medication not being licensed for use in the UK (aluminium flufenamate).</p> <p>Concomitant therapy: Other anti-arthritis agents were not allowed. Any pre-established physical therapy program was permitted to continue.</p>	<p>Mixed osteoarthritis (knee, hip, fingers or polyarticular) Mean age: Unclear N = 178</p> <p>Definition: Clinical and radiological diagnosis</p> <p>Severity: Not stated Duration of symptoms: Unclear Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	Study design classification: 4) Unclear
Karakaya 1977 ¹⁰⁴	<p>Non-steroidal anti-inflammatory drugs (n=20) Indomethacin 25mg three times a day for 4 weeks</p>	<p>Knee osteoarthritis Mean age: Not stated/unclear N = 60</p>	<p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p>	Study design classification: 4) Unclear

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Placebo (n=20)</p> <p>A third group (n=20) was not included in the analysis due to the medication not being licensed for use in the UK (proquazone).</p> <p>Concomitant therapy: No additional information</p>	<p>Definition: Clinical and radiological diagnosis</p> <p>Severity: Not stated</p> <p>Duration of symptoms: Not stated</p> <p>Presence of multimorbidities: Not stated/unclear</p>		
Kivitz 2001 ¹¹⁰	<p>Non-steroidal anti-inflammatory drugs (n=82) Ibuprofen 400mg once daily for 2 weeks</p> <p>Placebo (n=160)</p> <p>A third group (n=249) was not included in the analysis due to the medication not being licensed for use in the UK (oxaprozin).</p> <p>Concomitant therapy: Topical analgesics were allowed during the course of the study, provided they were not applied to the knee chosen for pain assessments. Topical and inhaled corticosteroids could also be continued if used at the time of study initiation. Aspirin ≤325mg/day could be used for cardiovascular prophylaxis.</p>	<p>Knee osteoarthritis</p> <p>Mean age (range): 59.8 (28-91) years N = 491</p> <p>Definition: Osteoarthritis for at least 6 months confirmed by weightbearing radiograph</p> <p>Severity: Not stated</p> <p>Duration of symptoms: Not stated</p> <p>Presence of multimorbidities: Not stated/unclear</p>	Serious adverse events 4: central nervous system adverse events at ≤3 months	<p>Study design classification: 1) Including only responders</p> <p>In Forest plots this study is referred to as Kivitz 2001A</p>

Study	Intervention and comparison	Population	Outcomes	Comments
Kivitz 2001 ¹¹¹	<p>Non-steroidal anti-inflammatory drugs (n=843) Naproxen 500mg twice a day or Celecoxib 100, 200, or 400mg/day for 12 weeks</p> <p>Placebo (n=218)</p> <p>Concomitant therapy: People were permitted to take up to 325mg aspirin daily, and up to 2g paracetamol daily for up to 3 consecutive days, when absolutely necessary for non-arthritis conditions. However, the use of paracetamol was prohibited within 48 hours of an assessment of arthritis efficacy.</p>	<p>Hip osteoarthritis Mean age (range): 62 (28-93) years N = 1061</p> <p>Definition: Fulfilment of the American College of Rheumatology clinical and radiographic criteria</p> <p>Severity: Functional class 1-3 Duration of symptoms (mean): 7.3 years Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p> <p>In Forest plots this study is referred to as Kivitz 2001B</p>
Kivitz 2002 ¹⁰⁸	<p>Non-steroidal anti-inflammatory drugs (n=205) Naproxen 500mg twice daily for 12 weeks</p> <p>Placebo (n=205)</p> <p>A third group (n=609) was not included in the analysis due to the medication not being licensed for use in the UK (valdecoxib).</p> <p>Concomitant therapy: People discontinued their normal medications at the</p>	<p>Knee osteoarthritis Mean age (SD): 59.8 (10.9) years N = 1019</p> <p>Definition: Diagnosed according to the modified criteria of the American College of Rheumatology</p> <p>Severity: Moderate to severe Duration of symptoms (mean [SD]): 9.1 (8.5) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months</p> <p>Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 3: hepatorenal adverse events at ≤3 months</p>	<p>Study design classification: 4) Unclear</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>following specified times before the baseline endoscopy: NSAIDs (including full dose aspirin at a dosage $\geq 325\text{mg/day}$) at 48 hours, corticosteroid injection or hyaluronic acid injections at 3 and 6 months respectively. The use of antiulcer drugs, including histamine-2 receptor antagonists, proton pump inhibitors, misoprostol, and sucralfate was discontinued at least 24 hours before the baseline endoscopy.</p>			
Kivitz 2004 ¹⁰⁹	<p>Non-steroidal anti-inflammatory drugs (n=410) Nabumetone 100mg once daily for 6 weeks</p> <p>Placebo (n=208)</p> <p>A third group (n=423) was not included in the analysis due to the medication not being licensed for use in the UK (rofecoxib).</p> <p>Concomitant therapy: Paracetamol up to 2600mg a day as rescue medication for osteoarthritis pain, except during the first 6 days of therapy and 24 hours before all efficacy evaluations</p>	<p>Knee osteoarthritis Mean age (SD): 63.2 (10.2) years N = 1041</p> <p>Definition: Osteoarthritis with a positive history of response to NSAIDs</p> <p>Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 6.1 (7.3) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤ 3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤ 3 months Serious adverse events 2: cardiovascular adverse events at ≤ 3 months Serious adverse events 4: central nervous system adverse events at ≤ 3 months</p>	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
Laine 1999 ¹¹⁶	<p>Non-steroidal anti-inflammatory drugs (n=184) Ibuprofen 800mg three times daily for 24 weeks</p> <p>Placebo (n=177)</p> <p>A third group (n=381) was not included in the analysis due to the medication not being licensed for use in the UK (rofecoxib).</p> <p>Concomitant therapy: People were permitted to take supplied paracetamol (up to 2600mg daily), non-NSAID pain medications and supplied antacid as needed.</p>	<p>Osteoarthritis (site unclear) Mean age (range): 61 (47-87) years N = 742</p> <p>Definition: People with osteoarthritis</p> <p>Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months</p>	<p>Study design classification: 4) Unclear</p>
Leatham 1983 ¹²²	<p>Non-steroidal anti-inflammatory drugs (n=36) Naproxen 250mg twice daily for 3 weeks</p> <p>Placebo (n=36)</p> <p>A third group (n=36) was not included in the analysis due to the medication not being licensed for use in the UK (antrafenine).</p> <p>Concomitant therapy:</p>	<p>Mixed osteoarthritis (knee and/or hip) Mean age (SD): Not stated/unclear N = 36</p> <p>Definition: Osteoarthritis with radiological confirmation</p> <p>Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months</p>	<p>Study design classification: 2) Excluding non-responders</p> <p>Crossover trial</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	No other analgesics or anti-rheumatic drugs were allowed except paracetamol alone as 'back up' therapy			
Lee 2017 ¹²³	<p>Non-steroidal anti-inflammatory drugs (n=145) Celecoxib 200mg once daily for 6 weeks</p> <p>Placebo (n=71)</p> <p>A third group (n=146) was not included in the analysis due to the medication not being licensed for use in the UK (polmacoxib).</p> <p>Concomitant therapy: Rescue medication (paracetamol 650mg per day) was allowed during the washout and follow up period. Rescue medication was not allowed during the treatment period or within 24 hours before a clinic visit.</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 62.4 (7.8) years N = 362</p> <p>Definition: Clinical diagnosis according to clinical and imaging criteria from the American College of Rheumatology guidelines</p> <p>Severity: Functional class 1-3 Duration of symptoms: At least 3 months Presence of multimorbidities: High comorbidity score</p>	<p>Pain at ≤3 months Physical function at ≤3 months</p>	<p>Study design classification: 4) Unclear</p>
Lehmann 2005 ¹²⁴	<p>Non-steroidal anti-inflammatory drugs (n=420) Celecoxib 200mg once a day for 13 weeks</p> <p>Placebo (n=424)</p>	<p>Knee osteoarthritis Mean age (SD): 62.4 (10.1) years N = 1684</p> <p>Definition: Primary osteoarthritis meeting the</p>	<p>Pain at ≤3 months Physical function at ≤3 months Serious adverse events 2: cardiovascular adverse events at ≤3 months</p>	<p>Study design classification: 2) Excluding non-responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>A third group (n=840) was not included in the analysis due to the medication not being licensed for use in the UK (lumiracoxib).</p> <p>Concomitant therapy: Paracetamol less than or equal to 2g/day was permitted as rescue medication throughout the study, including during the screening/washout period. Concomitant NSAID therapy was not allowed during the study, with the exception of low dose aspirin (less than or equal to 325mg/day) for prophylaxis against cardiovascular or cerebrovascular events in people considered at increased risk. Other permitted concomitant medications included chondroitin sulphate and/or glucosamine sulphate (if established stable dosage and regimen); corticosteroids (topical, ophthalmic, nasal or inhaled at usual labeled doses); histamine-2 receptor antagonists; proton pump inhibitors, antacids and cytoprotective agents (taken at usual labeled doses); and physiotherapy as prescribed by the physician (only when ongoing with a stable regimen).</p>	<p>American College of Rheumatology criteria</p> <p>Severity: Not stated Duration of symptoms (mean [SD]): 4.2 (5.8) years Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	

Study	Intervention and comparison	Population	Outcomes	Comments
Leigh 1989 ¹²⁵	<p>Non-steroidal anti-inflammatory drugs (n=12) Tenoxicam 20mg at night for 3 weeks</p> <p>Placebo (n=12)</p> <p>Concomitant therapy: Paracetamol 500mg four times a day was taken in constant dosage by all people throughout the study</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (range): 63 (48-72) years N = 12</p> <p>Definition: Radiological evidence of osteoarthritis of the hip or knee or both and symptoms to merit admission to hospital for intensive physiotherapy</p> <p>Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p>	<p>Study design classification: 6) No response criteria</p> <p>Crossover trial</p>
Leung 2002 ¹²⁷	<p>Non-steroidal anti-inflammatory drugs (n=445) Naproxen 500mg twice daily or Etoricoxib 60mg once daily</p> <p>Placebo (n=56)</p> <p>Concomitant therapy: People were permitted to use open-label paracetamol (up to 2600mg/day) for osteoarthritis pain of the study joint not adequately controlled by study medication</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 63.16 (9.19) years N = 501</p> <p>Definition: Diagnosis based on clinical and radiographic criteria</p> <p>Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 6.09 (6.25) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
Lohmander 2005 ¹²⁸	<p>Non-steroidal anti-inflammatory drugs (n=417) Naproxen 500mg twice daily for 6 weeks</p> <p>Placebo (n=116)</p> <p>A third group (n=437) was not included in the analysis due to the medication not being licensed for use in the UK (AZD3582).</p> <p>Concomitant therapy: People were allowed to take paracetamol up to 4000mg a day, provided by the investigator, for the control of pain during the washout period. If they used paracetamol, it was requested that it be discontinued 12 hours before the baseline visit</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 59.3 (8.5) years N = 970</p> <p>Definition: Symptomatic osteoarthritis with radiographic evidence</p> <p>Severity: Not stated Duration of symptoms: At least 3 months Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p>	Study design classification: 3) Selection of specific population
Lopez sanchez 1983 ¹³⁰	<p>Non-steroidal anti-inflammatory drugs (n=10) Naproxen 500mg/day for 6 weeks</p> <p>Placebo (n=10)</p> <p>A third group (n=10) and a fourth group (n=10) was not included in the analysis due to the medication not being</p>	<p>Mixed osteoarthritis (knee and/or hip) Median age (range): 52.3 (39-71) years N = 40</p> <p>Definition: Radiographically verified degenerative joint disease with pain</p> <p>Severity: Not stated</p>	Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months	Study design classification: 4) Unclear

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>licensed for use in the UK (meclofenamate sodium and phenylbutazone respectively).</p> <p>Concomitant therapy: People were asked to not take any other analgesic or anti-inflammatory medication during the study. If, however, additional analgesic medication was required, paracetamol was prescribed.</p>	<p>Duration of symptoms (median [range]): 2.25 (1-12) years</p> <p>Presence of multimorbidities: Not stated/unclear</p>		
Lund 1998 ¹³¹	<p>Non-steroidal anti-inflammatory drugs (n=274) Meloxicam 7.5mg or 15mg once daily for 3 weeks</p> <p>Placebo (n=137)</p> <p>A third group (n=102) receiving meloxicam was not included in the analysis as the data reported for this group was incomplete and could not be incorporated.</p> <p>Concomitant therapy: People receiving therapy for concomitant diseases were allowed to continue with their medication. People could use paracetamol as rescue medication throughout the course of the study. Massage and exercise were also</p>	<p>Knee osteoarthritis Mean age (SD): 68.5 (11.8) years N = 513</p> <p>Definition: Clinically and radiographically confirmed osteoarthritis</p> <p>Severity: Not stated Duration of symptoms (mean [SD]): 8.4 (8.4) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p> <p>Serious adverse events 3: hepatorenal adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
	permitted, provided the routines continued unchanged throughout the course of the study			
Makarowski 1996 ¹³²	<p>Non-steroidal anti-inflammatory drugs (n=231) Oxaprozin 1400mg once a day or nabumetone 1500mg once a day for 6 weeks</p> <p>Placebo (n=116)</p> <p>Concomitant therapy: No additional information</p>	<p>Knee osteoarthritis Mean age (range): 61.1 (26-88) years N = 347</p> <p>Definition: Clinical and radiographic osteoarthritis</p> <p>Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	Serious adverse events 4: central nervous system adverse events at ≤3 months	Study design classification: 1) Including only responders
Makarowski 2002 ¹³³	<p>Non-steroidal anti-inflammatory drugs (n=118) Naproxen 500mg twice a day for 12 weeks</p> <p>Placebo (n=118)</p> <p>A third group (n=231) was not included in the analysis due to the medication not being licensed for use in the UK (valdecoxib).</p> <p>Concomitant therapy: Oxaprozin, piroxicam and full dose aspirin (>325mg/day) were discontinued at least 4 days</p>	<p>Hip osteoarthritis Mean age (SD): 62.3 (11.8) years N = 467</p> <p>Definition: Symptomatic osteoarthritis</p> <p>Severity: Not stated Duration of symptoms (mean [SD]): 6.1 (6.7) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Physical function at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	Study design classification: 2) Excluding non-responders

Study	Intervention and comparison	Population	Outcomes	Comments
	before the baseline arthritis assessment.			
Mckenna 2001 ¹³⁸	<p>Non-steroidal anti-inflammatory drugs (n=63) Celecoxib 200mg once a day for 6 weeks</p> <p>Placebo (n=60)</p> <p>A third group (n=59) was not included in the analysis due to the medication not being licensed for use in the UK (rofecoxib).</p> <p>Concomitant therapy: Paracetamol up to 2g per day was permitted as rescue analgesia during the washout period but was prohibited for at least 48 hours prior to the person's return for the baseline visits. During the treatment phase, no other analgesic medications were allowed except for occasional paracetamol for non-arthritic pain and low-dose aspirin (≤ 325mg/day) for cardiovascular prophylaxis. Anticoagulant, antirheumatic and antiulcer medications were prohibited, although occasional antacid use was allowed</p>	<p>Knee osteoarthritis Mean age (SD): 62.2 (10.3) years N = 182</p> <p>Definition: Knee osteoarthritis as defined by the American College of Rheumatology criteria (unclear if imaging was involved)</p> <p>Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 10.9 (9.5) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤ 3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤ 3 months Serious adverse events 4: central nervous system adverse events at ≤ 3 months</p>	<p>Study design classification: 1) Including only responders</p> <p>In Forest plots this study is referred to as Mckenna 2001A</p>

Study	Intervention and comparison	Population	Outcomes	Comments
Mckenna 2001 ¹³⁷	<p>Non-steroidal anti-inflammatory drugs (n=400) Diclofenac 50mg three times a day or Celecoxib 100mg twice a day for 6 weeks</p> <p>Placebo (n=200)</p> <p>Concomitant therapy: People were allowed to continue using aspirin for non-arthritis related indications if the dose was stable.</p>	<p>Knee osteoarthritis Mean age (range): 61.7 (29-88) years N = 600</p> <p>Definition: Symptomatic osteoarthritis of the knee confirmed according to the American College of Rheumatology criteria</p> <p>Severity: Not stated Duration of symptoms (mean): 8.57 years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Physical function at ≤3 months Serious adverse events 2: cardiovascular adverse events at ≤3 months Serious adverse events 3: hepatorenal adverse events at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p> <p>In Forest plots this study is referred to as Mckenna 2001B</p>
Moss 2017 ¹⁴¹	<p>Non-steroidal anti-inflammatory drugs (n=40) Etoricoxib 60mg once a day for 14 days</p> <p>Placebo (n=40)</p> <p>Concomitant therapy: People were asked to refrain from taking rescue medication within 12 hours (paracetamol) or 24 hours (Tramadol) of testing</p>	<p>Knee osteoarthritis Mean age (range): 65.2 (50-86) years N = 80</p> <p>Definition: Painful osteoarthritis using the American College of Rheumatology criteria</p> <p>Severity: Not stated Duration of symptoms (range): 2-30 years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months</p>	<p>Study design classification: 4) Unclear</p>
Paul 2009 ¹⁵¹	<p>Non-steroidal anti-inflammatory drugs (n=282)</p>	<p>Knee osteoarthritis</p>	<p>Pain at ≤3 months</p>	<p>Study design classification: 4) Unclear</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Aceclofenac 100mg or nabumetone 750mg twice daily for 4 weeks</p> <p>Placebo (n=141)</p> <p>Concomitant therapy: No additional information</p>	<p>Mean age (range): 53.5 (40-64) years N = 423</p> <p>Definition: Osteoarthritis fulfilling radiographic criteria</p> <p>Severity: Kellgren Lawrence grade 2-3. Functional class 1-3.</p> <p>Duration of symptoms: At least 6 months</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p>	
<p>Pincus 2004¹⁵⁶ PACES trial</p>	<p>Paracetamol (n=631) Paracetamol 1000mg four times a day for 6 weeks</p> <p>Non-steroidal anti-inflammatory drugs (n=723) Celecoxib 200mg/day for 6 weeks</p> <p>Placebo (n=562)</p> <p>Concomitant therapy: Propoxyphene 65mg up to four times a day was given as rescue treatment; codeine 60mg or tramadol 100mg up to four times per day were provided as alternatives to fewer than 5% of people if propoxyphene was poorly tolerated or ineffective</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 63.45 (10.03) years N = 1916</p> <p>Definition: Radiographic and clinical osteoarthritis</p> <p>Severity: Kellgren Lawrence mean grade 2-3</p> <p>Duration of symptoms (mean [SD]): 9.36 (8.99) years</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 4) Unclear</p> <p>Pooled analysis of two trials</p> <p>Crossover trial</p>

Study	Intervention and comparison	Population	Outcomes	Comments
Puopolo 2007 ¹⁶¹	<p>Non-steroidal anti-inflammatory drugs (n=437) Ibuprofen 800mg three times a day for 12 weeks</p> <p>Placebo (n=111)</p> <p>Concomitant therapy: People taking stable doses of glucosamine or chondroitin sulfate for at least 6 months prior to the study were allowed to enroll. Low-dose aspirin (no more than 100mg daily) for cardioprophylaxis was allowed. Gastroprotective agents, such as proton pump inhibitors, histamine-2 receptor antagonists, sucralfate, and misoprostol, were allowed as necessary. Paracetamol was provided as rescue medication for pain, if needed</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 62.6 (9.5) years N = 548</p> <p>Definition: Clinical and radiographic diagnosis of osteoarthritis</p> <p>Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 6.6 (7.5) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months Serious adverse events 2: cardiovascular adverse events at ≤3 months</p>	Study design classification: 1) Including only responders
Rother 2007 ¹⁶⁸	<p>Oral non-steroidal anti-inflammatory drugs (n=132) Celecoxib 100mg twice a day for 6 weeks</p> <p>Topical non-steroidal anti-inflammatory drugs (n=138) 110mg epicutaneous ketoprofen in 4.8 grams Transfersome twice a day for 6 weeks</p>	<p>Knee osteoarthritis Mean age (SD): 62.8 (9.8) years N = 397</p> <p>Definition: Fulfilling clinical criteria for osteoarthritis</p> <p>Severity: Not stated Duration of symptoms: At least 6 months</p>	<p>Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Placebo (n=127)</p> <p>Concomitant therapy: People could take up to 2000mg paracetamol per day as rescue medication for knee pain for 3 days in any week, apart from the 48 hours preceding a study visit</p>	<p>Presence of multimorbidities: Not stated/unclear</p>		
Sanda 1983 ¹⁷²	<p>Non-steroidal anti-inflammatory drugs (n=42) Aspirin 2400-4800mg/day or etodolac 100-400mg/day for 12 weeks</p> <p>Placebo (n=16)</p> <p>Concomitant therapy: Non-narcotic, analgesic paracetamol (650mg four times daily PRN) was permitted only during the washout period</p>	<p>Hip osteoarthritis Mean age (range): 59 (33-70) years N = 58</p> <p>Definition: Osteoarthritis confirmed with clinical and radiographic evidence</p> <p>Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	Serious adverse events 4: central nervous system adverse events at ≤3 months	Study design classification: 1) Including only responders
Sandelin 1997 ¹⁷³	<p>Oral non-steroidal anti-inflammatory drugs (n=82) Diclofenac 50mg twice daily for 4 weeks</p> <p>Topical non-steroidal anti-inflammatory drugs (n=126) Elternac gel 1%, 3g (300mg Elternac) applied 3 times daily for 4 weeks</p>	<p>Knee osteoarthritis Mean age (SD): 61 (8.1) years N = 290</p> <p>Definition: Radiographically confirmed osteoarthritis with pain most days</p> <p>Severity: Not stated</p>	<p>Pain at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	Study design classification: 4) Unclear

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Placebo (n=82)</p> <p>Concomitant therapy: No additional treatment</p>	<p>Duration of symptoms: Not stated</p> <p>Presence of multimorbidities: Not stated/unclear</p>		
Schiff 1996 ¹⁷⁶	<p>Non-steroidal anti-inflammatory drugs (n=231) Naproxen (Naprelan) 1000mg once a day or naproxen (Naprosyn) 500mg twice a day for 12 weeks</p> <p>Placebo (n=116)</p> <p>Concomitant therapy: They were allowed to use commercially available paracetamol 325mg for rescue analgesia</p>	<p>Knee osteoarthritis Mean age (SE): Naprelan = 63.2 (0.84) years. Naprosyn = 64.1 (0.93) years. Placebo = 64.2 (0.87) years. N = 347</p> <p>Definition: Osteoarthritis of the knee diagnosed clinically</p> <p>Severity: Not stated Duration of symptoms: At least 6 months Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	Study design classification: 1) Including only responders
Schmitt 1999 ¹⁷⁷	<p>Non-steroidal anti-inflammatory drugs (n=337) Diclofenac dual release 75mg or 150mg once a day or diclofenac standard release 50mg three times a day</p> <p>Placebo (n=56)</p> <p>Concomitant therapy: Paracetamol was allowed until one day before the baseline visit</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 61 (9) years N = 393</p> <p>Definition: Activated osteoarthritis with clinical and radiological features</p> <p>Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months</p> <p>Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 3: hepatorenal adverse events at ≤3 months</p>	Study design classification: 2) Excluding non-responders

Study	Intervention and comparison	Population	Outcomes	Comments
Schnitzer 2004 ¹⁷⁹	<p>Non-steroidal anti-inflammatory drugs (n=94) Diclofenac 75mg twice a day for 4 weeks</p> <p>Placebo (n=97)</p> <p>A third group (n=390) was not included in the analysis due to the medication not being licensed for use in the UK (valdecoxib).</p> <p>Concomitant therapy: People were permitted a maximum of 6 tablets (total dose 3 grams) paracetamol per day as rescue medication</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 60.3 (9.2) years N = 581</p> <p>Definition: Clinical and radiographic diagnosis</p> <p>Severity: Not stated Duration of symptoms (mean [range]): 6.9 (0-55) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Physical function at ≤3 months Serious adverse events 2: cardiovascular adverse events at ≤3 months</p>	<p>Study design classification: 2) Excluding non-responders</p>
Schnitzer 2010 ¹⁸²	<p>Non-steroidal anti-inflammatory drugs (n=227) Naproxen 500mg twice a day for 13 weeks</p> <p>Placebo (n=221)</p> <p>A third group (n=470) was not included in the analysis due to the medication not being licensed for use in the UK (naproxcinod).</p> <p>Concomitant therapy: Rescue analgesia (paracetamol 500mg tablets) were provided</p>	<p>Knee osteoarthritis Mean age (SD): 61.4 (9.25) years N = 918</p> <p>Definition: Clinical and radiographic osteoarthritis of the knee</p> <p>Severity: Functional class 1-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Quality of life at ≤3 months Pain at ≤3 months Physical function at ≤3 months Psychological distress at ≤3 months Serious adverse events 2: cardiovascular adverse events at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	for use in case of increased osteoarthritis pain, with a maximum accepted dose of 2000mg/day			
Schnitzer 2011 ¹⁸⁰	<p>Non-steroidal anti-inflammatory drugs (n=419) Celecoxib 200mg once a day for 13 weeks</p> <p>Placebo (n=416)</p> <p>A third group (n=427) was not included in the analysis due to the medication not being licensed for use in the UK (valdecoxib).</p> <p>Concomitant therapy: The use of rescue medication paracetamol was permitted up to a maximum of 3g/day during the study. People who took >3g of paracetamol daily for four or more continuous days during the study were to be discontinued from the trial due to "unsatisfactory therapeutic effect". No analgesic rescue medications were to be taken in 24 hours before a study visit.</p>	<p>Hip osteoarthritis Mean age (SD): 61.6 (10.0) years N = 1262</p> <p>Definition: Symptomatic primary osteoarthritis with radiographic confirmation</p> <p>Severity: Not stated Duration of symptoms (mean [SD]): 3.9 (5.2) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months Serious adverse events 3: hepatorenal adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p> <p>In Forest plots this study is referred to as Schnitzer 2011A</p>
Schnitzer 2011 ¹⁸¹	<p>Non-steroidal anti-inflammatory drugs (n=256) Naproxen 500mg twice daily for 13 weeks</p>	<p>Knee osteoarthritis Mean age (SD): 59.8 (9.78) years N = 1002</p>	<p>Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1A: gastrointestinal (bleeding and</p>	<p>Study design classification: 1) Including only responders</p> <p>In Forest plots this study is referred to as Schnitzer 2011B</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Placebo (n=257)</p> <p>A third group (n=489) was not included in the analysis due to the medication not being licensed for use in the UK (naproxcinod).</p> <p>Concomitant therapy: Analgesics other than the study medication were not allowed during the study expect for low-dose aspirin (≤ 325mg/day) for cardioprotection and rescue medication (paracetamol up to 2000 mg/day); glucosamine and chondroitin were allowed only if the dose was stable for 3 months before screening/baseline and continued for the entire study duration</p>	<p>Definition: Clinical and radiographic diagnosis of osteoarthritis</p> <p>Severity: Kellgren Lawrence grade 1-3, functional class 1-3 Duration of symptoms: Not stated Presence of multimorbidities: Low comorbidity score</p>	<p>perforation) adverse events at ≤ 3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤ 3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤ 3 months</p>	
Schubiger 1980 ¹⁸⁵	<p>Non-steroidal anti-inflammatory drugs (n=114) Diclofenac 100mg sustained release once a day or diclofenac 50mg twice a day</p> <p>Placebo (n=34)</p> <p>Concomitant therapy: No additional information</p>	<p>Mixed osteoarthritis (hip and/or knee) Median age: 58 years N = 148</p> <p>Definition: Clinically diagnosed osteoarthritis</p> <p>Severity: Not stated Duration of symptoms: Not stated</p>	<p>Pain at ≤ 3 months</p> <p>Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤ 3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤ 3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤ 3 months</p>	Study design classification: 4) Unclear

Study	Intervention and comparison	Population	Outcomes	Comments
Scott 2000 ¹⁸⁶	<p>Non-steroidal anti-inflammatory drugs (n=202) Indomethacin 25mg three times a day for up to 5 years</p> <p>Placebo (n=303)</p> <p>A third group (n=307) was not included in the analysis due to the medication not being licensed for use in the UK (tiaprofenic acid).</p> <p>Concomitant therapy: Paracetamol tablets were available to all people throughout the study as escape analgesics, and people were allowed to take up to 8 tablets per day</p>	<p>Presence of multimorbidities: Not stated/unclear</p> <p>Knee osteoarthritis Mean age (range): 61 (27-87) years N = 812</p> <p>Definition: Symptomatic and radiological evidence of osteoarthritis</p> <p>Severity: Not stated Duration of symptoms (median [SD]): 61 (27-87) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months</p> <p>Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at >3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at >3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at >3 months</p> <p>Serious adverse events 4: central nervous system adverse events at >3 months</p>	<p>Study design classification: 4) Unclear</p>
Sheldon 2005 ¹⁸⁸	<p>Non-steroidal anti-inflammatory drugs (n=393) Celecoxib 200mg once a day for 13 weeks</p> <p>Placebo (n=382)</p> <p>A third group (n=776) was not included in the analysis due to the medication not being licensed for use in the UK (lumiracoxib).</p>	<p>Knee osteoarthritis Mean age (SD): 60.5 (10.8) years N = 1551</p> <p>Definition: Primary osteoarthritis based on American College of Rheumatology criteria</p> <p>Severity: Not stated</p>	<p>Pain at ≤3 months</p> <p>Physical function at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 3: hepatorenal adverse events at ≤3 months</p>	<p>Study design classification: 2) Excluding non-responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Concomitant therapy: Use of paracetamol (500mg tablet) as rescue medication was permitted throughout the study, including during the screening period. Other concomitant drug therapies were allowed (including during the screening period) including chondroitin sulfate and/or glucosamine sulfate (if the dose and regimen were established and stable), corticosteroids (topical, ophthalmic, nasal, or inhaled, at usual labeled doses), histamine-2 receptor antagonists, proton pump inhibitors, antacids and cytoprotective agents (taken at the usual labeled doses) and physiotherapy as prescribed by the physician</p>	<p>Duration of symptoms (mean [SD]): 7.0 (7.8) years Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	
Sikes 2002 ¹⁸⁹	<p>Non-steroidal anti-inflammatory drugs (n=419) Ibuprofen 800mg three times a day or diclofenac 75mg twice a day</p> <p>Placebo (n=210)</p> <p>A third group (n=423) was not included in the analysis due to the medication not being</p>	<p>Osteoarthritis (unclear site) Mean age: 59.9 years N = 1052</p> <p>Definition: Documented clinical diagnosis of osteoarthritis</p> <p>Severity: Not stated Duration of symptoms (mean): 10.4 years</p>	<p>Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 4) Unclear</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>licensed for use in the UK (valdecoxib).</p> <p>Concomitant therapy: Aspirin ≤ 325mg/day was permitted for non-arthritic reasons if being taken at a stable dose for at least 30 days before the first dose of study drug.</p>	<p>Presence of multimorbidities: Not stated/unclear</p>		
<p>Simon 2009¹⁹⁰ Subsidiary paper: Roth 2011¹⁶⁵</p>	<p>Oral non-steroidal anti-inflammatory drugs (n=151) Diclofenac slow release 100mg once a day for 12 weeks</p> <p>Topical non-steroidal anti-inflammatory drugs (n=154) Topical diclofenac solution (1.5% w/w diclofenac sodium in a vehicle containing 45.5% w/w dimethyl sulfoxide and other excipients) applied four times daily for 12 weeks</p> <p>Placebo (n=318)</p> <p>A fourth group (n=152) was reported which was not included in the analysis as it was excluded in the protocol (combination topical and oral NSAID).</p> <p>Concomitant therapy:</p>	<p>Knee osteoarthritis Mean age (SD): 61.6 (9.9) years N = 775</p> <p>Definition: Primary osteoarthritis based on standard radiological criteria and pain</p> <p>Severity (mean radiographic score [SD]): 16.5 (3.1) Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤ 3 months Physical function at ≤ 3 months Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤ 3 months</p>	<p>Study design classification: 1) Including only responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	Continuation of stable treatment with glucosamine, chondroitin, anti-depressants or a proton pump inhibitor (previous 90 days), or low dose (≤ 325 mg/day) acetylsalicylic acid (previous 30 days); paracetamol was provided and permitted (up to four 325mg caplets per day) except during the 3 days before each efficacy assessment. A person with a gastrointestinal adverse event was allowed to start a proton pump inhibitor.			
Smugar 2006 ¹⁹²	<p>Non-steroidal anti-inflammatory drugs (n=916) Celecoxib 200mg once a day for 6 weeks</p> <p>Placebo (n=301)</p> <p>A third group (n=1389) was not included in the analysis due to the medication not being licensed for use in the UK (rofecoxib).</p> <p>Concomitant therapy: Paracetamol was permitted as rescue medication</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (range): 61.7 (39-92) years N = 2606</p> <p>Definition: Clinical diagnosis of osteoarthritis</p> <p>Severity: Functional class 1-3 Duration of symptoms (mean): 1-10 years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤ 3 months Physical function at ≤ 3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤ 3 months Serious adverse events 2: cardiovascular adverse events at ≤ 3 months</p>	<p>Study design classification: 1) Including only responders</p> <p>Pooled analysis of 2 trials</p>
Strand 2017 ¹⁹⁴	Non-steroidal anti-inflammatory drugs (n=202)	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 61.6 (8.90) years</p>	<p>Quality of life at ≤ 3 months Pain at ≤ 3 months</p>	<p>Study design classification: 1) Including only responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>SoluMatrix diclofenac 35mg three times daily or twice daily for 12 weeks</p> <p>Placebo (n=103)</p> <p>Concomitant therapy: Paracetamol was permitted as a rescue medication during the washout and treatment periods (up to 3000mg daily) but was discouraged within 24 hours and prohibited within 12 hours prior to scheduled study visits on day 0 and at weeks 2, 6 and 12 during the treatment period</p>	<p>N = 305</p> <p>Definition: Radiographic evidence of osteoarthritis</p> <p>Severity: Kellgren Lawrence grade 2-3</p> <p>Duration of symptoms: Not stated</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>Physical function at ≤3 months</p>	<p>NCT01461369</p>
<p>Tannenbaum 2004¹⁹⁵</p>	<p>Non-steroidal anti-inflammatory drugs (n=481) Celecoxib 200mg once a day for 13 weeks</p> <p>Placebo (n=243)</p> <p>A third group (n=978) was not included in the analysis due to the medication not being licensed for use in the UK (lumiracoxib).</p> <p>Concomitant therapy: People were permitted to take paracetamol (≤2 grams/day). However, they were asked to refrain from using the rescue</p>	<p>Knee osteoarthritis Mean age (SD): 64.2 (10.4) years N = 1702</p> <p>Definition: Primary osteoarthritis according to the American College of Rheumatology criteria</p> <p>Severity: Not stated Duration of symptoms (median): 4.75 years Presence of multimorbidities: not stated/unclear</p>	<p>Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 2) Excluding non-responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	drug from midnight before each clinic visit. NSAIDs were not permitted during the course of the study, with the exception of low dose aspirin (≤ 325 mg/day) for a cardiovascular indication.			
Trudeau 2015 ²⁰³	<p>Non-steroidal anti-inflammatory drugs (n=63) Celecoxib 100mg twice a day for 1 week</p> <p>Placebo (n=63)</p> <p>Concomitant therapy: Paracetamol was allowed as rescue medication as needed (500mg maximum four times a day).</p>	<p>Knee osteoarthritis Age: Older than 21, otherwise not reported N = 63</p> <p>Definition: Primary osteoarthritis</p> <p>Severity: Functional class 1-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	Physical function at ≤ 3 months	<p>Study design classification: 1) Including only responders</p> <p>Crossover trial</p>
Truitt 2001 ²⁰⁴	<p>Non-steroidal anti-inflammatory drugs (n=115) Nabumetone 1500mg once daily for 6 weeks</p> <p>Placebo (n=52)</p> <p>A third group (n=174) was not included in the analysis due to the medication not being licensed for use in the UK (rofecoxib).</p> <p>Concomitant therapy:</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (range): 83.0 (80-95) years N = 341</p> <p>Definition: Clinical and radiographic diagnosis of osteoarthritis</p> <p>Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 15.0 (12.3) years</p>	<p>Pain at ≤ 3 months</p> <p>Physical function at ≤ 3 months</p> <p>Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤ 3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤ 3 months</p>	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	Ongoing use of low dose aspirin (up to 325mg daily) was permitted. People were provided with paracetamol tablets (325mg) as rescue medication for breakthrough osteoarthritis pain. People were otherwise allowed to continue their usual therapy (including antacids, ACE inhibitors, beta blockers, diuretics, calcium antagonists, thyroid therapy and vitamin E).	Presence of multimorbidities: Not stated/unclear		
Wanka 1964 ²¹⁴	<p>Non-steroidal anti-inflammatory drugs (n=18) Indomethacin 25mg three times a day for one week, 50mg twice a day for one week, and 50mg three times a day for two weeks (4 weeks in total)</p> <p>Placebo (n=18)</p> <p>Concomitant therapy: No additional information</p>	<p>Hip osteoarthritis Mean age (range): 65 (50-78) years N = 18</p> <p>Definition: Osteoarthritis with clinical and radiological features</p> <p>Severity: Radiographic severity 1-4 Duration of symptoms (mean [range]): 6 (1-14) years Presence of multimorbidities: Not stated/unclear</p>	Serious adverse events 2: cardiovascular adverse events at ≤3 months	<p>Study design classification: 4) Unclear</p> <p>Crossover trial</p>
Wasserman 1984 ²¹⁵	<p>Non-steroidal anti-inflammatory drugs (n=14) Indomethacin 25mg once a day for 2 weeks</p> <p>Placebo (n=14)</p>	<p>Mixed osteoarthritis (knee and/or hip) Age (range): 45-78 years N = 14</p> <p>Definition: Symptomatic osteoarthritis with clinical and</p>	<p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 4) Unclear</p> <p>Crossover trial</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>A third group (n=14) was not included in the analysis due to the medication not being licensed for use in the UK (carprofen).</p> <p>Concomitant therapy: Supplemental analgesics such as dextropropoxyphene or codeine, and supportive care involving heat, hydrotherapy and physiotherapy were allowed. The use of intra-articular injections of any experimental drug for one month prior to the study was not permitted for eight weeks prior to the study.</p>	<p>radiological evidence of disease</p> <p>Severity: Not stated Duration of symptoms: At least 6 months Presence of multimorbidities: Not stated/unclear</p>		
Wiesenhutter 2005 ²¹⁶	<p>Non-steroidal anti-inflammatory drugs (n=424) Ibuprofen 800mg three times a day or etoricoxib 30mg once daily for 12 weeks</p> <p>Placebo (n=104)</p> <p>Concomitant therapy: Only paracetamol was permitted for rescue pain medication if needed. People taking medications for chronic conditions were required to continue taking stable doses 2 weeks before and throughout the 12 week study. People taking stable doses of</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 62.0 (9.9) years N = 528</p> <p>Definition: Clinical and radiographic diagnosis</p> <p>Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 7.8 (7.9) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months Serious adverse events 2: cardiovascular adverse events at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	glucosamine or chondroitin sulfate for at least 6 months before the study were allowed to enroll. Low dose aspirin (no more than 100mg/day) for cardioprophylaxis was permitted. Gastroprotective agents such as proton pump inhibitors, histamine-2 receptor blockers, sucralfate and misoprostol were allowed as necessary.			
Williams 2000 ²¹⁷	<p>Non-steroidal anti-inflammatory drugs (n=454) Celecoxib 100mg twice a day or celecoxib 200mg once a day for 6 weeks</p> <p>Placebo (n=232)</p> <p>Concomitant therapy: People taking aspirin (≤ 325mg/day for conditions other than arthritis for at least 30 days before the first dose of study medication) were permitted to continue the same dose regimen. Paracetamol up to 2g per day was allowed if taken for reasons other than relief of arthritis symptoms and for no more than 3 consecutive days. Paracetamol must have been avoided within 48 hours before arthritis assessments performed at any visit.</p>	<p>Knee osteoarthritis Mean age (SD): 62.8 (10.9) years N = 686</p> <p>Definition: Clinical diagnosis of osteoarthritis</p> <p>Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 8.89 (8.33) years Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤ 3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤ 3 months</p> <p>Serious adverse events 3: hepatorenal adverse events at ≤ 3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤ 3 months</p>	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
Williams 2001 ²¹⁸	<p>Non-steroidal anti-inflammatory drugs (n=474) Celecoxib 100mg twice a day or 200mg once a day for 6 weeks</p> <p>Placebo (n=233)</p> <p>Concomitant therapy: People taking aspirin ≤325mg/day for reasons other than arthritis, for ≥30 days before the first dose of study medication, were permitted to continue with the same dosing regimen. People were permitted to take up to 2 grams/day of paracetamol, for 3 consecutive days, for reasons other than relief of arthritis symptoms (however, it must not have been taken within 48 hours of any visits).</p>	<p>Knee osteoarthritis Mean age (SD): 61.5 (11.9) years N = 718</p> <p>Definition: Clinical and radiographic diagnosis of osteoarthritis</p> <p>Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 9.5 (8.5) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	Study design classification: 1) Including only responders
Wittenberg 2006 ²²⁰	<p>Non-steroidal anti-inflammatory drugs (n=145) Celecoxib 200mg twice daily for 1 week</p> <p>Placebo (n=75)</p> <p>A third group (n=144) was not included in the analysis due to the medication not being licensed for use in the UK (lumiracoxib).</p>	<p>Knee osteoarthritis Mean age (SD): 65.0 (8.3) years N = 364</p> <p>Definition: Clinical osteoarthritis</p> <p>Severity: Moderate to severe Duration of symptoms (mean [SD]): 7.4 (7.1) years</p>	<p>Pain at ≤3 months</p> <p>Physical function at ≤3 months</p>	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Concomitant therapy: People were permitted to use rescue medication (paracetamol ≤3g/day) during the study, although use of rescue medication was prohibited from midnight before the baseline clinic visit</p>	<p>Presence of multimorbidities: Not stated/unclear</p>		
Yocum 2000 ²²²	<p>Non-steroidal anti-inflammatory drugs (n=617) Diclofenac 50mg twice daily or Meloxicam 3.75mg/day, 7.5mg/day or 15mg/day for 12 weeks</p> <p>Placebo (n=157)</p> <p>Concomitant therapy: No additional information</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 62.9 (10.3) years N = 774</p> <p>Definition: Radiographically confirmed osteoarthritis</p> <p>Severity: Not stated Duration of symptoms (mean [SD]): 8.2 (8.3) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p>
Zhao 1999 ²²⁶	<p>Non-steroidal anti-inflammatory drugs (n=873) Naproxen 500mg twice a day or Celecoxib 50mg, 100mg or 200mg twice a day for 12 weeks</p> <p>Placebo (n=219)</p> <p>Concomitant therapy:</p>	<p>Knee osteoarthritis Mean age (range): 62 (21-89) years N = 1092</p> <p>Definition: Symptomatic osteoarthritis fulfilling the American College of Rheumatology clinical criteria</p>	<p>Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	Low dose aspirin (≤ 325 mg/day) and paracetamol (up to 2g/day for no longer than 3 consecutive days) were allowed as concomitant therapy except within 48 hours before assessments, during which no analgesics were allowed.	Severity: Osteoarthritis severity index (0-24) (mean [SD]): 15.5 (3.5) Duration of symptoms (mean [SD]): 9.4 (8.3) years Presence of multimorbidities: Not stated/unclear		

1 **1.1.5.1.4 Non-steroidal anti-inflammatory drugs and gastroprotection compared to paracetamol**

2 **Table 5: Summary of studies included in the evidence review for non-steroidal anti-inflammatory drugs and gastroprotection compared**
3 **to paracetamol**

Study	Intervention and comparison	Population	Outcomes	Comments
Pincus 2001 ¹⁵⁷ (ACTA trial)	Paracetamol (n=631) Paracetamol 1000mg four times a day for 6 weeks Non-steroidal anti-inflammatory drugs and gastroprotection (n=723) Diclofenac 75mg with misoprostol 200 micrograms twice a day for 6 weeks Concomitant therapy: Propoxyphene could be taken as rescue medication during the washout period.	Mixed osteoarthritis (knee or hip) Mean age (SE): 61.5 (1.37) years N = 227 Definition: Radiographic and clinical osteoarthritis Severity: Mean Kellgren Lawrence (SE): 2.8 (0.089). Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Quality of life at ≤ 3 months Pain at ≤ 3 months Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤ 3 months Serious adverse events 2: cardiovascular system adverse events at ≤ 3 months Serious adverse events 3: hepatorenal adverse events at ≤ 3 months Serious adverse events 4: central nervous system adverse events at ≤ 3 months	Study design classification: 6) No response criteria Crossover trial

1 **1.1.5.1.5 Non-steroidal anti-inflammatory drugs and gastroprotection compared to oral non-steroidal anti-inflammatory drugs**

2 **Table 6: Summary of studies included in the evidence review for non-steroidal anti-inflammatory drugs and gastroprotection compared**
3 **to oral non-steroidal anti-inflammatory drugs**

Study	Intervention and comparison	Population	Outcomes	Comments
Bocanegra 1998 ²⁷	<p>Non-steroidal anti-inflammatory drugs (n=154) Diclofenac 75mg twice a day for 6 weeks</p> <p>Non-steroidal anti-inflammatory drugs and gastroprotection (n=327) Diclofenac 50mg with misoprostol 200 microgram three times a day or diclofenac 75mg with misoprostol 200 microgram two times a day for 6 weeks</p> <p>Placebo (n=91)</p> <p>Concomitant therapy: No additional information - all antiinflammatory drugs were not permitted (with the exception of aspirin \leq325mg/day).</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 62.5 (10.4) years N = 572</p> <p>Definition: Symptomatic osteoarthritis with a functional classification of 1-3</p> <p>Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 11.2 (8.7) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at \leq3 months</p> <p>Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at \leq3 months</p> <p>Serious adverse events 3: hepatorenal adverse events at \leq3 months</p>	Study design classification: 1) Including only responders
Bolten 1992 ²⁹	<p>Non-steroidal anti-inflammatory drugs and gastroprotection (n=178) Diclofenac 50mg with misoprostol 200 micrograms twice or three times a day for 4 weeks</p>	<p>Mixed osteoarthritis (knee and/or hip) Mean age (SD): 60.3 (12.0) years N = 361</p>	<p>Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at \leq3 months</p> <p>Serious adverse events 4: central nervous system adverse events at \leq3 months</p>	Study design classification: 4) Unclear

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Non-steroidal anti-inflammatory drugs (n=183) Diclofenac 50mg two to three times a day for 4 weeks</p> <p>Concomitant therapy: The use of any other NSAIDs, analgesics or antiulcer drugs during the study was prohibited</p>	<p>Definition: A confirmed diagnosis of osteoarthritis (at least clinical assessment)</p> <p>Severity: Functional class 1-4. Mean osteoarthritis severity index (SD): 11.2 (3.7). Duration of symptoms (median): 1-10 years Presence of multimorbidities: Not stated/unclear</p>		
<p>Chan 2010⁴⁴ Subsidiary paper: Kellner 2012¹⁰⁷</p>	<p>Non-steroidal anti-inflammatory drugs and gastroprotection (n=2246) Diclofenac slow release 75mg twice a day plus omeprazole 20mg once a day for 26 weeks</p> <p>Non-steroidal anti-inflammatory drugs (n=2238) Celecoxib 200mg twice a day for 26 weeks</p> <p>Concomitant therapy: After randomisation people could take antacids or non-NSAID analgesic drugs, including paracetamol up to 4g per day and histamine-2-receptor antagonists no more than 3 days per week. Corticosteroids (prednisolone no more than 10mg daily), disease-modifying antirheumatic drugs, or biological treatments were</p>	<p>Osteoarthritis (unclear site) 17% of people had rheumatoid arthritis Mean age (SD): 65 (7.7) years N = 4484</p> <p>Definition: Clinical diagnosis of osteoarthritis or rheumatoid arthritis</p> <p>Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at >3 months</p>	<p>Study design classification: 6) No response criteria</p> <p>NCT00141102</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	only allowed if people had been taking a stable dose 12 or more weeks at randomisation.			
Cryer 2011 ⁵⁵	<p>Non-steroidal anti-inflammatory drugs (n=494) Celecoxib 200mg once daily for 12 weeks</p> <p>Non-steroidal anti-inflammatory drugs with gastroprotection (n=492) Naproxen 500mg and esomeprazole 20mg twice daily for 12 weeks</p> <p>Placebo (n=248)</p> <p>Concomitant therapy: Incidental use of rescue antacid (≤ 6 tablets per day) and supplemental use of rescue paracetamol (≤ 3g/day) were allowed during the study. Concomitant use of oral prednisone (≤ 7.5mg/day), low dose aspirin (≤ 325mg/day) and antiplatelet agents (non-concomitant with aspirin) were allowed.</p>	<p>Knee osteoarthritis Mean age (range): 61.9 (49-90) years N = 1234</p> <p>Definition: Symptomatic, clinically diagnosed osteoarthritis</p> <p>Severity: Functional class I-III Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤ 3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤ 3 months</p>	<p>Study design classification: 1) Including only responders</p> <p>Pooled analysis of 2 trials</p>
Goldstein 2007 ⁹¹	<p>Non-steroidal anti-inflammatory drugs and gastroprotection (n=529) Naproxen 500mg twice daily plus lansoprazole 30mg once daily</p>	<p>Osteoarthritis (no statement about the joint site) Mean age (SD): 56.7 (11.2)years N = 1045</p>	<p>Serious adverse event 1: gastrointestinal adverse events at ≤ 3 months</p> <p>Serious adverse event 2: cardiovascular adverse events at ≤ 3 months</p>	<p>Study design classification: 3) Selection of specific population</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Non-steroidal anti-inflammatory drugs (n=516) Celecoxib 200mg once daily</p> <p>Concomitant therapy: All received 81 or 325mg aspirin once daily.</p>	<p>Definition: Osteoarthritis diagnosis (no additional information)</p> <p>Severity: Not stated/unclear Duration of symptoms (mean [SD]): 114.6 (103.1) months Presence of multimorbidities: Not stated/unclear</p>		
Melo gomes 1993 ¹³⁹	<p>Non-steroidal anti-inflammatory drugs and gastroprotection (n=216) Diclofenac 50mg with misoprostol 200 micrograms twice daily for 4 weeks</p> <p>Non-steroidal anti-inflammatory drugs (n=427) Piroxicam 10mg twice daily or naproxen 375mg twice daily for 4 weeks</p> <p>Concomitant therapy: Paracetamol was permitted</p>	<p>Mixed osteoarthritis (knee and/or hip) Mean age (range): 63.6 (26-89) years N = 643</p> <p>Definition: Radiographic and symptomatic evidence of osteoarthritis</p> <p>Severity: Not stated Duration of symptoms: 0-15+ years (median 1-9.9 years) Presence of multimorbidities: Not stated/unclear</p>	Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months	Study design classification: 2) Excluding non-responders

1 **1.1.5.1.6 Non-steroidal anti-inflammatory drugs and gastroprotection compared to placebo**

2 **Table 7: Summary of studies included in the evidence review for non-steroidal anti-inflammatory drugs and gastroprotection compared to placebo**

Study	Intervention and comparison	Population	Outcomes	Comments
Bocanegra 1998 ²⁷	Non-steroidal anti-inflammatory drugs (n=154)	Mixed osteoarthritis (knee or hip)	Pain at ≤3 months	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Diclofenac 75mg twice a day for 6 weeks</p> <p>Non-steroidal anti-inflammatory drugs and gastroprotection (n=327) Diclofenac 50mg with misoprostol 200 microgram three times a day or diclofenac 75mg with misoprostol 200 microgram two times a day for 6 weeks</p> <p>Placebo (n=91)</p> <p>Concomitant therapy: No additional information - all antiinflammatory drugs were not permitted (with the exception of aspirin \leq325mg/day).</p>	<p>Mean age (SD): 62.5 (10.4) years N = 572</p> <p>Definition: Symptomatic osteoarthritis with a functional classification of 1-3</p> <p>Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 11.2 (8.7) years Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at \leq3 months</p> <p>Serious adverse events 3: hepatorenal adverse events at \leq3 months</p>	
Cryer 2011 ⁵⁵	<p>Non-steroidal anti-inflammatory drugs (n=494) Celecoxib 200mg once daily for 12 weeks</p> <p>Non-steroidal anti-inflammatory drugs with gastroprotection (n=492) Naproxen 500mg and esomeprazole 20mg twice daily for 12 weeks</p> <p>Placebo (n=248)</p>	<p>Knee osteoarthritis Mean age (range): 61.9 (49-90) years N = 1234</p> <p>Definition: Symptomatic, clinically diagnosed osteoarthritis</p> <p>Severity: Functional class I-III Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at \leq3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at \leq3 months</p>	<p>Study design classification: 1) Including only responders</p> <p>Pooled analysis of 2 trials</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Concomitant therapy: Incidental use of rescue antacid (≤ 6 tablets per day) and supplemental use of rescue paracetamol ($\leq 3g/day$) were allowed during the study. Concomitant use of oral prednisone ($\leq 7.5mg/day$), low dose aspirin ($\leq 325mg/day$) and antiplatelet agents (non-concomitant with aspirin) were allowed.</p>			

1 **1.1.5.1.7 Weak opioids compared to placebo**

2 **Table 8: Summary of studies included in the evidence review for weak opioids compared to placebo**

Study	Intervention and comparison	Population	Outcomes	Comments
Peloso 2000 ¹⁵⁴	<p>Weak opioids (n=51) Controlled release codeine 100mg twice a day escalated to a maximum of 400mg per day for 4 weeks</p> <p>Placebo (n=52)</p> <p>Concomitant therapy: Use of additional anti-inflammatory or analgesic medication, other than paracetamol 650mg up to 3 times daily for control of pain not managed by controlled release codeine or placebo, was not permitted.</p>	<p>Mixed osteoarthritis (knee and/or hip) Mean age (SD): 62.2 (10.5) years N = 103</p> <p>Definition: Symptomatic, radiographically confirmed osteoarthritis</p> <p>Severity: At least radiographic grade 2 Duration of symptoms (mean [SD]): 10.3 (7.5) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤ 3 months Physical function at ≤ 3 months</p>	<p>Study design classification: 1) Including only responders</p>

1 **1.1.5.1.8 Strong opioids compared to oral non-steroidal anti-inflammatory drugs**

2 **Table 9: Summary of studies included in the evidence review for strong opioids compared to oral non-steroidal anti-inflammatory drugs**

Study	Intervention and comparison	Population	Outcomes	Comments
Banerjee 2016 ¹⁴	<p>Strong opioids (n=108) Tapentadol 100mg twice daily for 12 weeks</p> <p>Non-steroidal anti-inflammatory drugs (n=110) Etoricoxib 30mg twice daily for 12 weeks</p> <p>Concomitant therapy: Paracetamol 500mg tablets were used as rescue medication, only if there is severe unbearable pain in the signal knee</p>	<p>Knee osteoarthritis Mean age (SD): 53.6 (6.56) years N = 218</p> <p>Definition: Primary symptomatic osteoarthritis with radiographic evidence</p> <p>Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Serious adverse events 3: hepatorenal adverse events at ≤3 months</p>	Study design classification: 6) No response criteria
Beaulieu 2008 ¹⁸	<p>Strong opioids (n=62) Controlled release tramadol 200mg for 6 weeks</p> <p>Non-steroidal anti-inflammatory drugs (n=66) Diclofenac 75mg each morning for 6 weeks</p> <p>Concomitant therapy: Breakthrough pain was managed with 325mg to 650mg paracetamol every 4 to 6 hours, as required</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 62.1 (8.7) years N = 128</p> <p>Definition: Primary osteoarthritis with symptoms and radiological verification</p> <p>Severity: At least radiographic grade 2 Duration of symptoms (mean [SD]): 10.7 (9.4) years</p>	<p>Pain at ≤3 months Physical function at ≤3 months</p>	Study design classification: 3) Selection of specific population

Study	Intervention and comparison	Population	Outcomes	Comments
		Presence of multimorbidities: Not stated/unclear		
Delemos 2011 ⁶⁰	<p>Non-steroidal anti-inflammatory drugs (n=203) Celecoxib 200mg once a day for 12 weeks</p> <p>Strong opioids (n=606) Tramadol 100mg once to three times a day for 12 weeks</p> <p>Placebo (n=202)</p> <p>Concomitant therapy: Aspirin up to 325mg/day for cardiovascular prophylaxis was allowed as was paracetamol up to 2g/day for up to 3 consecutive days for reasons other than osteoarthritis or chronic pain if absolutely necessary.</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 59.92 (10.96) years N = 1011</p> <p>Definition: Radiologically confirmed osteoarthritis</p> <p>Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 8.1 (7.9) years Presence of multimorbidities: Not stated/unclear</p>	<p>Quality of life at ≤3 months Pain at ≤3 months Physical function at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p>
Pavelka 1998 ¹⁵³	<p>Strong opioids (n=60) Tramadol 50mg-100mg up to 3 times a day as required for 4 weeks</p> <p>Non-steroidal anti-inflammatory drugs (n=60) Diclofenac 25mg-50mg up to 3 times a day as required for 4 weeks</p> <p>Concomitant therapy:</p>	<p>Mixed osteoarthritis (knee or hip) Age range: 44-85 years N = 60</p> <p>Definition: Radiologically confirmed osteoarthritis</p> <p>Severity: Kellgren Lawrence grade 2-4 Duration of symptoms (median [IQR]): group 1: 5.25</p>	<p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 6) No response criteria</p> <p>Crossover trial</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	During the washout period people were only allowed to take paracetamol.	(3.00 to 10.00) years, group 2: 8.00 (3.00 to 10.00) years Presence of multimorbidities: Not stated/unclear		

1 **1.1.5.1.9 Strong opioids compared to placebo**

2 **Table 10: Summary of studies included in the evidence review for strong opioids compared to placebo**

Study	Intervention and comparison	Population	Outcomes	Comments
Afilalo 2010 ²	<p>Strong opioids (n=691) Tapentadol extended release 100-250mg twice daily or oxycodone controlled release 20-50mg twice daily for 12 weeks</p> <p>Placebo (n=339)</p> <p>Concomitant therapy: Additional analgesic medication was not allowed during the maintenance period (except paracetamol ≤1000mg/day, maximum, 3 consecutive days when deemed necessary for relief of pain unrelated to the index joint)</p>	<p>Knee osteoarthritis Mean age (SD): 58.3 (9.9) years N = 1030</p> <p>Definition: Osteoarthritis according to the American College of Rheumatology criteria</p> <p>Severity: Majority severe pain at baseline Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Quality of life at ≤3 months Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 3) Selection of specific population</p>
Babul 2004 ¹⁰	<p>Strong opioids (n=124) Tramadol extended release 100mg daily increased to a maximum of 400mg daily for 12 weeks</p> <p>Placebo (n=122)</p>	<p>Knee osteoarthritis Mean age (SD): 61.4 (10.1) years N = 246</p> <p>Definition: Primary osteoarthritis meeting the</p>	<p>Pain at ≤3 months Physical function at ≤3 months</p>	<p>Study design classification: 2) Excluding non-responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Concomitant therapy: Aspirin ≤325mg/day for cardiovascular prophylaxis was permitted. Paracetamol up to 2000mg per day was permitted for reasons other than for chronic pain but for no more than 3 consecutive days and not within 24 hours of a visit.</p>	<p>American College of Rheumatology diagnostic criteria with radiographic evidence</p> <p>Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 12.9 (10.5) years Presence of multimorbidities: Not stated/unclear</p>		
Burch 2007 ³⁷	<p>Strong opioids (n=432) Tramadol con tramid once daily starting at 100mg increasing a maximum of 300mg for 12 weeks</p> <p>Placebo (n=214)</p> <p>Concomitant therapy: Paracetamol could be used during the titration phase. During the study, people 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 osteoarthritis. They could only be taken for a maximum of 3 consecutive days and not within 3 days of an assessment visit.</p>	<p>Knee osteoarthritis Mean age (SD): 62 (9) years N = 646</p> <p>Definition: Symptomatic osteoarthritis</p> <p>Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	Pain at ≤3 months	Study design classification: 1) Including only responders
Caldwell 2002 ³⁹	<p>Strong opioids (n=222) Morphine Avinsa 30mg once a day or morphine sulphate contin</p>	<p>Mixed osteoarthritis (knee and/or hip)</p>	Pain at ≤3 months Physical function at ≤3 months	Study design classification: 3) Selection of specific population

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>15mg twice a day for 4 weeks. The dose could be increased if insufficient pain relief.</p> <p>Placebo (n=73)</p> <p>Concomitant therapy: The use of analgesic preparations other than the cardiovascular prophylactic doses of aspirin (up to 325mg/day) and paracetamol for non-osteoarthritis symptomatology (up to 2000mg/day for a maximum of 3 consecutive days) was prohibited. Inhaled and topical steroids were permitted for the treatment of respiratory and dermatological disorders respectively.</p>	<p>Mean age (SD): 62.4 (10.5) years N = 295</p> <p>Definition: Clinical diagnosis of osteoarthritis with radiographic evidence</p> <p>Severity: Radiographic grade 2-4 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>		
Chindalore 2005 ⁴⁸	<p>Strong opioids (n=103) Oxycodone starting at 2.5mg four times a day increasing to a maximum of 10mg four times a day for 3 weeks</p> <p>Placebo (n=52)</p> <p>A third group (n=207) was reported which was not included in the analysis as it was excluded in the protocol (oxycodone and naltrexone).</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (range): 54.3 (21-70) years N = 362</p> <p>Definition: Moderate to severe pain caused by osteoarthritis</p> <p>Severity: Moderate to severe Duration of symptoms: At least 3 months</p>	<p>Pain at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 2) Excluding non-responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Concomitant therapy: Aspirin up to 325mg/day was allowed for cardiovascular prophylaxis. Paracetamol up to five 500mg caplets per day was allowed during the washout period.</p>	<p>Presence of multimorbidities: Not stated/unclear</p>		
Delemos 2011 ⁶⁰	<p>Non-steroidal anti-inflammatory drugs (n=203) Celecoxib 200mg once a day for 12 weeks</p> <p>Strong opioids (n=606) Tramadol 100mg once to three times a day for 12 weeks</p> <p>Placebo (n=202)</p> <p>Concomitant therapy: Aspirin up to 325mg/day for cardiovascular prophylaxis was allowed as was paracetamol up to 2g/day for up to 3 consecutive days for reasons other than osteoarthritis or chronic pain if absolutely necessary.</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 59.92 (10.96) years N = 1011</p> <p>Definition: Radiologically confirmed osteoarthritis</p> <p>Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 8.1 (7.9) years Presence of multimorbidities: Not stated/unclear</p>	<p>Quality of life at ≤3 months Pain at ≤3 months Physical function at ≤3 months Psychological distress at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p>
Fishman 2007 ⁷³ Subsidiary paper: Kean 2009 ¹⁰⁶	<p>Strong opioids (n=325) Tramadol Contramid OAD 100mg, 200mg or 300mg once daily for 12 weeks</p> <p>Placebo (n=227)</p> <p>Concomitant therapy:</p>	<p>Knee osteoarthritis Mean age (SD): 61.2 (9.3) years N = 552</p> <p>Definition: Osteoarthritis according to the American</p>	<p>Pain at ≤3 months</p>	<p>Study design classification: 2) Excluding non-responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	Rescue medication for pain due to osteoarthritis was not permitted. Short-acting analgesics for acute pain due to conditions other than osteoarthritis were allowed up to 3 days. However, use of the short-acting analgesics had to be stopped 3 days in advance of any study visit.	College of Rheumatology criteria Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear		
Fleischmann 2001 ⁷⁵	Strong opioids (n=63) Tramadol 50mg titrated up to a target dose of 200mg per day for 13 weeks Placebo (n=66) Concomitant therapy: No rescue medication was permitted. People were instructed to maintain a constant level of activity throughout the study. Physiotherapy (ie. hot/cold packs and massages) initiated before the double-blind phase was continued throughout the study, although it could not be initiated during the double blind phase. People were not to use other adjunctive therapy (eg. topical therapy, acupuncture) during the study.	Knee osteoarthritis Mean age (SD): 62.5 (9.17) years N = 129 Definition: Symptomatic osteoarthritis with radiographic evidence Severity: Not stated Duration of symptoms (mean [SD]): 7.85 (6.58) years Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months	Study design classification: 2) Excluding non-responders
Friedmann 2011 ⁸²	Strong opioids (n=205)	Mixed osteoarthritis (knee and/or hip)	Pain at ≤3 months	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Oxycodone extended release 5mg twice daily increased up to 20mg twice daily for 12 weeks</p> <p>Placebo (n=207)</p> <p>Concomitant therapy: Low dose aspirin (≤ 325mg per day) was allowed for cardiovascular prophylaxis. A stable dose for more than 4 weeks was required for monoaminoxidase inhibitors, tricyclic antidepressants, serotonin reuptake inhibitors or other antidepressants, gabapentin, pregabalin, and glucosamine/chondroitin.</p>	<p>Mean age (SD): 58.3 (8.2) years N = 412</p> <p>Definition: Osteoarthritis with clinical and radiographic evidence</p> <p>Severity: Moderate to severe Duration of symptoms: At least 3 months Presence of multimorbidities: Not stated/unclear</p>		
<p>Gana 2006⁸³ Subsidiary papers: Florete 2008⁷⁷, Kosinski 2007¹¹³</p>	<p>Strong opioids (n=806) Tramadol extended release 100, 200, 300 or 400mg once daily for 12 weeks</p> <p>Placebo (n=205)</p> <p>Concomitant therapy: People could take up to 200mg/day of paracetamol for no more than 3 consecutive days for reasons other than osteoarthritis of chronic pain. The use of paracetamol was prohibited during the washout period and in the 48 hours</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 58.2 (10.0) years N = 1011</p> <p>Definition: Radiographically confirmed osteoarthritis</p> <p>Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 7.8 (7.3) years Presence of multimorbidities: Not stated/unclear</p>	<p>Quality of life at ≤ 3 months Pain at ≤ 3 months Physical function at ≤ 3 months Serious adverse events 2: cardiovascular adverse events at ≤ 3 months</p>	<p>Study design classification: 2) Excluding non-responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	before each study visit after the screening visit.			
Malonne 2004 ¹³⁴	<p>Strong opioids (n=111) Tramadol LP 200mg once daily for 14 days</p> <p>Placebo (n=119)</p> <p>Concomitant therapy: During the second week of the study, concomitant use of paracetamol ≤2g/day (500mg capsules) was allowed as rescue analgesia for uncontrolled pain.</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 66.7 (8.3) years N = 230</p> <p>Definition: Symptomatic osteoarthritis</p> <p>Severity: Not stated Duration of symptoms (mean [SD]): 5.7 (5.1) years Presence of multimorbidities: Not stated/unclear</p>	Pain at ≤3 months	Study design classification: 3) Selection of specific population
Matsumoto 2005 ¹³⁶	<p>Strong opioids (n=125) Oxymorphone extended release 20 or 40mg or oxycodone controlled release 20mg given every 12 hours for 4 weeks</p> <p>Placebo (n=124)</p> <p>A third group (n=240) that received oxycodone was reported. This group will not be included in the analysis as oxycodone is not licensed for use in the United Kingdom.</p> <p>Concomitant therapy: No additional information</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SE): 62.3 (0.98) years N = 491</p> <p>Definition: Symptomatic and radiographic evidence of osteoarthritis</p> <p>Severity: Minimum Kellgren Lawrence grade 2 Duration of symptoms: 146 were <5 years, 342 were more than or equal to 5 years. Presence of multimorbidities: Not stated/unclear</p>	Quality of life at ≤3 months Pain at ≤3 months	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
<p>Serrie 2017¹⁸⁷ Subsidiary papers: Biondi 2015²⁴, Etropolski 2015²⁸, Lange 2010¹¹⁷, Lange 2018¹¹⁸, Lange 2017¹¹⁹</p>	<p>Strong opioids (n=650) Tapentadol prolonged release 50mg twice daily or oxycodone controlled release 10mg twice daily increased to 100mg twice daily or 50mg twice daily respectively over 3 weeks, with treatment for an additional 12 weeks</p> <p>Placebo (n=337)</p> <p>Concomitant therapy: Aspirin at ≤325mg/day was allowed for cardiovascular prophylaxis. Paracetamol was allowed as rescue medications until the last 3 days of the titration period and then intermittent use for no more than 3 consecutive days was permitted during maintenance for reasons other than study-related chronic pain. Medications for psychiatric or neurological conditions not stated in the exclusion criteria were allowed if they were at a stable dose for ≥3 months prior to randomisation.</p>	<p>Knee osteoarthritis Mean age (SD): 62.1 (9.3) years N = 987</p> <p>Definition: Diagnosis of osteoarthritis based on the American College of Rheumatology criteria</p> <p>Severity: Majority pain severity severe, functional class 1-3 Duration of symptoms: At least 3 months Presence of multimorbidities: Not stated/unclear</p>	<p>Quality of life at ≤3 months Pain at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months Serious adverse events 2: cardiovascular adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 3) Selection of specific population</p>
<p>Thorne 2008¹⁹⁷</p>	<p>Strong opioids (n=100) Tramadol 150mg once daily increased to the maximal tolerated dose for 4 weeks</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 61.0 (10.3) years N = 100</p>	<p>Quality of life at ≤3 months Pain at ≤3 months Physical function at ≤3 months</p>	<p>Study design classification: 3) Selection of specific population</p> <p>Crossover trial</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Placebo (n=100)</p> <p>Concomitant therapy: Breakthrough pain was managed throughout the study with 325mg to 650mg plain paracetamol every 4 to 6 hours as required.</p>	<p>Definition: Symptomatic and radiographic evidence of osteoarthritis</p> <p>Severity: Osteoarthritis grade 2-3</p> <p>Duration of symptoms (mean [SD]): 8.3 (6.8) years</p> <p>Presence of multimorbidities: Not stated/unclear</p>		
Vojtassak 2011 ²¹¹	<p>Strong opioids (n=139) OROS hydromorphone hydrochloride 4mg once daily titrated up to a maximum dose of 32mg for 12 weeks</p> <p>Placebo (n=149)</p> <p>Concomitant therapy: Paracetamol was allowed as rescue medication, provided that a subject did not exceed the total permitted daily dose (4grams per day until day 8 and then 2g per day for the remainder of the study).</p>	<p>Mixed osteoarthritis (knee or hip)</p> <p>Median age (range): 65 (43-85) years</p> <p>N = 288</p> <p>Definition: Symptomatic osteoarthritis</p> <p>Severity: Moderate-to-severe</p> <p>Duration of symptoms: At least 3 months</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>Quality of life at ≤3 months</p> <p>Pain at ≤3 months</p> <p>Physical function at ≤3 months</p>	<p>Study design classification: 4)</p> <p>Unclear</p>
Zautra 2005 ²²⁴	<p>Strong opioids (n=56) Oxycodone 10mg twice a day uptitrated to a maximum final dose of 12 tablets per day for 2 weeks</p> <p>Placebo (n=51)</p>	<p>Osteoarthritis (site unclear)</p> <p>Mean age (SD): 63.3 (11.6) years</p> <p>N = 107</p> <p>Definition: Osteoarthritis defined by the guidelines of</p>	<p>Pain at ≤3 months</p> <p>Psychological distress at ≤3 months</p>	<p>Study design classification: 1)</p> <p>Including only responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Concomitant therapy: Stable regimens of paracetamol, NSAIDs or oral steroids were allowed, but rescue medication was not.</p>	<p>the American College of Rheumatology</p> <p>Severity: Not stated</p> <p>Duration of symptoms: Not stated</p> <p>Presence of multimorbidities: Not stated/unclear</p>		

1 **1.1.5.1.10 Anti-epileptic drugs compared to antidepressant drugs**

2 **Table 11: Summary of studies included in the evidence review for anti-epileptic drugs compared to antidepressant drugs**

Study	Intervention and comparison	Population	Outcomes	Comments
Enteshari-Moghaddam 2019 ⁶⁶	<p>Antidepressant drugs(n=50) Duloxetine 30mg daily increased to a maximum of 60mg daily after two weeks</p> <p>Anti-epileptic drugs (n=50) Gabapentin 300mg daily increased to a maximum of 600mg daily after two weeks</p> <p>Paracetamol (n=50) Paracetamol 1000mg daily increased to a maximum of 2000mg daily after two weeks</p> <p>Concomitant therapy: Opioid usage was not allowed during the intervention period. People were asked to continue their previous medications for</p>	<p>Knee osteoarthritis</p> <p>Mean age (SD): 54.44 (7.17) years</p> <p>N = 150</p> <p>Definition: Moderate to severe idiopathic knee osteoarthritis able to walk with knee pain more than five by visual analogue scale or more than 48 score in the WOMAC score with radiographic evidence of osteoarthritis with Kellgren Lawrence score of III-IV.</p> <p>Severity: Kellgren Lawrence grade II-III</p> <p>Duration of symptoms (mean [SD]): 8.44 (4.07) years</p>	<p>Pain at ≤3 months</p> <p>Physical function at ≤3 months</p> <p>Serious adverse event 2: Central nervous system adverse events at ≤3 months</p>	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
	osteoarthritis, except corticosteroids. People were asked to report the use of NSAIDs (ibuprofen with maximum dose of 2400mg daily, naproxen with maximum dose of 1500mg daily, indomethacin 150mg daily) during the study period.	Presence of multimorbidities: Not stated/unclear		
Sofat 2017 ¹⁹³	<p>Anti-epileptic drugs (n=22) Pregabalin 150mg once a day for 1 week, 300mg once a day for 10 weeks, and 150mg once a day for 2 more weeks</p> <p>Antidepressant drugs (n=21) Duloxetine 30mg once a day for 1 week, 60mg once a day for 10 weeks, and 30mg once a day for 2 more weeks</p> <p>Placebo (n=22)</p> <p>Concomitant therapy: No additional information</p>	<p>Hand osteoarthritis Mean age (SD): 62.9 (7.2) years N = 65</p> <p>Definition: Osteoarthritis diagnosed by the American College of Rheumatology criteria</p> <p>Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Physical function at ≤3 months Psychological distress at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months Serious adverse events 2: cardiovascular adverse events at ≤3 months</p>	Study design classification: 6) No response criteria

1 **1.1.5.1.11 Anti-epileptic drugs compared to placebo**

2 **Table 12: Summary of studies included in the evidence review for anti-epileptic drugs compared to placebo**

Study	Intervention and comparison	Population	Outcomes	Comments
Sofat 2017 ¹⁹³	<p>Anti-epileptic drugs (n=22) Pregabalin 150mg once a day for 1 week, 300mg once a day</p>	<p>Hand osteoarthritis Mean age (SD): 62.9 (7.2) years N = 65</p>	<p>Pain at ≤3 months Physical function at ≤3 months</p>	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>for 10 weeks, and 150mg once a day for 2 more weeks</p> <p>Antidepressant drugs (n=21) Duloxetine 30mg once a day for 1 week, 60mg once a day for 10 weeks, and 30mg once a day for 2 more weeks</p> <p>Placebo (n=22)</p> <p>Concomitant therapy: No additional information</p>	<p>Definition: Osteoarthritis diagnosed by the American College of Rheumatology criteria</p> <p>Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Psychological distress at ≤ 3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤ 3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤ 3 months</p>	

1 **1.1.5.1.12 Anti-epileptic drugs compared to paracetamol**

2 **Table 13: Summary of studies included in the evidence review for anti-epileptic drugs compared to paracetamol**

Study	Intervention and comparison	Population	Outcomes	Comments
Enteshari-Moghaddam 2019 ⁶⁶	<p>Antidepressant drugs (n=50) Duloxetine 30mg daily increased to a maximum of 60mg daily after two weeks</p> <p>Anti-epileptic drugs (n=50) Gabapentin 300mg daily increased to a maximum of 600mg daily after two weeks</p> <p>Paracetamol (n=50) Paracetamol 1000mg daily increased to a maximum of 2000mg daily after two weeks</p>	<p>Knee osteoarthritis Mean age (SD): 54.44 (7.17) years N = 150</p> <p>Definition: Moderate to severe idiopathic knee osteoarthritis able to walk with knee pain more than five by visual analogue scale or more than 48 score in the WOMAC score with radiographic evidence of osteoarthritis with Kellgren Lawrence score of III-IV.</p>	<p>Pain at ≤ 3 months</p> <p>Physical function at ≤ 3 months</p> <p>Serious adverse event 2: Central nervous system adverse events at ≤ 3 months</p>	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Concomitant therapy: Opioid usage was not allowed during the intervention period. People were asked to continue their previous medications for osteoarthritis, except corticosteroids. People were asked to report the use of NSAIDs (ibuprofen with maximum dose of 2400mg daily, naproxen with maximum dose of 1500mg daily, indomethacin 150mg daily) during the study period.</p>	<p>Severity: Kellgren Lawrence grade II-III Duration of symptoms (mean [SD]): 8.44 (4.07) years Presence of multimorbidities: Not stated/unclear</p>		

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2 **1.1.5.1.12 Antidepressant drugs compared to placebo**

3 **Table 14: Summary of studies included in the evidence review for antidepressant drugs compared to placebo**

Study	Intervention and comparison	Population	Outcomes	Comments
Abou-raya 2012 ¹	<p>Antidepressant drugs (n=144) Duloxetine 60mg/day for 16 weeks</p> <p>Placebo (n=144)</p> <p>Concomitant therapy: Concomitant rescue medication use, including paracetamol up to 4g/day and NSAIDs was allowed to continue provided they did not increase the dose</p>	<p>Knee osteoarthritis Mean age (SD): 68.7 (6.0) years N = 288</p> <p>Definition: American College of Rheumatology clinical and radiographic criteria of primary knee osteoarthritis</p> <p>Severity: Kellgren Lawrence grade II-III (majority grade II)</p>	<p>Pain at ≤3 months Physical function at ≤3 months Psychological distress at ≤3 months</p>	<p>Study design classification: 6) No response criteria</p> <p>NCT01425827</p>

Study	Intervention and comparison	Population	Outcomes	Comments
		Duration of symptoms (mean [SD]): 5.7 (4.7) years Presence of multimorbidities: Low comorbidity score (184 had 0-1 comorbidities, 38 had at least 2 comorbidities).		
Chappell 2009 ⁴⁶	<p>Antidepressant drugs (n=111) Duloxetine 30mg once daily increased up to 60mg after 2 weeks, continued for 5 weeks then people were randomly assigning to remaining at 60mg or increasing to 120mg for 6 weeks. This was then tapered down over 2 more weeks.</p> <p>Placebo (n=120)</p> <p>Concomitant therapy: People who entered the trial taking an NSAID or paracetamol were allowed to continue taking the drug(s) during the study. People were not allowed to have their dose of NSAIDs or paracetamol increased over what they were taking at visit 1 but were allowed to have their dose decreased or discontinued. Episodic use (no more than 3 consecutive days and not to exceed 20 total days during the study) of short-acting analgesics was allowed for acute injury or</p>	<p>Knee osteoarthritis Mean age (SD): 62.3 (9.5) years N = 231</p> <p>Definition: Clinical and radiographic evidence of osteoarthritis</p> <p>Severity: Not stated Duration of symptoms (mean [SD]): 7.0 (7.8) years Presence of multimorbidities: Not stated/unclear</p>	Quality of life at ≤3 months Pain at ≤3 months Psychological distress at ≤3 months	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
Chappell 2011 ⁴⁵	<p>surgery or for rescue from an osteoarthritis knee pain flare.</p> <p>Antidepressant drugs (n=128) Duloxetine 60-120mg once daily for 13 weeks</p> <p>Placebo (n=128)</p> <p>Concomitant therapy: People who entered the trial taking an NSAID or paracetamol were allowed to continue taking it provided that the dosage was not increased during the study. After randomisation, episodic use (≤ 3 consecutive days and was not to exceed 20 total days during the study) of short acting analgesics was allowed for acute injury or surgery or for rescue from osteoarthritis flare up pain.</p>	<p>Knee osteoarthritis Mean age (SD): 62.6 (9.0) years N = 256</p> <p>Definition: Clinical and radiographic evidence of osteoarthritis</p> <p>Severity: Not stated Duration of symptoms (mean [SD]): 5.9 (6.1) years Presence of multimorbidities: Not stated/unclear</p>	<p>Quality of life at ≤ 3 months Pain at ≤ 3 months Physical function at ≤ 3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤ 3 months Serious adverse events 2: cardiovascular adverse events at ≤ 3 months Serious adverse events 3: hepatorenal adverse events at ≤ 3 months Serious adverse events 4: central nervous system adverse events at ≤ 3 months</p>	<p>Study design classification: 6) No response criteria</p> <p>NCT00433290</p>
Frakes 2011 ⁷⁸	<p>Antidepressant drugs (n=264) Duloxetine starting at 30mg/day increased up to 120mg/day for 10 weeks</p> <p>Placebo (n=260)</p> <p>Concomitant therapy: Before the study started, each person had their NSAID therapy optimised. During the study they stayed on the same dose</p>	<p>Knee osteoarthritis Mean age (SD): 61.0 (9.2) years N = 524</p> <p>Definition: Clinical and radiographic evidence of osteoarthritis</p> <p>Severity: Not stated Duration of symptoms (mean [SD]): 9.5 (8.9) years</p>	<p>Pain at ≤ 3 months Physical function at ≤ 3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤ 3 months Serious adverse events 2: cardiovascular adverse events at ≤ 3 months Serious adverse events 3: hepatorenal adverse events at ≤ 3 months</p>	<p>Study design classification: 6) No response criteria</p> <p>NCT01018680</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	throughout the study period. People continued omeprazole 20mg daily to reduce the risk of upper GI bleeding. Paracetamol (650mg orally every 6 hours, not to exceed 2.6g/day or to be used for more than 25 days total throughout the course of the study) was permitted as rescue medication. For pain related to acute trauma or minor surgery, opioids could be used for up to three consecutive days, with total use not to exceed 10 days. Continued use of routine medication was permitted, as was the use of herbal therapies and nonpharmacological treatments such as physical therapy if they had been used routinely prior to study entry.	Presence of multimorbidities: Not stated/unclear	Serious adverse events 4: central nervous system adverse events at ≤3 months	
Hudson 2021 ¹⁰⁰	<p>Antidepressant drugs (n=102) Nortriptyline 25mg daily for 2 weeks, after which the dose could be adjusted (over the next 6 weeks in 2 week intervals) to a maximum dose of four capsules daily (100mg nortriptyline). At 8 weeks, people were instructed to maintain their current dose until week 14.</p> <p>Placebo (n=103)</p> <p>Concomitant therapy:</p>	<p>Knee osteoarthritis Mean age (SD): 64.5 (9.2) years N = 205</p> <p>Definition: Knee osteoarthritis assessed by an orthopaedic surgeon through referral letters and accompanying pre-referral X-rays)</p> <p>Severity: Not stated/unclear Duration of symptoms (mean [SD]): 7.6 (7.6) years</p>	<p>Quality of life at ≤3 months</p> <p>Pain at ≤3 months</p> <p>Physical function at ≤3 months</p> <p>Serious adverse event 2: cardiovascular adverse events at ≤3 months</p> <p>Serious adverse event 2: renal and hepatic adverse events at ≤3 months</p> <p>Serious adverse event 2: central nervous system adverse events at ≤3 months</p>	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
	People were free to use and adjust their usual analgesic medication as prescribed by their GP, but were requested not to use any other antidepressants or receive intra-articular steroid injections.	Presence of multimorbidities: High comorbidity score- People with chronic conditions = 121		
Sofat 2017 ¹⁹³	<p>Anti-epileptic drugs (n=22) Pregabalin 150mg once a day for 1 week, 300mg once a day for 10 weeks, and 150mg once a day for 2 more weeks</p> <p>Antidepressant drugs (n=21) Duloxetine 30mg once a day for 1 week, 60mg once a day for 10 weeks, and 30mg once a day for 2 more weeks</p> <p>Placebo (n=22)</p> <p>Concomitant therapy: No additional information</p>	<p>Hand osteoarthritis Mean age (SD): 62.9 (7.2) years N = 65</p> <p>Definition: Osteoarthritis diagnosed by the American College of Rheumatology criteria</p> <p>Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months</p> <p>Physical function at ≤3 months</p> <p>Psychological distress at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p>	Study design classification: 6) No response criteria
Uchio 2018 ²⁰⁶ Subsidiary paper: Uchio 2018 ²⁰⁷	<p>Antidepressant drugs (n=178) Duloxetine 20mg increased up to 60mg for 14 weeks</p> <p>Placebo (n=176)</p> <p>Concomitant therapy: Drugs with analgesic effect (e.g. NSAIDs) were permitted as rescue medication for up to 3</p>	<p>Knee osteoarthritis Mean age (SD): 66.0 (8.2) years N = 354</p> <p>Definition: Clinical and radiographic evidence of osteoarthritis</p> <p>Severity: Kellgren Lawrence grade 1-4</p>	<p>Quality of life at ≤3 months</p> <p>Pain at ≤3 months</p> <p>Physical function at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p>	<p>Study design classification: 6) No response criteria</p> <p>NCT02248480</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	consecutive days and a cumulative total of 20 days.	Duration of symptoms (mean [SD]): 4.2 (4.3) years Presence of multimorbidities: Not stated/unclear		
Wang 2017 ²¹³	<p>Antidepressant drugs (n=205) Duloxetine 30mg once a day for 1 week and 60mg once a day for 12 weeks</p> <p>Placebo (n=202)</p> <p>Concomitant therapy: No additional information (paracetamol, NSAIDs and opioids were not allowed).</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 60.5 (8.3) years N = 407</p> <p>Definition: Clinical and radiographic evidence of osteoarthritis</p> <p>Severity: Not stated Duration of symptoms (mean [SD]): 8.0 (7.5) years Presence of multimorbidities: Not stated/unclear</p>	Pain at ≤3 months Physical function at ≤3 months	Study design classification: 6) No response criteria

1 **1.1.5.1.12 Antidepressant drugs compared to paracetamol**

2 **Table 15: Summary of studies included in the evidence review for antidepressant drugs compared to paracetamol**

Study	Intervention and comparison	Population	Outcomes	Comments
Enteshari-Moghaddam 2019 ⁶⁶	<p>Antidepressant drugs (n=50) Duloxetine 30mg daily increased to a maximum of 60mg daily after two weeks</p> <p>Anti-epileptic drugs (n=50) Gabapentin 300mg daily increased to a maximum of 600mg daily after two weeks</p>	<p>Knee osteoarthritis Mean age (SD): 54.44 (7.17) years N = 150</p> <p>Definition: Moderate to severe idiopathic knee osteoarthritis able to walk with knee pain more than five by visual</p>	Pain at ≤3 months Physical function at ≤3 months Serious adverse event 2: Central nervous system adverse events at ≤3 months	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Paracetamol(n=50) Paracetamol 1000mg daily increased to a maximum of 2000mg daily after two weeks</p> <p>Concomitant therapy: Opioid usage was not allowed during the intervention period. People were asked to continue their previous medications for osteoarthritis, except corticosteroids. People were asked to report the use of NSAIDs (ibuprofen with maximum dose of 2400mg daily, naproxen with maximum dose of 1500mg daily, indomethacin 150mg daily) during the study period.</p>	<p>analogue scale or more than 48 score in the WOMAC score with radiographic evidence of osteoarthritis with Kellgren Lawrence score of III-IV.</p> <p>Severity: Kellgren Lawrence grade II-III Duration of symptoms (mean [SD]): 8.44 (4.07) years Presence of multimorbidities: Not stated/unclear</p>		

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2 **1.1.5.1.13 Glucosamine compared to paracetamol**

3 **Table 16: Summary of studies included in the evidence review for glucosamine compared to paracetamol**

Study	Intervention and comparison	Population	Outcomes	Comments
Herrero-beaumont 2007 ⁹⁶	<p>Paracetamol (n=108) Paracetamol 1 gram three times a day and matching placebo for 26 weeks</p> <p>Glucosamine (n=106)</p>	<p>Knee osteoarthritis Mean age (SD): 63.9 (7.0) years N = 318</p> <p>Definition: Primary symptomatic knee</p>	<p>Pain at >3 months Physical function at >3 months Serious adverse events 2: cardiovascular adverse events at >3 months</p>	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Glucosamine 1500mg oral powder for solution per day and matching placebo for 26 weeks</p> <p>Glucosamine purity: Not stated</p> <p>Placebo (n=104)</p> <p>Concomitant therapy: Ibuprofen 400mg was permitted for rescue medication</p>	<p>osteoarthritis according to the clinical and radiographic American College of Rheumatology criteria</p> <p>Severity: Kellgren Lawrence grade 2-3</p> <p>Duration of symptoms (mean [SD]): 7.0 (5.7) years</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 3: hepatorenal adverse events at >3 months</p>	

1 **1.1.5.1.14 Glucosamine compared to oral non-steroidal anti-inflammatory drugs**

2 **Table 17: Summary of studies included in the evidence review for glucosamine compared to oral non-steroid anti-inflammatory drugs**

Study	Intervention and comparison	Population	Outcomes	Comments
Chopra 2013 ⁵²	<p>Glucosamine (n=110) Glucosamine sulphate 2 grams daily for 26 weeks</p> <p>Non-steroidal anti-inflammatory drugs (n=110) Celecoxib 200mg daily for 26 weeks</p> <p>A third group (n=220) was reported which was not included in the analysis as it was excluded in the protocol (Ayurvedic preparations).</p> <p>Glucosamine purity: Statement regarding purity</p>	<p>Knee osteoarthritis</p> <p>Mean age (SD): 55.7 (8.3) years N = 440</p> <p>Definition: Clinical evidence of osteoarthritis</p> <p>Severity: Not stated</p> <p>Duration of symptoms (mean [SD]): 54.9 (51.9) months</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at >3 months</p> <p>Physical function at >3 months</p> <p>Serious adverse events 3: hepatorenal adverse events at >3 months</p>	<p>Study design classification: 6) No response criteria</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Concomitant therapy: Paracetamol (500mg tablet) was provided for emergency analgesic use. Ongoing concomitant medication for concurrent chronic illness was permitted.</p>			
<p>Clegg 2006⁵¹ GAIT trial</p> <p>Subsidiary papers: Hochberg 2008⁹⁷ Sawitzke 2008¹⁷⁴ Sawitzke 2010¹⁷⁵</p>	<p>Non-steroidal anti-inflammatory drugs (n=318) Celecoxib 200mg daily for 24 weeks</p> <p>Glucosamine (n=317) Glucosamine hydrochloride 500mg three times daily for 24 weeks</p> <p>Placebo (n=313)</p> <p>A fourth and fifth group (n=635) was reported which was not included in the analysis as it was excluded in the protocol (combination glucosamine and chondroitin sulfate, or chondroitin sulfate alone).</p> <p>Glucosamine purity: Statement regarding purity</p> <p>Concomitant therapy: People were allowed to take paracetamol up to 4000mg per</p>	<p>Knee osteoarthritis Mean age (SD): 58.6 (10.4) years N = 1583</p> <p>Definition: Clinical and radiographic evidence of osteoarthritis</p> <p>Severity: Kellgren Lawrence grade 2-3. Functional class 1-3.</p> <p>Duration of symptoms (mean [SD]): 10.0 (9.8) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at >3 months Physical function at >3 months Serious adverse events 2: cardiovascular adverse events at >3 months</p>	<p>Study design classification: 6) No response criteria</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	day, except during the 24 hours before a clinical evaluation for joint pain.			
Lopes vaz 1982 ¹²⁹	<p>Glucosamine (n=20) Glucosamine 500mg three times a day for 8 weeks</p> <p>Non-steroidal anti-inflammatory drugs (n=20) Ibuprofen 300mg three times a day for 8 weeks</p> <p>Glucosamine purity: Purity not stated</p> <p>Concomitant therapy: No additional information</p>	<p>Knee osteoarthritis Mean age (SD): 57.8 (5.5) years N = 40</p> <p>Definition: Unilateral osteoarthritis</p> <p>Severity: Not stated Duration of symptoms (mean [SD]): 3.2 (2.0) years Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	Study design classification: 4) Unclear
Muller-fassbender 1994 ¹⁴²	<p>Glucosamine (n=100) Glucosamine sulfate 500mg three times a day for 4 weeks</p> <p>Non-steroidal anti-inflammatory drugs (n=100) Ibuprofen 400mg three times a day for 4 weeks</p> <p>Glucosamine purity: Purity not stated</p> <p>Concomitant therapy: The person's program for physical therapy (including exercise, cold or heat</p>	<p>Knee osteoarthritis Mean age (SD): 54 (8.5) years N = 200</p> <p>Definition: Painful, active osteoarthritis based on Lequesne's clinical and radiographic criteria</p> <p>Severity: Not stated Duration of symptoms (mean [SD]): 4.8 (3.4) years Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p>	Study design classification: 4) Unclear

Study	Intervention and comparison	Population	Outcomes	Comments
	application, etc.), if any, was allowed and had to be registered. Other treatments for concomitant diseases were allowed, provided that they were recorded			
Nowlan 2003 ¹⁴⁹	<p>Glucosamine (n=20) Glucosamine sulfate 500mg three times a day for 12 weeks</p> <p>Non-steroidal anti-inflammatory drugs (n=20) Ibuprofen 400mg three times daily for 12 weeks</p> <p>Glucosamine purity: Purity not stated</p> <p>Concomitant therapy: Paracetamol 500mg to be used as necessary as an adjuvant medicine for relief of arthritis pain</p>	<p>Osteoarthritis (unclear site) Mean age (SD): 65.2 (9.0) years N = 40</p> <p>Definition: Diagnosis with either radiographic or clinical evidence of osteoarthritis</p> <p>Severity: Not stated Duration of symptoms (mean [SD]): 65.2 (9.0) years Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	Study design classification: 4) Unclear
Qiu 1998 ¹⁶²	<p>Glucosamine (n=88) Glucosamine 500mg three times a day for 4 weeks</p> <p>Non-steroidal anti-inflammatory drugs (n=90) Ibuprofen 400mg three times a day for 4 weeks</p> <p>Glucosamine purity: Purity not stated</p>	<p>Knee osteoarthritis Mean age (SD): 56 (10) years N = 178</p> <p>Definition: People with osteoarthritis of the knee</p> <p>Severity: Not stated Duration of symptoms: Not stated</p>	<p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p> <p>Serious adverse events 3: hepatorenal adverse events at ≤3 months</p>	Study design classification: 4) Unclear

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: No additional information	Presence of multimorbidities: Not stated/unclear	Serious adverse events 4: central nervous system adverse events at ≤3 months	

1 **1.1.5.1.15 Glucosamine compared to placebo**

2 **Table 18: Summary of studies included in the evidence review for glucosamine compared to placebo**

Study	Intervention and comparison	Population	Outcomes	Comments
Ammendolia 2021 ⁵	<p>Glucosamine (n=40) Glucosamine was administered as a sachet of powder in a 1500 mg oral solution, once daily without food for 2 months.</p> <p>Placebo (n=50) Glucosamine purity: Purity not stated</p> <p>Concomitant therapy: People were instructed to avoid taking an analgesic, corticosteroids or other NSAIDs for the duration of the study. All people received 12 sessions, 3 per week, with diode laser applied in the perirotulum area, at the level of the articular hemirimes for a duration of 20 minutes with a wavelength of 905 nanometer, power of 4.5 Watt, dose of 70 J/cm², pulse duration of 100 nanoseconds.</p>	<p>Knee osteoarthritis Mean age (SD): 55 (10) years N = 90</p> <p>Definition: Diagnosis of knee osteoarthritis according to the criteria of the American College of Rheumatology; Grade 2 according to the radiographic scale of Kellgren-Lawrence</p> <p>Severity: Kellgren-Lawrence grade 2 Duration of symptoms (mean [SD]): 13 (11) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months and >3 months</p> <p>Serious adverse event 1: gastrointestinal adverse events at ≤3 months</p> <p>Serious adverse event 2: Central nervous system adverse events at ≤3 months</p>	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
Cahlin 2011 ³⁸	<p>Glucosamine (n=30) Glucosamine 400mg three times a day for 6 weeks</p> <p>Placebo (n=29)</p> <p>Glucosamine purity: Purity not stated</p> <p>Concomitant therapy: Paracetamol 1000mg could be used for rescue medication</p>	<p>Temporomandibular joint osteoarthritis Mean age (SD): 59 (12) years N = 59</p> <p>Definition: Radiographically confirmed osteoarthritis</p> <p>Severity: Not stated Duration of symptoms: 2 to >24 months (median 13-24 months) Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p>	Study design classification: 6) No response criteria
Cibere 2004 ⁵⁰	<p>Glucosamine (n=71) Glucosamine 1500mg per day as a potassium salt for 26 weeks</p> <p>Placebo (n=66)</p> <p>Glucosamine purity: Purity not stated</p> <p>Concomitant therapy: Rescue analgesic medications including paracetamol and NSAIDs were allowed and recorded by the patient in a daily diary</p>	<p>Knee osteoarthritis Mean age (range): 65 (40-88) years N = 137</p> <p>Definition: Clinical and radiographic evidence of osteoarthritis</p> <p>Severity: Kellgren Lawrence grade 2-4 Duration of symptoms (median [range]): 3 (0-29) years Presence of multimorbidities: Not stated/unclear</p>	<p>Quality of life at >3 months Pain at >3 months Physical function at >3 months Osteoarthritis flares at >3 months</p>	Study design classification: 3) Selection of specific population
Clegg 2006 ⁵¹ GAIT trial Subsidiary papers:	<p>Non-steroidal anti-inflammatory drugs (n=318)</p>	<p>Knee osteoarthritis Mean age (SD): 58.6 (10.4) years</p>	<p>Pain at >3 months Physical function at >3 months</p>	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
Hochberg 2008 ⁹⁷ Sawitzke 2008 ¹⁷⁴ Sawitzke 2010 ¹⁷⁵	<p>Celecoxib 200mg daily for 24 weeks</p> <p>Glucosamine (n=317) Glucosamine hydrochloride 500mg three times daily for 24 weeks</p> <p>Placebo (n=313)</p> <p>A fourth and fifth group (n=635) was reported which was not included in the analysis as it was excluded in the protocol (combination glucosamine and chondroitin sulfate, or chondroitin sulfate alone).</p> <p>Glucosamine purity: Statement regarding purity</p> <p>Concomitant therapy: People were allowed to take paracetamol up to 4000mg per day, except during the 24 hours before a clinical evaluation for joint pain.</p>	<p>N = 1583</p> <p>Definition: Clinical and radiographic evidence of osteoarthritis</p> <p>Severity: Kellgren Lawrence grade 2-3. Functional class 1-3.</p> <p>Duration of symptoms (mean [SD]): 10.0 (9.8) years</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 2: cardiovascular adverse events at >3 months</p>	
Fransen 2015 ⁷⁹ (LEGS trial)	<p>Glucosamine (n=152) Glucosamine sulfate potassium chloride 1506mg once a day for 2 years</p> <p>Placebo (n=151)</p>	<p>Knee osteoarthritis</p> <p>Mean age (SD): 60.5 (8.1) years</p> <p>N = 605</p>	<p>Quality of life at >3 months</p> <p>Pain at >3 months</p> <p>Physical function at >3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at >3 months</p>	<p>Study design classification: 6) No response criteria</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>A third and fourth group (total n=302) was reported which was not included in the analysis as it was excluded in the protocol (chondroitin and combined glucosamine and chondroitin).</p> <p>Glucosamine purity: Statement on purity</p> <p>Concomitant therapy: No additional information</p>	<p>Definition: Symptomatic and radiographic evidence of osteoarthritis</p> <p>Severity: 48-61% had less than Kellgren-Lawrence grade 2 osteoarthritis</p> <p>Duration of symptoms: Not stated</p> <p>Presence of multimorbidities: Not stated</p>		
<p>Frestedt 2008⁸⁰ Subsidiary paper: Frestedt 2009⁸¹</p>	<p>Glucosamine (n=19) Glucosamine sulfate 1500mg per day for 12 weeks</p> <p>Placebo (n=16)</p> <p>A third group (n=35) was reported which was not included in the analysis as it was excluded in the protocol (Aquamin and combined glucosamine and Aquamin).</p> <p>Glucosamine purity: Purity not stated</p> <p>Concomitant therapy: The rescue medication was paracetamol, 325mg, 1-2 tablets every 4-6 hours as needed for intractable pain.</p>	<p>Knee osteoarthritis</p> <p>Mean age (SD): 59.2 (9.7) years N = 70</p> <p>Definition: Clinical diagnosis of osteoarthritis</p> <p>Severity: Not stated</p> <p>Duration of symptoms: Not stated</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months</p> <p>Physical function at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 6) No response criteria</p>

Study	Intervention and comparison	Population	Outcomes	Comments
Giordano 2009 ⁸⁹	<p>Glucosamine (n=30) Glucosamine 1500mg once a day for 12 weeks</p> <p>Placebo (n=30) Glucosamine purity: Purity not stated</p> <p>Concomitant therapy: For rescue analgesia, people were allowed paracetamol 500mg, diclofenac 150mg, piroxicam 20mg, naproxen 750mg, or aceclofenac 200mg, all of which were to be used as needed and noted daily in a diary.</p>	<p>Knee osteoarthritis Mean age (SD): 57.7 (7.8) years N = 60</p> <p>Definition: Osteoarthritis diagnosed according to the American Rheumatism Association criteria</p> <p>Severity: Kellgren Lawrence grade 1-3 Duration of symptoms (mean [SD]): 6.3 (4.8) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months and >3 months Physical function at ≤3 months and >3 months Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	Study design classification: 6) No response criteria
Herrero-beaumont 2007 ⁹⁶	<p>Paracetamol (n=108) Paracetamol 1 gram three times a day and matching placebo for 26 weeks</p> <p>Glucosamine (n=106) Glucosamine 1500mg oral powder for solution per day and matching placebo for 26 weeks</p> <p>Glucosamine purity: Purity not stated</p> <p>Placebo (n=104)</p>	<p>Knee osteoarthritis Mean age (SD): 63.9 (7.0) years N = 318</p> <p>Definition: Primary symptomatic knee osteoarthritis according to the clinical and radiographic American College of Rheumatology criteria</p> <p>Severity: Kellgren Lawrence grade 2-3 Duration of symptoms (mean [SD]): 7.0 (5.7) years</p>	<p>Pain at >3 months Physical function at >3 months Serious adverse events 2: cardiovascular adverse events at >3 months Serious adverse events 3: hepatorenal adverse events at >3 months</p>	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Concomitant therapy: Ibuprofen 400mg was permitted for rescue medication</p>	<p>Presence of multimorbidities: Not stated/unclear</p>		
Houpt 1999 ⁹⁸	<p>Glucosamine (n=58) Glucosamine hydrochloride 500mg three times a day for 8 weeks</p> <p>Placebo (n=60) Glucosamine purity: Purity not stated</p> <p>Concomitant therapy: People were permitted to use paracetamol 500mg up to a maximum of eight capsules per day</p>	<p>Knee osteoarthritis Mean age (SD): 64.5 (9.8) years N = 118</p> <p>Definition: Clinical and radiological evidence of osteoarthritis</p> <p>Severity: Radiological score median grade 2 (range 1-4) Duration of symptoms (mean [SD]): 8.3 (8.3) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p>	Study design classification: 6) No response criteria
Hughes 2002 ¹⁰¹	<p>Glucosamine (n=40) Glucosamine sulphate 1500mg a day for 24 weeks</p> <p>Placebo (n=40) Glucosamine purity: Purity not stated</p> <p>Concomitant therapy: All people were permitted to continue their existing NSAID medication and encouraged to avoid changing their dose or medication during the course of</p>	<p>Knee osteoarthritis Mean age (SD): 62.28 (9.12) years N = 80</p> <p>Definition: Radiologically defined, symptomatic osteoarthritis</p> <p>Severity: Kellgren Lawrence grades 1-4, median grade 3 Duration of symptoms (mean [SD]): 7.62 (8.06) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at >3 months Physical function at >3 months</p>	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
	the study. Use of NSAIDs was recorded at each follow up assessment. People were allowed access to paracetamol or other proprietary or prescribed simple analgesic and reported use of analgesia was collected using a patient diary and recorded at each follow-up assessment			
Kwoh 2014 ¹¹⁵	<p>Glucosamine (n=98) Glucosamine 1500mg once a day for 24 weeks</p> <p>Placebo (n=103)</p> <p>Glucosamine purity: Purity not stated</p> <p>Concomitant therapy: Paracetamol was the only analgesic allowed during the study</p>	<p>Knee osteoarthritis Mean age (SD): 52.23 (6.40) years N = 201</p> <p>Definition: Symptomatic osteoarthritis</p> <p>Severity: Kellgren Lawrence grade Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months and >3 months</p> <p>Physical function at ≤3 months and >3 months</p>	Study design classification: 6) No response criteria
Noack 1994 ¹⁴⁷	<p>Glucosamine (n=126) Glucosamine 500mg three times a day for 4 weeks</p> <p>Placebo (n=126)</p> <p>Glucosamine purity: Purity not stated</p> <p>Concomitant therapy:</p>	<p>Knee osteoarthritis Mean age (SD): 55 (14.5) years N = 252</p> <p>Definition: Osteoarthritis defined according to the clinical and radiological criteria of Lequesne</p>	<p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
	Other treatments for concomitant diseases were allowed, but had to be recorded.	Severity: Radiological stage (Jager and Wirth) 1-3, clinical stage (Weseloh and Liebig) 1-4 Duration of symptoms: Median 2-10 years Presence of multimorbidities: Not stated/unclear		
Pavelka 2002 ¹⁵² Subsidiary paper: Bruyere 2004 ³⁵	<p>Glucosamine (n=101) Glucosamine sulfate 1500mg per day for 3 years</p> <p>Placebo (n=101)</p> <p>Glucosamine purity: Purity not stated</p> <p>Concomitant therapy: Paracetamol in 500mg tablets was provided for rescue medication as needed, and its use was recorded in a patient daily diary. No other pharmacologic treatments for osteoarthritis or other formulations containing analgesics were allowed. Among physical therapies, only hydrotherapy, exercise and ultrasound, alone or in combination were allowed if the person was following a stable regimen.</p>	<p>Knee osteoarthritis Mean age (SD): 62.4 (7.2) years N = 202</p> <p>Definition: Clinical and radiologically defined osteoarthritis</p> <p>Severity: Kellgren and Lawrence grade 2-3 Duration of symptoms (mean [SD]): 10.6 (7.5) years Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at >3 months Physical function at >3 months Serious adverse events 2: cardiovascular adverse events at >3 months</p>	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
Pujalte 1980 ¹⁵⁹	<p>Glucosamine (n=12) Glucosamine 500mg three times daily for 6-8 weeks</p> <p>Placebo (n=12) Glucosamine purity: Purity not stated</p> <p>Concomitant therapy: No other analgesic, antirheumatic or anti-inflammatory drug was allowed during the observation period</p>	<p>Knee osteoarthritis Mean age (range): 61.7 (45-73) years N = 24</p> <p>Definition: Clinical and radiological osteoarthritis</p> <p>Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	Serious adverse events 4: central nervous system adverse events at ≤3 months	Study design classification: 4) Unclear
Rindone 2000 ¹⁶⁴	<p>Glucosamine (n=54) Glucosamine 500mg three times day for 8 weeks</p> <p>Placebo (n=54) Glucosamine purity: Purity not stated</p> <p>Concomitant therapy: People who were taking other analgesics were instructed to continue them for the duration of the study.</p>	<p>Knee osteoarthritis Mean age (SD): 64.5 (11.5) years N = 108</p> <p>Definition: Clinical and radiographic osteoarthritis of the knee</p> <p>Severity: Radiographic stage 1-4 Duration of symptoms (mean [SD]): 13 (12) years Presence of multimorbidities: Not stated</p>	Pain at ≤3 months	Study design classification: 6) No response criteria
Rozendaal 2008 ¹⁷⁰ Subsidiary paper: Rozendaal 2009 ¹⁷¹	<p>Glucosamine (n=111) Glucosamine sulfate 1500mg/day for 2 years</p>	<p>Hip osteoarthritis Mean age (SD): 63.4 (9.0) years N = 222</p>	Pain at ≤3 months and >3 months Physical function at ≤3 months and >3 months	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Placebo (n=111)</p> <p>Glucosamine purity: Purity not stated</p> <p>Concomitant therapy: No additional information</p>	<p>Definition: Clinical osteoarthritis</p> <p>Severity: Kellgren Lawrence grade 1-4</p> <p>Duration of symptoms: Majority >3 years</p> <p>Presence of multimorbidities: Not stated/unclear</p>		
Zenk 2002 ²²⁵	<p>Glucosamine (n=14) Glucosamine 500mg three times a day for 6 weeks</p> <p>Placebo (n=14)</p> <p>A third group (n=14) was reported which was not included in the analysis as it was excluded in the protocol (milk protein concentrate).</p> <p>Glucosamine purity: Purity not stated</p> <p>Concomitant therapy: The use of approved rescue medications were permitted, including naproxen 220mg, ibuprofen 200mg, paracetamol 325mg, and acetylsalicylic acid 325mg</p>	<p>Osteoarthritis (site unclear) Mean age (SD): 58 (12) years N = 42</p> <p>Definition: Physician diagnosed osteoarthritis with symptoms</p> <p>Severity: Not stated</p> <p>Duration of symptoms: Not stated</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months</p> <p>Physical function at ≤3 months</p>	<p>Study design classification: 6) No response criteria</p>

1 **1.1.5.2 Topical (local) (including comparisons to oral formulations)**

2 **1.1.5.2.1 Capsaicin compared to placebo for knee osteoarthritis**

3 **Table 19: Summary of studies included in the evidence review for capsaicin compared to placebo for knee osteoarthritis**

Study	Intervention and comparison	Population	Outcomes	Comments
Kosuwon 2010 ¹¹⁴	<p>Capsaicin (n=99) Capsicum tincture 45.50 grams (equivalent to capsaicin 0.0125%) per 100g of Capsika gel. 2 inches applied three times a day for 4 weeks.</p> <p>Placebo (n=99)</p> <p>Concomitant therapy: People were permitted to take paracetamol for pain (500mg three times a day or every 4-6 hours) but not any other topical analgesics, NSAIDs or COX-2 inhibitors</p>	<p>Knee osteoarthritis Mean age (range): 61 (44-82) years N = 198</p> <p>Definition: Idiopathic osteoarthritis with radiographic evidence</p> <p>Severity: Kellgren Lawrence grade 2-3 Duration of symptoms: At least 6 months Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months Serious adverse events 2: cardiovascular adverse events at ≤3 months Serious adverse events 3: hepatorenal adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	Study design classification: 6) No response criteria

4 **1.1.5.2.2 Capsaicin compared to placebo for knee osteoarthritis**

5 **Table 20: Summary of studies included in the evidence review for capsaicin compared to placebo for hand osteoarthritis**

Study	Intervention and comparison	Population	Outcomes	Comments
Schnitzer 1994 ¹⁷⁸	<p>Capsaicin (n=29) 0.025% capsaicin cream. Applied four times a day for 3 weeks, then twice a day for 6 weeks</p> <p>Placebo (n=30)</p>	<p>Hand osteoarthritis Mean age (SD): 68.0 (8.8) years N = 59</p>	Pain at ≤3 months	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: People taking medication for other conditions could be continue their medication	Definition: Primary osteoarthritis in one or both hands Severity: Not stated Duration of symptoms (mean [SD]): 10.2 (7.6) years Presence of multimorbidities: Not stated/unclear		

1 **1.1.5.2.3 Topical non-steroidal anti-inflammatory drugs compared to oral non-steroidal anti-inflammatory drugs**

2 **Table 21: Summary of studies included in the evidence review for topical non-steroidal anti-inflammatory drugs compared to oral non-**
3 **steroidal anti-inflammatory drugs for knee osteoarthritis**

Study	Intervention and comparison	Population	Outcomes	Comments
Conaghan 2013 ⁵³	Oral non-steroidal anti-inflammatory drugs (n=235) Celecoxib 100mg twice a day for 12 weeks Topical non-steroidal anti-inflammatory drugs (n=463) Ketoprofen gel either 50mg or 100mg in 2.2 or 4.4 grams respectively applied twice a day for 12 weeks Oral placebo (n=228) Topical placebo (n=473) Ketoprofen gel vehicle without the ketoprofen	Knee osteoarthritis Mean age (range): 61.2 (24-90) years N = 1399 Definition: Primary diagnosis meeting the American College of Rheumatology clinical classification. People aged 18-45 were permitted if they had radiological confirmation of osteoarthritis Severity: Functional class 1-3 Duration of symptoms (mean [SD]): Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months Serious adverse events 2: cardiovascular adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months	Study design classification: 2) Excluding non-responders When comparing to placebo, one the placebo of the same formulation was used (for example: oral non-steroidal anti-inflammatory drugs compared to oral placebo).

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Concomitant therapy: Paracetamol 500mg up to four times a day was permitted for intermittent pain treatment, although not within 24 hours of the next study visit or between the baseline visits. People requiring ≥ 2 grams of paracetamol or other analgesic medication for longer than 3 consecutive days were considered treatment failures and withdrawn from the study.</p>			
Dickson 1991 ⁶²	<p>Topical non-steroidal anti-inflammatory drugs (n=117) Piroxicam gel, 1 gram applied to the affected knee three times daily for 4 weeks</p> <p>Oral non-steroidal anti-inflammatory drugs (n=118) Ibuprofen 400mg three times day for 4 weeks</p> <p>Concomitant therapy: During the washout period and throughout the trial, paracetamol up to 4 grams per day was allowed as rescue analgesia</p>	<p>Knee osteoarthritis Mean age (SD): 62.5 (11.5) years N = 235</p> <p>Definition: Well document osteoarthritis</p> <p>Severity: Mild Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤ 3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤ 3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤ 3 months</p>	Study design classification: 6) No response criteria
Rother 2007 ¹⁶⁸	<p>Oral non-steroidal anti-inflammatory drugs (n=132) Celecoxib 100mg twice a day for 6 weeks</p>	<p>Knee osteoarthritis Mean age (SD): 62.8 (9.8) years N = 397</p>	<p>Pain at ≤ 3 months</p> <p>Physical function at ≤ 3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding</p>	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Topical non-steroidal anti-inflammatory drugs (n=138) 110mg epicutaneous ketoprofen in 4.8 grams Transfersome twice a day for 6 weeks</p> <p>Placebo (n=127)</p> <p>Concomitant therapy: People could take up to 2000mg paracetamol per day as rescue medication for knee pain for 3 days in any week, apart from the 48 hours preceding a study visit</p>	<p>Definition: Fulfilling clinical criteria for osteoarthritis</p> <p>Severity: Not stated</p> <p>Duration of symptoms: At least 6 months</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	
<p>Simon 2009¹⁹⁰ Subsidiary paper: Roth 2011¹⁶⁵</p>	<p>Oral non-steroidal anti-inflammatory drugs (n=151) Diclofenac slow release 100mg once a day for 12 weeks</p> <p>Topical non-steroidal anti-inflammatory drugs (n=154) Topical diclofenac solution (1.5% w/w diclofenac sodium in a vehicle containing 45.5% w/w dimethyl sulfoxide and other excipients) applied four times daily for 12 weeks</p> <p>Placebo (n=318)</p> <p>A fourth group (n=152) was reported which was not included in the analysis as it was excluded in the protocol</p>	<p>Knee osteoarthritis Mean age (SD): 61.6 (9.9) years N = 775</p> <p>Definition: Primary osteoarthritis based on standard radiological criteria and pain</p> <p>Severity (mean radiographic score [SD]): 16.5 (3.1)</p> <p>Duration of symptoms: Not stated</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months</p> <p>Physical function at ≤3 months</p> <p>Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>(combination topical and oral NSAID).</p> <p>Concomitant therapy: Continuation of stable treatment with glucosamine, chondroitin, anti-depressants or a proton pump inhibitor (previous 90 days), or low dose ($\leq 325\text{mg/day}$) acetylsalicylic acid (previous 30 days); paracetamol was provided and permitted (up to four 325mg caplets per day) except during the 3 days before each efficacy assessment. A person with a gastrointestinal adverse event was allowed to start a proton pump inhibitor.</p>			
Tiso 2010 ¹⁹⁸	<p>Topical non-steroidal anti-inflammatory drugs (n=10) Ibuprofen gel 4%, 2mL applied to the target area four times daily for 2 weeks</p> <p>Oral non-steroidal anti-inflammatory drugs (n=10) Ibuprofen 800mg three times daily for 2 weeks</p> <p>Concomitant therapy: No additional information</p>	<p>Knee osteoarthritis Mean age (SD): 57.9 (9.2) years N = 20</p> <p>Definition: Pain for at least 3 months</p> <p>Severity: Chronic pain grade 1-4, median grade 3 Duration of symptoms: Median >12 months Presence of multimorbidities: Not stated/unclear</p>	<p>Quality of life at ≤ 3 months Pain at ≤ 3 months Physical function at ≤ 3 months</p>	<p>Study design classification: 6) No response criteria</p>

Study	Intervention and comparison	Population	Outcomes	Comments
Tugwell 2004 ²⁰⁵	<p>Topical non-steroidal anti-inflammatory drugs (n=311) Topical diclofenac solution (1.5% w/w) in 45.5% (w/w) dimethyl sulfoxide plus oral placebo capsules. 50 drops applied to the knee three times a day, with placebo capsules three times a day.</p> <p>Oral non-steroidal anti-inflammatory drugs (n=311) Placebo solution applied to the knee three times a day, with oral diclofenac 50mg capsules three times a day.</p> <p>Concomitant therapy: Concomitant medications, including NSAID, acetylsalicylic acid, paracetamol and other analgesic medications were prohibited during the study, but people were allowed to continue stable acetylsalicylic acid therapy (up to 325 mg/day) for cardiovascular prophylactic purposes.</p>	<p>Knee osteoarthritis Mean age (SD): 63.5 (10.0) years N = 622</p> <p>Definition: clinical and radiographic osteoarthritis</p> <p>Severity: Total x-ray score (0-27) mean (SD): 6.3 (3.7) Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p>	<p>Study design classification: 2) Excluding non-responders</p>
<p>Underwood 2008²⁰⁹</p> <p>Subsidiary paper: Underwood 2008²⁰⁸</p>	<p>Topical non-steroidal anti-inflammatory drugs (n=138) Ibuprofen gel applied for 24 months</p> <p>Oral non-steroidal anti-inflammatory drugs (n=144)</p>	<p>Knee osteoarthritis Median age (IQR): 60 (56-69) years N = 282</p>	<p>Quality of life at ≤3 months and >3 months Pain at ≤3 months and >3 months Physical function at ≤3 months and >3 months</p>	<p>Study design classification: 4) Unclear</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Ibuprofen up to a maximum of 1.2 grams per day for 24 months</p> <p>Concomitant therapy: No additional information</p>	<p>Definition: Clinical osteoarthritis</p> <p>Severity: Not stated</p> <p>Duration of symptoms: Not stated</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at >3 months</p>	

1 **1.1.5.2.4 Topical non-steroidal anti-inflammatory drugs compared to placebo for knee osteoarthritis**

2 **Table 22: Summary of studies included in the evidence review for topical non-steroidal anti-inflammatory drugs compared to placebo for**
3 **knee osteoarthritis**

Study	Intervention and comparison	Population	Outcomes	Comments
Baer 2005 ¹¹	<p>Topical non-steroidal anti-inflammatory drugs (n=107) Diclofenac solution 1.5% (w/w) in 45.5% (w/w) dimethylsulfoxide, propylene glycol, glycerine, ethanol and water. 40 drops four times daily for up to 6 weeks</p> <p>Placebo (n=109)</p> <p>Concomitant therapy: Paracetamol (up to four 325mg tablets per day) was permitted for residual knee or other body pain throughout the treatment period, but not during the washout period prior to baseline assessment or during the week prior to final assessment at</p>	<p>Knee osteoarthritis Mean age (SD): 64.8 (11.0) years N = 216</p> <p>Definition: Radiographic evidence of osteoarthritis</p> <p>Severity: Total X-ray score (0-27) mean (SD): 7.3 (5.2)</p> <p>Duration of symptoms: Not stated</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months</p> <p>Physical function at ≤3 months</p> <p>Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p> <p>ISRCTN53366886</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	week 6. Acetylsalicylic acid (no more than 325mg/day) was permitted for cardiovascular prophylaxis			
Baraf 2010 ¹⁵	<p>Topical non-steroidal anti-inflammatory drugs (n=208) Diclofenac sodium gel 4g per knee 4 times daily for 12 weeks</p> <p>Placebo (n=212)</p> <p>Concomitant therapy: Paracetamol (1-2 500mg tablets, every 4 hours as needed, maximum 4g/day) were allowed as rescue medication, but was to be withheld for 48 hours before each visit. Prohibitions included corticosteroids, nonstudy analgesics (except stable doses of aspirin \leq162mg/day started \geq30 days before randomisation), topical analgesics applied to the knee, and intra- or periarticular knee injections</p>	<p>Knee osteoarthritis Mean age (SD): 61.4 (10.9) years N = 420</p> <p>Definition: Clinical and radiographic osteoarthritis</p> <p>Severity: Kellgren Lawrence grade 1-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at \leq3 months Physical function at \leq3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at \leq3 months Serious adverse events 2: cardiovascular system adverse events at \leq3 months Serious adverse events 3: hepatorenal adverse events at \leq3 months Serious adverse events 4: central nervous system adverse events at \leq3 months</p>	Study design classification: 1) Including only responders
Barthel 2009 ¹⁶	<p>Topical non-steroidal anti-inflammatory drugs (n=254) Diclofenac gel 1% 4 grams applied 4 times daily for 12 weeks</p> <p>Placebo (n=238)</p>	<p>Knee osteoarthritis Mean age (SD): 59.5 (10.6) years N = 492</p> <p>Definition: Radiographic and clinical osteoarthritis</p>	<p>Pain at \leq3 months Physical function at \leq3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at \leq3 months</p>	Study design classification: 4) Unclear

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Concomitant therapy: Rescue medication (paracetamol 500mg tablets) were supplied by the investigator to be used as an adjunct and to treat other aches and pains experience by people during the trial, such as headache. Doses of 1 or 2 tablets were permitted to a maximum of 8 tablets (4g) per day, with ≥ 4 hours between doses. Rescue medication was not to be used for at least 24 hours before assessments</p>	<p>Severity: Kellgren Lawrence grade 1-3 Duration of symptoms: At least 3 months Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 2: cardiovascular adverse events at ≤ 3 months Serious adverse events 4: central nervous system adverse events at ≤ 3 months</p>	
Bhatia 2020 ²²	<p>Topical non-steroidal anti-inflammatory drugs (n=24) The gel was applied to the knee twice a day for 6 weeks.</p> <p>Placebo (n=12) Placebo gel</p> <p>Concomitant therapy: No further details</p>	<p>Knee osteoarthritis Age range: 23 to 75 years N = 37</p> <p>Definition: People with signs and symptoms of osteoarthritis of the knee</p> <p>Severity: Not stated/unclear Duration of symptoms: Not stated/unclear Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤ 3 months Physical function at ≤ 3 months Serious adverse event 1: gastrointestinal adverse events at ≤ 3 months</p>	Study design classification: 6) No response criteria
Bookman 2004 ³⁰	<p>Topical non-steroidal anti-inflammatory drugs (n=84) Diclofenac gel 1.5% (wt/wt) In a carrier containing dimethylsulfoxide (45.5% wt/wt),</p>	<p>Knee osteoarthritis Mean age (SD): 61.8 (11.5) years N = 248</p>	<p>Pain at ≤ 3 months Physical function at ≤ 3 months Serious adverse events 3: hepatorenal adverse events at ≤ 3 months</p>	Study design classification: 2) Excluding non-responders

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>propylene glycol, glycerine, ethanol and water for 4 weeks</p> <p>Placebo (n=164)</p> <p>Concomitant therapy: The use of acetylsalicylic acid (no more than 325mg/day) was permitted for cardiovascular prophylaxis.</p>	<p>Definition: Primary osteoarthritis verified radiologically</p> <p>Severity: Not stated</p> <p>Duration of symptoms: Not stated</p> <p>Presence of multimorbidities: Not stated/unclear</p>		
Conaghan 2013 ⁵³	<p>Oral non-steroidal anti-inflammatory drugs (n=235) Celecoxib 100mg twice a day for 12 weeks</p> <p>Topical non-steroidal anti-inflammatory drugs (n=463) Ketoprofen gel either 50mg or 100mg in 2.2 or 4.4 grams respectively applied twice a day for 12 weeks</p> <p>Oral placebo (n=228)</p> <p>Topical placebo (n=473) Ketoprofen gel vehicle without the ketoprofen</p> <p>Concomitant therapy: Paracetamol 500mg up to four times a day was permitted for intermittent pain treatment, although not within 24 hours of the next study visit or between</p>	<p>Knee osteoarthritis Mean age (range): 61.2 (24-90) years N = 1399</p> <p>Definition: Primary diagnosis meeting the American College of Rheumatology clinical classification. People aged 18-45 were permitted if they had radiological confirmation of osteoarthritis</p> <p>Severity: Functional class 1-3</p> <p>Duration of symptoms (mean [SD]): Not stated</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 2) Excluding non-responders</p> <p>When comparing to placebo, one the placebo of the same formulation was used (for example: oral non-steroidal anti-inflammatory drugs compared to oral placebo).</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	the baseline visits. People requiring ≥ 2 grams of paracetamol or other analgesic medication for longer than 3 consecutive days were considered treatment failures and withdrawn from the study.			
Dehghan 2020 ⁵⁹	<p>Topical non-steroidal anti-inflammatory drugs (n=49) Diclofenac 1% gel - one 60 gram tube. Gel was applied three times a day for 6 weeks applied over 3-5 minutes each time.</p> <p>Placebo (n=48)</p> <p>A third arm (n=48) was included in the study but not extracted in this review as it did not fulfil the inclusion criteria.</p> <p>Concomitant therapy: All people were given celecoxib 200mg capsules daily in addition to the topical gels</p>	<p>Knee osteoarthritis Age range: 45 to 75 years N = 145</p> <p>Definition: Primary osteoarthritis in at least one knee with orthopedic diagnosis based on radiological criteria in knee image, having experienced pain for at least 2 weeks before treatment and having age above 45 years.</p> <p>Severity: Not stated/unclear Duration of symptoms: Not stated/unclear Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤ 3 months Physical function at ≤ 3 months</p>	<p>Study design classification: 6) No response criteria</p>
Grace 1999 ⁹⁴	<p>Topical non-steroidal anti-inflammatory drugs (n=38) Diclofenac gel 2.5 grams for 2 weeks</p> <p>Placebo (n=36)</p> <p>Concomitant therapy:</p>	<p>Knee osteoarthritis Mean age (SD): 62.0 (13.0) years N = 74</p> <p>Definition: Symptomatic and radiologic osteoarthritis</p>	<p>Pain at ≤ 3 months Physical function at ≤ 3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤ 3 months</p>	<p>Study design classification: 1) Including only responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	People were allowed to maintain normal physical activities. Paracetamol was allowed as rescue medications (1000mg up to three times daily)	Severity: Functional class 1-4 Duration of symptoms (mean [SD]): 135.8 (163) months Presence of multimorbidities: Low comorbidity score	Serious adverse events 4: central nervous system adverse events at ≤3 months	
Kneer 2013 ¹¹²	<p>Topical non-steroidal anti-inflammatory drugs (n=667) Ketoprofen gel either 25, 50 or 100mg of ketoprofen in a Transfersome gel applied twice daily for 12 weeks</p> <p>Placebo (n=199)</p> <p>Concomitant therapy: Paracetamol, up to a maximum daily dose of 2g/day for up to 5 days during any 7-day period, were permitted for breakthrough pain or non-OA pain. Rescue medication use was not allowed within 48 hours before the study visits</p>	<p>Knee osteoarthritis Mean age (SD): 61.7 (9.3) years N = 866</p> <p>Definition: Clinical and radiographic osteoarthritis</p> <p>Severity: Kellgren Lawrence grade 2-3 Duration of symptoms: At least 6 months Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Physical function at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p> <p>Serious adverse events 3: hepatorenal adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	Study design classification: 1) Including only responders
Niethard 2005 ¹⁴⁶	<p>Topical non-steroidal anti-inflammatory drugs (n=117) Diclofenac diethylamine gel 1.16% 4 grams applied four times a day for 3 weeks</p> <p>Placebo (n=121)</p> <p>Concomitant therapy: People were permitted to use up to 4 tablets of rescue medication</p>	<p>Knee osteoarthritis Mean age (SD): 66 (9) years N = 238</p> <p>Definition: Clinically diagnosed osteoarthritis with radiographic evidence</p> <p>Severity: Not stated Duration of symptoms: At least 6 months</p>	<p>Pain at ≤3 months Physical function at ≤3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p> <p>Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	Study design classification: 2) Excluding non-responders

Study	Intervention and comparison	Population	Outcomes	Comments
	(paracetamol 500mg) per day for all pains they experienced regardless of origin	Presence of multimorbidities: Not stated/unclear		
Roth 2004 ¹⁶⁶	<p>Topical non-steroidal anti-inflammatory drugs (n=164) Diclofenac solution. 1.3mL applied to the affected knee 4 times daily for up to 12 weeks</p> <p>Placebo (n=162)</p> <p>Concomitant therapy: Rescue analgesia with paracetamol (up to four 325mg tablets per day) was permitted for residual knee or other body pain throughout the treatment period, except during the washout period before baseline and the 3 calendar days before the scheduled final assessment at week 12. Aspirin (no more than 325mg/day) was permitted for cardiovascular prophylaxis</p>	<p>Knee osteoarthritis Mean age (SD): 64.2 (10.6) years N = 326</p> <p>Definition: Symptomatic and radiological evidence of osteoarthritis</p> <p>Severity: Total radiographic score (0-27) (mean [SD]): 6.8 (3.7) Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months Serious adverse events 2: cardiovascular adverse events at ≤3 months</p>	Study design classification: 1) Including only responders
Rother 2007 ¹⁶⁸	<p>Oral non-steroidal anti-inflammatory drugs (n=132) Celecoxib 100mg twice a day for 6 weeks</p> <p>Topical non-steroidal anti-inflammatory drugs (n=138) 110mg epicutaneous ketoprofen in 4.8 grams Transfersome twice a day for 6 weeks</p>	<p>Knee osteoarthritis Mean age (SD): 62.8 (9.8) years N = 397</p> <p>Definition: Fulfilling clinical criteria for osteoarthritis</p> <p>Severity: Not stated</p>	<p>Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>Placebo (n=127)</p> <p>Concomitant therapy: People could take up to 2000mg paracetamol per day as rescue medication for knee pain for 3 days in any week, apart from the 48 hours preceding a study visit</p>	<p>Duration of symptoms: At least 6 months</p> <p>Presence of multimorbidities: Not stated/unclear</p>		
Rother 2013 ¹⁶⁷	<p>Topical non-steroidal anti-inflammatory drugs (n=274) Ketoprofen gel, 100mg in 4.4g transfersome gel (IDEA-033) applied twice daily for 12 weeks</p> <p>Placebo (n=281)</p> <p>Concomitant therapy: Rescue medication (500mg paracetamol, up to 4 times per day, total 2g) was permitted for the treatment of intermittent pain, but not within 24 hours of the next study visit or between B1 and B2. People who required ≥ 2g/day of rescue or other analgesic medication for >3 consecutive days were considered to be treatment failures and were withdrawn from the study</p>	<p>Knee osteoarthritis Mean age (SD): 62.2 (10.4) years N = 555</p> <p>Definition: Clinical osteoarthritis</p> <p>Severity: Functional class 1-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤ 3 months</p> <p>Physical function at ≤ 3 months</p> <p>Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤ 3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤ 3 months</p>	Study design classification: 1) Including only responders
Rovensky 2001 ¹⁶⁹	<p>Topical non-steroidal anti-inflammatory drugs (n=50)</p>	<p>Knee osteoarthritis Mean age (SD): 63.4 (8.3) years</p>	<p>Pain at ≤ 3 months</p>	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>5% ibuprofen cream applied 3 times daily for 1 week</p> <p>Placebo (n=50)</p> <p>Concomitant therapy: During the washout period, peripherally acting oral analgesics, such as paracetamol, were allowed as escape medication up to 2 days before the start of the study treatment</p>	<p>N = 100</p> <p>Definition: Primary osteoarthritis defined clinically and radiographically</p> <p>Severity: Kellgren Lawrence grade 2-3</p> <p>Duration of symptoms: At least 1 month</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>Serious adverse events 3: hepatorenal adverse events at ≤3 months</p>	
<p>Simon 2009¹⁹⁰ Subsidiary paper: Roth 2011¹⁶⁵</p>	<p>Oral non-steroidal anti-inflammatory drugs (n=151) Diclofenac slow release 100mg once a day for 12 weeks</p> <p>Topical non-steroidal anti-inflammatory drugs (n=154) Topical diclofenac solution (1.5% w/w diclofenac sodium in a vehicle containing 45.5% w/w dimethyl sulfoxide and other excipients) applied four times daily for 12 weeks</p> <p>Placebo (n=318)</p> <p>A fourth group (n=152) was reported which was not included in the analysis as it was excluded in the protocol</p>	<p>Knee osteoarthritis Mean age (SD): 61.6 (9.9) years N = 775</p> <p>Definition: Primary osteoarthritis based on standard radiological criteria and pain</p> <p>Severity (mean radiographic score [SD]): 16.5 (3.1)</p> <p>Duration of symptoms: Not stated</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months</p> <p>Physical function at ≤3 months</p> <p>Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>(combination topical and oral NSAID).</p> <p>Concomitant therapy: Continuation of stable treatment with glucosamine, chondroitin, anti-depressants or a proton pump inhibitor (previous 90 days), or low dose (≤ 325mg/day) acetylsalicylic acid (previous 30 days); paracetamol was provided and permitted (up to four 325mg caplets per day) except during the 3 days before each efficacy assessment. A person with a gastrointestinal adverse event was allowed to start a proton pump inhibitor.</p>			
Trnavsky 2004 ²⁰²	<p>Topical non-steroidal anti-inflammatory drugs (n=25) Ibuprofen cream 5%, 1cm cream three times daily for 8 days</p> <p>Placebo (n=25)</p> <p>Concomitant therapy: It was assured that people received any medically necessary treatment (e.g. antihypertensives). During the washout period, peripherally-acting oral analgesics such as paracetamol were allowed as</p>	<p>Knee osteoarthritis Mean age (SD): 67.0 (7.1) years N = 50</p> <p>Definition: Radiographical and clinical osteoarthritis</p> <p>Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤ 3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤ 3 months Serious adverse events 2: cardiovascular adverse events at ≤ 3 months Serious adverse events 3: hepatorenal adverse events at ≤ 3 months Serious adverse events 4: central nervous system adverse events at ≤ 3 months</p>	<p>Study design classification: 4) Unclear</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	rescue medication up to 2 days before the start of the study treatment			
Wadsworth 2016 ²¹²	<p>Topical non-steroidal anti-inflammatory drugs (n=130) Diclofenac 1.5% gel, 2mL applied twice a day for 4 weeks</p> <p>Placebo (n=129)</p> <p>Concomitant therapy: People were allowed paracetamol as rescue medication on an as needed basis (up to 1950mg/day) except for 3 days prior to a clinic visit</p>	<p>Knee osteoarthritis Mean age (SD): 61.1 (9.2) years N = 259</p> <p>Definition: Radiographically confirmed primary osteoarthritis</p> <p>Severity: Kellgren Lawrence grade 2-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Physical function at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p> <p>NCT01119898</p>

1 **1.1.5.2.5 Topical non-steroidal anti-inflammatory drugs compared to placebo for hand osteoarthritis**

2 **Table 23: Summary of studies included in the evidence review for topical non-steroidal anti-inflammatory drugs compared to placebo for**
3 **hand osteoarthritis**

Study	Intervention and comparison	Population	Outcomes	Comments
Altman 2009 ³	<p>Topical non-steroidal anti-inflammatory drugs (n=198) Diclofenac sodium gel 2 grams 4 times daily for 8 weeks</p> <p>Placebo (n=187)</p> <p>Concomitant therapy:</p>	<p>Hand osteoarthritis Mean age (SD): 64.1 (10.0) years N = 385</p> <p>Definition: Primary osteoarthritis confirmed with imaging</p>	<p>Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months</p>	<p>Study design classification: 1) Including only responders</p> <p>NCT00171665</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	Rescue medication (paracetamol 500mg tablet) was allowed to a maximum dose of 4g daily during washout and throughout double-blind treatment, excluding the 36 hours before each evaluation. The same rescue medication was to be used for any other pain experienced during the trial, such as headache.	Severity: Kellgren Lawrence grade 1-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Serious adverse events 4: central nervous system adverse events at ≤3 months	

1 **1.1.5.2.6 Topical non-steroidal anti-inflammatory drugs compared to capsaicin**

2 **Table 24: Summary of studies included in the evidence review for topical non-steroidal anti-inflammatory drugs compared to capsaicin**

Study	Intervention and comparison	Population	Outcomes	Comments
Persson 2021 ¹⁵⁵	<p>Topical non-steroidal anti-inflammatory drugs (n= 22) 5% w/w ibuprofen gel. Applied four times daily to the painful knee(s).</p> <p>Capsaicin(n=22) 0.025% w/w capsaicin cream applied four times daily to the painful knee(s).</p> <p>Concomitant therapy: People continued to use their regular medications, including oral analgesics, throughout the trial provided the frequency/dose had remained stable for 3 months. Non-permitted concomitant therapies</p>	<p>Knee osteoarthritis Mean age (SD): 67.0 (9.3) years N = 22</p> <p>Definition: Chronic knee pain and radiographic knee osteoarthritis (i.e. definite narrowing and definite osteophyte in the tibiofemoral and/or patellofemoral compartments as per Nottingham line drawing atlas scoring.</p> <p>Severity: Total NLDA score (median [IQR]) = 13 (9 to 18) Duration of symptoms (mean [SD]): 7.6 (7.6) years</p>	Pain at ≤3 months	<p>Study design classification: 5) All treatment naïve</p> <p>Crossover study (washout: 4 weeks)</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	were additional topical analgesics for the affected knee, regular oral NSAIDs, joint infection or surgery.	Presence of multimorbidities: Low comorbidity score- 9 had increased scores for HADS anxiety subscale, 4 had increased scores for HADS depression subscale, 2 met the criteria for fibromyalgia		

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2 **1.1.5.3 Topical (systemic) (including comparisons to oral formulations)**3 **1.1.5.3.1 Transdermal opioids compared to oral strong opioids**4 **Table 25: Summary of studies included in the evidence review for transdermal opioids compared to oral strong opioids**

Study	Intervention and comparison	Population	Outcomes	Comments
Karlsson 2009 ¹⁰⁵	<p>Transdermal opioids (n=69) 7 day buprenorphine patches including 5, 10, 15, and 20 micrograms/hour with up to 2 patches being able to be worn at the same time for 12 weeks</p> <p>Oral strong opioids (n=66) Tramadol twice daily, the possible doses were 150, 200, 300 and 400mg/day for 12 weeks</p> <p>Concomitant therapy: Paracetamol could be used for rescue medication</p>	<p>Mixed osteoarthritis (knee and/or hip) Mean age (SD): 64.3 (10.3) years N = 135</p> <p>Definition: Clinical diagnosis based on the American College of Rheumatology and radiographic criteria</p> <p>Severity: Not stated Duration of symptoms: Not stated</p> <p>Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months</p> <p>Serious adverse events 2: cardiovascular adverse events at ≤3 months</p>	<p>Study design classification: 3) Selection of specific population</p>

1 **1.1.5.3.2 Transdermal opioids compared to placebo**

2 **Table 26: Summary of studies included in the evidence review for transdermal opioids compared to placebo**

Study	Intervention and comparison	Population	Outcomes	Comments
Breivik 2010 ³³	<p>Transdermal opioids (n=100) Buprenorphine patch, initial dose 5 microgram/hour</p> <p>Placebo (n=99)</p> <p>Concomitant therapy: Continuation of their current NSAID or coxib analgesic regimen at a stable frequency and dose. Rescue analgesia was provided as paracetamol tablets 0.5g for breakthrough osteoarthritis pain until the end of the double blind phase, up to 4g allowed daily</p>	<p>Mixed osteoarthritis (knee and/or hip) Mean age (SD): 62.9 (9.5) years N = 199</p> <p>Definition: Clinical and radiographic osteoarthritis</p> <p>Severity: Kellgren Lawrence grade 2-4 Duration of symptoms: At least 1 year Presence of multimorbidities: Not stated/unclear</p>	<p>Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months</p>	<p>Study design classification: 3) Selection of specific population</p>
Langford 2006 ¹²⁰	<p>Transdermal opioids (n=216) Fentanyl patch. 1 week run in with a dosage of 25 micrograms/hour replaced every 72 hours. Increased to a maximum of 100 micrograms/hour for 6 weeks</p> <p>Placebo (n=200)</p> <p>Concomitant therapy: People were asked to continue to receive stable doses of antiinflammatory agents (steroids or NSAIDs, including</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (range): 66 (40-90) years N = 416</p> <p>Definition: Clinical and radiographic osteoarthritis</p> <p>Severity: Not stated Duration of symptoms: At least 3 months Presence of multimorbidities: Not stated/unclear</p>	<p>Quality of life at ≤3 months Pain at ≤3 months Physical function at ≤3 months</p>	<p>Study design classification: 2) Excluding non-responders</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	COX-2 inhibitors) that were prescribed before the study, but all weak opioids were stopped. People could also take up to 4 grams of paracetamol per day (but not combination preparations of paracetamol and weak opioids). People were encouraged to take metoclopramide (supplied as 10mg tablets) immediately if they experienced any nausea or vomiting. They were also encouraged to take a laxative if they had constipation.			
Munera 2010 ¹⁴³	<p>Transdermal opioids (n=152) Buprenorphine transdermal system 5 microgram/hour uptitrated to 10-20 microgram/hour as needed for 4 weeks</p> <p>Placebo (n=163)</p> <p>Concomitant therapy: Before the study started there was a 1 week run-in period where previous medication was discontinued and people were maintained on 1600mg/day ibuprofen (400mg four times a day). If they had an average pain intensity of 7 or greater then they were permitted to enter the study. On entry to the study the ibuprofen was</p>	<p>Mixed osteoarthritis (knee or hip) Mean age (SD): 61.0 (12.7) years N = 315</p> <p>Definition: Radiological evidence of osteoarthritis</p> <p>Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear</p>	Pain at ≤3 months	Study design classification: 3) Selection of specific population

Study	Intervention and comparison	Population	Outcomes	Comments
	discontinued. No rescue medication was allowed during this period			

1 See [Evidence review I OTT appendices A-D](#) for full evidence tables.

2 **1.1.5.4 Summary matrices**

3 **Table 27: Summary matrix for pharmacological agents compared to placebo for quality of life, pain, physical function, psychological**
4 **distress and osteoarthritis flares**

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Intervention (versus placebo)	Time period	Quality of life	Pain	Physical function	Psychological distress	Osteoarthritis flares
Paracetamol	<3 months	1 GRADE Outcome (1 study) N = 542 Very Low	1 GRADE Outcome (6 studies) N = 3659 Low	1 GRADE Outcome (5 studies) N = 2537 Low	No evidence identified.	No evidence identified
	≥3 months	No evidence identified	1 GRADE Outcome (1 study) N = 212 Low	1 GRADE Outcome (1 study) N = 212 Very Low	No evidence identified	No evidence identified
NSAIDs	<3 months	10 GRADE Outcomes (3 studies) N = 1034 Low-Very Low	2 GRADE Outcomes (56 studies) N = 25065 Very Low	2 GRADE Outcomes (32 studies) N = 15518 Low	No evidence identified	No evidence identified
	≥3 months	No evidence identified	1 GRADE Outcome (1 study) N = 631 High	No evidence identified	No evidence identified	No evidence identified
NSAIDs and gastroprotection	<3 months	No evidence identified	1 GRADE Outcome (1 study) N = 418 Very Low	No evidence identified	No evidence identified	No evidence identified
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Weak opioids	<3 months	No evidence identified	1 GRADE Outcome (1 study) N = 66 Very Low	1 GRADE Outcome (1 study) N = 66 Very Low	No evidence identified	No evidence identified
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Strong opioids	<3 months	8 GRADE Outcomes (7 studies) N = 4522	2 GRADE Outcomes (16 studies)	2 GRADE Outcomes (8 studies)	1 GRADE Outcome (1 study)	No evidence identified

		Low-Very Low	N = 6457 Very Low	N = 3226 Low-Very Low	N = 107 Low	
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Anti-epileptic drugs	<3 months	No evidence identified	1 GRADE Outcome (1 study) N = 44 Low	1 GRADE Outcome (1 study) N = 44 Low	1 GRADE Outcome (1 study) N = 44 Low	No evidence identified
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Antidepressant drugs	<3 months	1 GRADE Outcome (4 studies) N = 1020 Moderate-Very Low	1 GRADE Outcome (7 studies) N = 1955 Moderate	1 GRADE Outcome (5 studies) N = 1510 Moderate	2 GRADE Outcomes (2 studies) N = 216 Moderate-Very Low	No evidence identified
	≥3 months	No evidence identified	1 GRADE Outcome (1 study) N = 288 Low	1 GRADE Outcome (1 study) N = 288 Low	1 GRADE Outcome (1 study) N = 288 Moderate	No evidence identified
Glucosamine	<3 months	No evidence identified	2 GRADE Outcomes (9 studies) N = 888 Low-Very Low	2 GRADE Outcomes (6 studies) N = 669 Low	No evidence identified	No evidence identified
	≥3 months	3 GRADE Outcomes (2 studies) N = 440 Low-Very Low	2 GRADE Outcomes (10 studies) N = 2115 Moderate	2 GRADE Outcomes (9 studies) N = 2043 Moderate-Low	No evidence identified	1 GRADE Outcome (1 study) N = 137 Low

Capsaicin cream - Knee	<3 months	No evidence identified	1 GRADE Outcome (1 study) N = 198 Moderate	1 GRADE Outcome (1 study) N = 198 Low	No evidence identified	No evidence identified
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Capsaicin cream - Hand	<3 months	No evidence identified	1 GRADE Outcome (1 study) N = 59 Very Low	No evidence identified	No evidence identified	No evidence identified
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Topical NSAIDs - Knee	<3 months	No evidence identified	2 GRADE Outcomes (17 studies) N = 5593 Moderate-Very Low	2 GRADE Outcomes (12 studies) N = 4374 Moderate-Low	No evidence identified	No evidence identified
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Topical NSAIDs - Hand	<3 months	No evidence identified	1 GRADE Outcome (1 study) N = 385 Moderate	1 GRADE Outcome (1 study) N = 385 Moderate	No evidence identified	No evidence identified
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Rubefaciants	<3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Local anaesthetic	<3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Transdermal opioids	<3 months	8 GRADE Outcomes (1 study) N = 399 Very Low	1 GRADE Outcome (2 studies) N = 710 Very Low	1 GRADE Outcome (1 study) N = 399 Low	No evidence identified	No evidence identified
	≥3 months	No evidence identified	1 GRADE Outcome (1 study) N = 194 Low	1 GRADE Outcome (1 study) N = 190 Low	No evidence identified	No evidence identified

1

1 **Table 28: Summary matrix for pharmacological agents compared to placebo for serious adverse events**

Intervention (versus placebo)	Time period	Serious adverse events 1A: Gastrointestinal (bleeding or perforation) events	Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) events	Serious adverse events 2: Cardiovascular events	Serious adverse events 3: Hepatorenal events	Serious adverse events 4: Central nervous system events
Paracetamol	<3 months	1 GRADE Outcome (1 study) N = 303 Moderate	1 GRADE Outcome (4 studies) N = 2758 Low	1 GRADE Outcome (3 studies) N = 1602 Low	1 GRADE Outcome (3 studies) N = 1732 Moderate	1 GRADE Outcome (6 studies) N = 4117 Very Low
	≥3 months	No evidence identified	No evidence identified	1 GRADE Outcome (1 study) N = 212 Very Low	1 GRADE Outcome (1 study) N = 212 Low	No evidence identified
NSAIDs	<3 months	1 GRADE Outcome (19 studies) N = 9096 Very Low	1 GRADE Outcome (47 studies) N = 22694 Very Low	1 GRADE Outcome (27 studies) N = 14246 Very Low	1 GRADE Outcome (12 studies) N = 5773 Very Low	1 GRADE Outcome (39 studies) N = 18239 Low
	≥3 months	No evidence identified	1 GRADE Outcome (1 study) N = 89 Very Low	1 GRADE Outcome (2 studies) N = 1136 Low	1 GRADE Outcome (1 study) N = 89 Very Low	No evidence identified
NSAIDs and gastroprotection	<3 months	1 GRADE Outcome (1 study) N = 418 Very Low	1 GRADE Outcome (1 study) N = 736 Low	1 GRADE Outcome (1 study) N = 736 Low	1 GRADE Outcome (1 study) N = 418 Very Low	No evidence identified
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Weak opioids	<3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Strong opioids	<3 months	No evidence identified	1 GRADE Outcome (3 studies) N = 2163 Very Low	1 GRADE Outcome (2 studies) N = 1998 Very Low	No evidence identified	1 GRADE Outcome (3 studies) N = 2163 Low
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Anti-epileptic drugs	<3 months	No evidence identified	1 GRADE Outcome (1 study) N = 44 Very Low	1 GRADE Outcome (1 study) N = 44 Very Low	No evidence identified	No evidence identified
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Antidepressant drugs	<3 months	No evidence identified	1 GRADE Outcome (3 studies) N = 823 Very Low	1 GRADE Outcome (5 studies) N = 1378 Very Low	1 GRADE Outcome (3 studies) N = 981 Very Low	1 GRADE Outcome (3 studies) N = 981 Very Low
	≥3 months	No evidence identified	1 GRADE Outcome (1 study) N = 90 Very Low	No evidence identified	No evidence identified	1 GRADE Outcome (1 study) N = 90 Very Low
Glucosamine	<3 months	No evidence identified	1 GRADE Outcome (4 studies) N = 464 Very Low	1 GRADE Outcome (2 studies) N = 287 Very Low	No evidence identified	1 GRADE Outcome (4 studies) N = 367 Very Low

	≥3 months	No evidence identified	1 GRADE Outcome (1 study) N = 90 Very Low	1 GRADE Outcome (4 studies) N = 1345 Very Low	1 GRADE Outcome (1 study) N = 211 Very Low	1 GRADE Outcome (1 study) N = 90 Very Low
Capsaicin cream - Knee	<3 months	No evidence identified	1 GRADE Outcome (1 study) N = 198 Low	1 GRADE Outcome (1 study) N = 198 Low	1 GRADE Outcome (1 study) N = 198 Low	1 GRADE Outcome (1 study) N = 198 Low
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Capsaicin cream - Hand	<3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Topical NSAIDs - Knee	<3 months	1 GRADE Outcome (3 studies) N = 1014 Very Low	1 GRADE Outcome (9 studies) N = 3895 Very Low	1 GRADE Outcome (7 studies) N = 3644 Very Low	1 GRADE Outcome (4 studies) N = 1247 Very Low	1 GRADE Outcome (8 studies) N = 3340 Very Low
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Topical NSAIDs - Hand	<3 months	No evidence identified	1 GRADE Outcome (1 study) N = 385 Very Low	No evidence identified	No evidence identified	1 GRADE Outcome (1 study) N = 385 Very Low
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

Rubefaciants	<3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Local anaesthetic	<3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Transdermal opioids	<3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	≥3 months	No evidence identified	1 GRADE Outcome (1 study) N = 199 Low	No evidence identified	No evidence identified	1 GRADE Outcome (1 study) N = 199 Low

1 **Table 29: Summary matrix for pharmacological agents compared to other pharmacological agents for quality of life, pain, physical**
 2 **function, psychological distress and osteoarthritis flares**
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Intervention 1 (versus intervention 2)	Time period	Quality of life	Pain	Physical function	Psychological distress	Osteoarthritis flares
NSAIDs compared to paracetamol	<3 months	1 GRADE Outcome (1 study) N=104 Very Low	2 GRADE Outcomes (11 studies) N= 3501 Moderate-Very Low	2 GRADE Outcomes (8 studies) N = 2004 Low	No evidence identified	No evidence identified
	≥3 months	No evidence identified	1 GRADE Outcome (1 study) N= 51 Very Low	No evidence identified	No evidence identified	No evidence identified
NSAIDs and gastroprotection compared to paracetamol	<3 months	1 GRADE Outcome (1 study) N = 436 Very Low	1 GRADE Outcome (1 study) N = 436 Low	No evidence identified	No evidence identified	No evidence identified
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
NSAIDs and gastroprotection compared to NSAIDs	<3 months	No evidence identified	1 GRADE Outcome (1 study) N = 481 Low	No evidence identified	No evidence identified	No evidence identified
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Strong opioids compared to NSAIDs	<3 months	2 GRADE Outcomes (1 study) N = 801 Low-Very Low	2 GRADE Outcomes (3 studies) N = 1116 Low-Very Low	1 GRADE Outcome (2 studies) N = 898 Very Low	No evidence identified	No evidence identified
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Anti-epileptic drugs compared to paracetamol	<3 months	No evidence identified	1 GRADE Outcome (1 study) N = 100 Low	1 GRADE Outcome (1 study) N = 100 Low	No evidence identified	No evidence identified

	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Anti-epileptic drugs compared to antidepressant drugs	<3 months	No evidence identified	2 GRADE Outcomes (2 studies) N = 143 Low-Very low	2 GRADE Outcomes (2 studies) N = 143 Low-Very low	2 GRADE Outcomes (1 study) N = 43 Low	No evidence identified
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Antidepressant drugs compared to paracetamol	<3 months	No evidence identified	1 GRADE Outcome (1 study) N = 100 Low	1 GRADE Outcome (1 study) N = 100 Low	No evidence identified	No evidence identified
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Glucosamine compared to paracetamol	<3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	≥3 months	No evidence identified	1 GRADE Outcome (1 study) N = 214 Low	1 GRADE Outcome (1 study) N = 214 Low	No evidence identified	No evidence identified
Glucosamine compared to NSAIDs	<3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	≥3 months	No evidence identified	1 GRADE Outcome (2 studies) N = 855 Very Low	1 GRADE Outcome (2 studies) N = 855 Low	No evidence identified	No evidence identified
Topical NSAIDs compared to oral NSAIDs	<3 months	2 GRADE Outcomes (2 studies) N = 301 Moderate	1 GRADE Outcome (6 studies) N = 2064 Moderate	1 GRADE Outcome (5 studies) N = 1368 Low	No evidence identified	No evidence identified
	≥3 months	2 GRADE Outcomes (1 study) N = 282 Low-Very Low	1 GRADE Outcome (1 study) N = 282 Low	1 GRADE Outcome (1 study) N = 282 Low	No evidence identified	No evidence identified

Topical NSAIDs compared to capsaicin	<3 months	No evidence identified	1 GRADE Outcome (1 study) N = 44 Low	No evidence identified	No evidence identified	No evidence identified
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Transdermal opioids compared to oral strong opioids	<3 months	No evidence identified	1 GRADE Outcome (1 study) N = 134 Low	No evidence identified	No evidence identified	No evidence identified
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

1 **Table 30: Summary matrix for pharmacological agents compared to other pharmacological agents for serious adverse events**

Intervention 1 (versus intervention 2)	Time period	Serious adverse events 1A: Gastrointestinal (bleeding or perforation) events	Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) events	Serious adverse events 2: Cardiovascular events	Serious adverse events 3: Hepatorenal events	Serious adverse events 4: Central nervous system events
NSAIDs compared to paracetamol	<3 months	1 GRADE Outcome (1 study) N = 310 Very Low	1 GRADE Outcome (6 studies) N = 2341 Low	1 GRADE Outcome (6 studies) N = 1802 Very Low	1 GRADE Outcome (3 studies) N = 574 Very Low	1 GRADE Outcome (6 studies) N = 2965 Very Low
	≥3 months	No evidence identified	1 GRADE Outcome (1 study) N = 178 Very Low	1 GRADE Outcome (2 studies) N = 749 Very Low	1 GRADE Outcome (1 study) N = 178 Very Low	1 GRADE Outcome (1 study) N = 178 Very Low
NSAIDs and gastroprotection compared to paracetamol	<3 months	1 GRADE Outcome (1 study) N = 436 Very Low	No evidence identified	1 GRADE Outcome (1 study) N = 436 Very Low	1 GRADE Outcome (1 study) N = 436 Very Low	1 GRADE Outcome (1 study) N = 436 Very Low
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
NSAIDs and gastroprotection compared to NSAIDs	<3 months	1 GRADE Outcome (4 studies) N = 2307 Very Low	1 GRADE Outcome (1 study) N = 978 Low	1 GRADE Outcome (2 studies) N = 2023 Moderate	1 GRADE Outcome (1 study) N = 481 Very Low	1 GRADE Outcome (1 study) N = 361 Low
	≥3 months	1 GRADE Outcome (1 study) N = 4484 Low	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Strong opioids compared to NSAIDs	<3 months	No evidence identified	No evidence identified	No evidence identified	1 GRADE Outcome (1 study) N = 218 Very Low	1 GRADE Outcome (1 study) N = 120 Very Low
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

Anti-epileptic drugs compared to paracetamol	<3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 GRADE Outcome (1 study) N = 100 Very Low
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Anti-epileptic drugs compared to antidepressant drugs	<3 months	No evidence identified	1 GRADE Outcome (1 study) N = 43 Low	1 GRADE Outcome (1 study) N = 43 Very Low	No evidence identified	1 GRADE Outcome (1 study) N = 100 Very Low
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Anti-depressant drugs compared to paracetamol	<3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	1 GRADE Outcome (1 study) N = 100 Very Low
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Glucosamine compared to paracetamol	<3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	≥3 months	No evidence identified	No evidence identified	1 GRADE Outcome (1 study) N = 214 Very Low	1 GRADE Outcome (1 study) N = 214 Low	No evidence identified
Glucosamine compared to NSAIDs	<3 months	1 GRADE Outcome (1 study) N = 199 Very Low	1 GRADE Outcome (4 studies) N = 455 Very Low	1 GRADE Outcome (2 studies) N = 218 Very Low	1 GRADE Outcome (1 study) N = 178 Low	1 GRADE Outcome (3 studies) N = 256 Very Low
	≥3 months	No evidence identified	No evidence identified	1 GRADE Outcome (1 study) N = 635 Low	1 GRADE Outcome (1 study) N = 213 Very Low	No evidence identified

Topical NSAIDs compared to oral NSAIDs	<3 months	1 GRADE Outcome (1 study) N = 305 Very Low	1 GRADE Outcome (4 studies) N = 2122 Very Low	1 GRADE Outcome (2 studies) N = 1170 Very Low	No evidence identified	1 GRADE Outcome (3 studies) N = 1440 Very Low
	≥3 months	No evidence identified	1 GRADE Outcome (1 study) N = 282 Low	No evidence identified	No evidence identified	No evidence identified
Topical NSAIDs compared to capsaicin	<3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified
Transdermal opioids compared to oral strong opioids	<3 months	No evidence identified	No evidence identified	1 GRADE Outcome (1 study) N = 134 Very Low	No evidence identified	No evidence identified
	≥3 months	No evidence identified	No evidence identified	No evidence identified	No evidence identified	No evidence identified

1 **1.1.6 Summary of the effectiveness evidence**

2 **1.1.6.1 Oral**

3 **1.1.6.1.1 Paracetamol compared to placebo**

4 **Table 31: Clinical evidence summary: paracetamol compared to placebo**

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with paracetamol	
Quality of life (Nottingham health profile energy subscale, 0-100, high is good, change score) at ≤3 months	542 (1 RCT)	⊕⊕○○ LOW _a	-	The mean quality of life was 1.72	MD 0.28 higher (0.07 higher to 0.49 higher)	MID = 0.5 SD (SMD)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with paracetamol	
	follow up: 12 weeks					
Pain (WOMAC, Multidimensional Health Assessment Questionnaire [different scale ranges], high is poor, change scores) at ≤3 months	3659 (6 RCTs) follow up: mean 12 weeks	⊕⊕○○ LOW _a	-	-	SMD 0.05 SD lower (0.11 lower to 0.02 higher)	MID = 0.5 SD (SMD)
Pain (WOMAC, 0-20, high is poor, change score) at >3 months	212 (1 RCT) follow up: 26 weeks	⊕⊕○○ LOW _a	-	The mean pain was -1.8	MD 0.6 lower (1.56 lower to 0.36 higher)	MID = 0.5 SD (SMD)
Physical function (WOMAC [different scale ranges], high is poor, change scores) at ≤3 months	2537 (5 RCTs) follow up: mean 12 weeks	⊕⊕○○ LOW _a	-	-	SMD 0.09 SD lower (0.17 lower to 0.01 lower)	MID = 0.5 SD (SMD)
Physical function (WOMAC, 0-68, high is poor, change score) at >3 months	212 (1 RCT) follow up: 26 weeks	⊕○○○ VERY LOW _{a,b}	-	The mean physical function was -5.5	MD 3.2 lower (6.12 lower to 0.28 lower)	MID = 0.5 SD (SMD)
Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months	303 (1 RCT) follow up: 2 weeks	⊕⊕⊕○ MODERATE _a	RD 0.00 (-0.01 to 0.01)	0 per 1,000	0 fewer per 1,000 (10 fewer to 10 more) _c	Sample size used to determine precision: 75-150 = serious imprecision, <75 = very serious imprecision.
				95 per 1,000	15 more per 1,000 (8 fewer to 48 more)	
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months	2758 (4 RCTs) follow up: mean 7 weeks	⊕⊕○○ LOW _{a,b}	RR 1.16 (0.92 to 1.46)	95 per 1,000	15 more per 1,000 (8 fewer to 48 more)	MID (precision) = RR 0.8-1.25.

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with paracetamol	
Serious adverse events 2: Cardiovascular adverse events at ≤3 months	1552 (3 RCTs) follow up: mean 9 weeks	⊕⊕○○ LOW ^{a,b}	RR 1.00 (0.09 to 1.03)	9 per 1,000	0 fewer per 1,000 (8 fewer to 0 fewer) ^c	MID (precision) = RR 0.8-1.25.
Serious adverse events 2: Cardiovascular adverse events at >3 months	212 (1 RCT) follow up: 26 weeks	⊕○○○ VERY LOW ^{a,b}	RR 0.96 (0.06 to 15.19)	10 per 1,000	0 fewer per 1,000 (9 fewer to 142 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 3: Hepatorenal adverse events at ≤3 months	1732 (3 RCTs) follow up: mean 12 weeks	⊕⊕⊕○ MODERATE ^a	RR 6.10 (2.35 to 15.84)	7 per 1,000	36 more per 1,000 (9 more to 104 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 3: Hepatorenal adverse events at >3 months	212 (1 RCT) follow up: 26 weeks	⊕⊕○○ LOW ^a	RR 3.37 (1.42 to 8.02)	58 per 1,000	137 more per 1,000 (24 more to 407 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 4: Central nervous system adverse events at ≤3 months	4007 (6 RCTs) follow up: mean 8 weeks	⊕○○○ VERY LOW ^{a,b,d}	RR 0.91 (0.59 to 1.42)	58 per 1,000	5 fewer per 1,000 (24 fewer to 24 more)	MID (precision) = RR 0.8-1.25.

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study
d. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

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1.1.6.1.2 Oral non-steroidal anti-inflammatory drugs compared to paracetamol

Table 32: Clinical evidence summary: oral non-steroidal anti-inflammatory drugs compared to paracetamol

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with paracetamol	Risk difference with oral non-steroidal anti-inflammatory drugs	
Quality of life (EQ-5D, 0-1, high is good, final value) at ≤3 months	104 (1 RCT) follow up: 12 weeks	⊕○○○ VERY LOW _{a,b}	-	The mean quality of life was 0.8	MD 0 (0.06 lower to 0.06 higher)	MID = 0.03 (pragmatic value agreed between the NGC and NICE)
Pain (WOMAC, VAS, MDHAQ, Hospital assessment questionnaire pain score [different scale ranges], high is poor, change scores) at ≤3 months	3367 (9 RCTs) follow up: mean 7 weeks	⊕⊕⊕○ MODERATE _a	-	-	SMD 0.15 SD lower (0.22 lower to 0.09 lower)	MID = 0.5 SD (SMD)
Pain (KOOS, VAS, 0-100, high is poor, final values) at ≤3 months	134 (2 RCTs) follow up: mean 7 weeks	⊕○○○ VERY LOW _{a,b}	-	The mean pain was 26.7	MD 3.47 higher (3.46 lower to 10.41 higher)	MID = 8.4 (0.5 x median baseline control group SD)
Pain (VAS, 0-10, high is poor, change score) at >3 months	51 (1 RCT) follow up: 24 months	⊕○○○ VERY LOW _{a,b}	-	The mean pain was -1	MD 1 lower (2.52 lower to 0.52 higher)	MID = 0.5 SD (SMD)
Physical function (WOMAC, Hospital assessment questionnaire disability score [different scale ranges], high is poor, change scores) at ≤3 months	1895 (7 RCTs) follow up: mean 7 weeks	⊕⊕○○ LOW _a	-	-	SMD 0.23 SD lower (0.32 lower to 0.13 lower)	MID = 0.5 SD (SMD)
Physical function (KOOS, 0-100, high is poor, final value) at ≤3 months	104 (1 RCT)	⊕○○○ VERY LOW _{a,b}	-	The mean physical function was 28.4	MD 3 higher (4.63 lower to 10.63 higher)	MID = 0.5 SD (SMD)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with paracetamol	Risk difference with oral non-steroidal anti-inflammatory drugs	
	follow up: 12 weeks					
Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months	310 (1 RCT) follow up: 2 weeks	⊕○○○ VERY LOW _{a,b}	Peto OR 6.86 (0.71 to 66.61)	0 per 1,000	20 more per 1,000 (10 fewer to 40 more) _c	MID (precision) = Peto OR 0.8-1.25.
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months	2341 (6 RCTs) follow up: mean 5 weeks	⊕⊕○○ LOW _{a,b}	RR 1.26 (1.04 to 1.58)	118 per 1,000	31 more per 1,000 (5 more to 68 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at >3 months	178 (1 RCT) follow up: 24 months	⊕○○○ VERY LOW _{a,b,d}	RR 2.77 (1.15 to 6.70)	68 per 1,000	120 more per 1,000 (10 more to 388 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 2: Cardiovascular adverse events at ≤3 months	1611 (5 RCTs) follow up: mean 5 weeks	⊕○○○ VERY LOW _{a,b,e}	RR 1.1 (0.6 to 2.0)	19 per 1,000	10 more per 1,000 (10 fewer to 20 more) _c	MID (precision) = RR 0.8-1.25.
Serious adverse events 2: Cardiovascular adverse events at >3 months	749 (2 RCTs) follow up: mean 18 months	⊕○○○ VERY LOW _{a,b,f}	RR 1.74 (0.32 to 9.45)	22 per 1,000	16 more per 1,000 (15 fewer to 186 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 3: Hepatorenal adverse events at ≤3 months	574 (3 RCTs) follow up: mean 4 weeks	⊕○○○ VERY LOW _{a,b,e}	Peto OR 0.40 (0.04 to 4.04)	12 per 1,000	0 fewer per 1,000 (20 fewer to 10 more) _c	MID (precision) = Peto OR 0.8-1.25.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with paracetamol	Risk difference with oral non-steroidal anti-inflammatory drugs	
Serious adverse events 3: Hepatorenal adverse events at >3 months	178 (1 RCT) follow up: 24 months	⊕○○○ VERY LOW a,b,d	Peto OR 7.23 (0.14 to 364.29)	0 per 1,000	10 more per 1,000 (20 fewer to 40 more) ^c	MID (precision) = Peto OR 0.8-1.25.
Serious adverse events 4: Central nervous system adverse events at ≤3 months	2965 (6 RCTs) follow up: mean 5 weeks	⊕○○○ VERY LOW ^{a,b}	RR 0.96 (0.69 to 1.34)	48 per 1,000	2 fewer per 1,000 (15 fewer to 16 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 4: Central nervous system adverse events at >3 months	178 (1 RCT) follow up: 24 months	⊕○○○ VERY LOW a,b,d	Peto OR 0.13 (0.00 to 6.67)	11 per 1,000	10 fewer per 1,000 (40 fewer to 20 more) ^c	MID (precision) = Peto OR 0.8-1.25.

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

d. Downgraded by 1 or 2 increments because of outcome indirectness

e. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

f. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

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1 **1.1.6.1.3 Oral non-steroidal anti-inflammatory drugs compared to placebo**

2 **Table 33: Clinical evidence summary: oral non-steroidal anti-inflammatory drugs compared to placebo**

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with oral non-steroidal anti-inflammatory drugs	
Quality of life (SF-36 physical component summary, 0-100, high is good, change score) at ≤3 months	729 (2 RCTs) follow up: mean 13 weeks	⊕○○○ VERY LOW _{a,b}	-	The mean quality of life was 4.1	MD 2.89 higher (1.67 higher to 4.12 higher)	MID = 2 (established value)
Quality of life (SF-36 mental component summary, 0-100, high is good, change score) at ≤3 months	729 (2 RCTs) follow up: mean 13 weeks	⊕⊕○○ LOW _a	-	The mean quality of life was 0.85	MD 0.38 higher (0.86 lower to 1.61 higher)	MID = 3 (established value)
Quality of life (SF-36 bodily pain subscale, 0-100, high is good, change score) at ≤3 months	305 (1 RCT) follow up: 12 weeks	⊕⊕○○ LOW _a	-	The mean quality of life was 12.8	MD 9.1 higher (3.85 higher to 14.35 higher)	MID = 3 (established value)
Quality of life (SF-36 physical functioning subscale, 0-100, high is good, change score) at ≤3 months	305 (1 RCT) follow up: 12 weeks	⊕⊕○○ LOW _a	-	The mean quality of life was 7.5	MD 7 higher (1.59 higher to 12.41 higher)	MID = 3 (established value)
Quality of life (SF-36 role physical subscale, 0-100, high is good, change score) at ≤3 months	305 (1 RCT) follow up: 12 weeks	⊕○○○ VERY LOW _{a,b}	-	The mean quality of life was 11	MD 6.2 higher (0.31 higher to 12.09 higher)	MID = 3 (established value)
Quality of life (SF-36 vitality subscale, 0-100, high is good, change score) at ≤3 months	305 (1 RCT) follow up: 12 weeks	⊕○○○ VERY LOW _{a,b}	-	The mean quality of life was 3	MD 5.9 higher (1.72 higher to 10.08 higher)	MID = 2 (established value)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with oral non-steroidal anti-inflammatory drugs	
Quality of life (SF-36 general health subscale, 0-100, high is good, change score) at ≤3 months	305 (1 RCT) follow up: 12 weeks	⊕○○○ VERY LOW a,b	-	The mean quality of life was -0.1	MD 2.1 higher (2.02 lower to 6.22 higher)	MID = 2 (established value)
Quality of life (SF-36 mental health subscale, 0-100, high is good, change score) at ≤3 months	305 (1 RCT) follow up: 12 weeks	⊕○○○ VERY LOW a,b	-	The mean quality of life was 1.9	MD 2.4 higher (1.53 lower to 6.33 higher)	MID = 3 (established value)
Quality of life (SF-36 role emotional subscale, 0-100, high is good, change score) at ≤3 months	305 (1 RCT) follow up: 12 weeks	⊕○○○ VERY LOW a,b	-	The mean quality of life was 7.2	MD 2.1 higher (3.82 lower to 8.02 higher)	MID = 4 (established value)
Quality of life (SF-36 social functioning subscale, 0-100, high is good, change score) at ≤3 months	305 (1 RCT) follow up: 12 weeks	⊕○○○ VERY LOW a,b	-	The mean quality of life was 7	MD 4.6 higher (0.83 lower to 10.03 higher)	MID = 3 (established value)
Pain (WOMAC, VAS [different scale ranges], high is poor, change scores) at ≤3 months	21754 (45 RCTs) follow up: mean 9 weeks	⊕○○○ VERY LOW a,c	-	-	SMD 0.37 SD lower (0.45 lower to 0.28 lower)	MID = 0.5 SD (SMD)
Pain (WOMAC, VAS [different scale ranges], high is poor, final values) at ≤3 months	3311 (11 RCTs) follow up: mean 5 weeks	⊕○○○ VERY LOW a,b,c	-	-	SMD 0.46 SD lower (0.61 lower to 0.3 lower)	MID = 0.5 SD (SMD)
Pain (WOMAC, 0-500, high is poor, change score) at >3 months	631 (1 RCT) follow up: 24 weeks	⊕⊕⊕⊕ HIGH	-	The mean pain was -86.1	MD 13.9 lower (30.87 lower to 3.07 higher)	MID = 0.5 SD (SMD)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with oral non-steroidal anti-inflammatory drugs	
Physical function (WOMAC [different scale ranges], high is poor, change scores) at ≤3 months	14144 (31 RCTs) follow up: mean 9 weeks	⊕⊕○○ LOW _a	-	-	SMD 0.32 SD lower (0.37 lower to 0.27 lower)	MID = 0.5 SD (SMD)
Physical function (WOMAC [different scale ranges], high is poor, final values) at ≤3 months	1374 (2 RCTs) follow up: mean 8 weeks	⊕⊕○○ LOW _{a,b}	-	-	SMD 0.47 SD lower (0.6 lower to 0.35 lower)	MID = 0.5 SD (SMD)
Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months	9953 (19 RCTs) follow up: mean 8 weeks	⊕○○○ VERY LOW _{a,d}	RD 0.02 (0.01 to 0.03)	15 per 1,000	20 more per 1,000 (10 more to 30 more) _e	Precision calculated through Optimal Information Size (OIS) due to zero events in some studies (0.8-0.9 = serious, <0.8 = very serious).
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months	22694 (47 RCTs) follow up: mean 7 weeks	⊕○○○ VERY LOW _{a,d}	RD 0.01 (0.01 to 0.02)	112 per 1,000	10 more per 1,000 (10 more to 20 more) _e	Precision calculated through Optimal Information Size (OIS) due to zero events in some studies (0.8-0.9 = serious, <0.8 = very serious).
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at >3 months	89 (1 RCT) follow up: 24 months	⊕○○○ VERY LOW _{a,b,e}	RR 1.17 (0.39 to 3.57)			
				114 per 1,000	19 more per 1,000 (70 fewer to 293 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 2: Cardiovascular adverse events at ≤3 months	14247 (27 RCTs) follow up: mean 8 weeks	⊕○○○ VERY LOW _{a,b,d}	RR 1.15 (0.84 to 1.56)	16 per 1,000	2 more per 1,000 (3 fewer to 9 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 2: Cardiovascular adverse events at >3 months	1136 (2 RCTs)	⊕⊕○○ LOW _{a,b}	RR 2.30 (0.99 to 5.36)	15 per 1,000	20 more per 1,000 (0 fewer to 30 more) _e	MID (precision) = RR 0.8-1.25.

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with oral non-steroidal anti-inflammatory drugs	
	follow up: mean 13 months					
Serious adverse events 3: Hepatorenal adverse events at ≤3 months	5773 (12 RCTs) follow up: mean 7 weeks	⊕○○○ VERY LOW a,d	RD 0.00 (0.00 to 0.00)	7 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer) ^e	Precision calculated through Optimal Information Size (OIS) due to zero events in some studies (0.8-0.9 = serious, <0.8 = very serious).
Serious adverse events 3: Hepatorenal adverse events at >3 months	89 (1 RCT) follow up: 24 months	⊕○○○ VERY LOW a,b	RR 1.96 (0.18 to 20.80)	23 per 1,000	22 more per 1,000 (19 fewer to 455 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 4: Central nervous system adverse events at ≤3 months	18239 (39 RCTs) follow up: mean 7 weeks	⊕⊕○○ LOW ^a	RR 0.89 (0.81 to 0.99)	79 per 1,000	9 fewer per 1,000 (15 fewer to 1 fewer)	MID (precision) = RR 0.8-1.25.

- a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
- b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
- c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis
- d. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- e. Absolute effect calculated by risk difference due to zero events in at least one arm of one study
- f. Downgraded by 1 or 2 increments because of outcome indirectness

1 **1.1.6.1.4 Non-steroidal anti-inflammatory drugs and gastroprotection compared to paracetamol**

2 **Table 34: Clinical evidence summary: non-steroidal anti-inflammatory drugs and gastroprotection compared to paracetamol**

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with paracetamol	Risk difference with non-steroidal anti-inflammatory drugs and gastroprotection	
Quality of life (SF-36 bodily pain subscale, 0-100, high is good, change score) at ≤3 months	436 (1 RCT) follow up: 6 weeks	⊕○○○ VERY LOW a,b	-	-	MD 3.83 higher (2.36 higher to 5.3 higher)	MID = 3 (established value)
Pain (MDHAQ VAS, 0-100, high is poor, change score) at ≤3 months	436 (1 RCT) follow up: 6 weeks	⊕⊕○○ LOW _a	-	-	MD 14.6 lower (18.15 lower to 11.05 lower)	MID = 0.5 SD (SMD)
Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months	436 (1 RCT) follow up: 6 weeks	⊕○○○ VERY LOW a,b	Peto OR 7.39 (0.15 to 372.38)	0 per 1,000	0 fewer per 1,000 (10 fewer to 20 more) ^c	MID (precision) = Peto OR 0.8-1.25.
Serious adverse events 2: Cardiovascular adverse events at ≤3 months	436 (1 RCT) follow up: 6 weeks	⊕○○○ VERY LOW a,b	RR 2.00 (0.18 to 21.89)	5 per 1,000	5 more per 1,000 (4 fewer to 104 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 3: Hepatorenal adverse events at ≤3 months	436 (1 RCT) follow up: 6 weeks	⊕○○○ VERY LOW a,b	RR 2.20 (1.07 to 4.54)	46 per 1,000	55 more per 1,000 (3 more to 163 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 4: Central nervous system adverse events at ≤3 months	436 (1 RCT) follow up: 6 weeks	⊕○○○ VERY LOW a,b	RR 0.71 (0.23 to 2.22)	32 per 1,000	9 fewer per 1,000 (25 fewer to 39 more)	MID (precision) = RR 0.8-1.25.

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with paracetamol	Risk difference with non-steroidal anti-inflammatory drugs and gastroprotection	
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs						
c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study						

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1.1.6.1.5 Non-steroidal anti-inflammatory drugs and gastroprotection compared to oral non-steroidal anti-inflammatory drugs

Table 35: Clinical evidence summary: non-steroidal anti-inflammatory drugs and gastroprotection compared to oral non-steroidal anti-inflammatory drugs

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with oral non-steroidal anti-inflammatory drugs	Risk difference with non-steroidal anti-inflammatory drugs and gastroprotection	
Pain (VAS, 0-10, high is poor, change score) at ≤3 months	481 (1 RCT) follow up: 6 weeks	⊕⊕○○ LOW ^a	-	The mean pain was -2.87	MD 0.02 lower (0.6 lower to 0.56 higher)	MID = 0.5 SD (SMD)
Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months	2307 (4 RCTs) follow up: mean 7 weeks	⊕○○○ VERY LOW ^{a,b,c}	RR 0.56 (0.35 to 0.91)	150 per 1,000	66 fewer per 1,000 (97 fewer to 13 fewer)	MID (precision) = RR 0.8-1.25.
Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at >3 months	4484 (1 RCT) follow up: 26 weeks	⊕⊕○○ LOW ^a	RR 4.04 (2.48 to 6.56)	9 per 1,000	27 more per 1,000 (13 more to 50 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months	978 (1 RCT) follow up: 12 weeks	⊕⊕○○ LOW ^{c,d}	RR 0.92 (0.71 to 1.20)	193 per 1,000	15 fewer per 1,000 (56 fewer to 39 more)	MID (precision) = RR 0.8-1.25.

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with oral non-steroidal anti-inflammatory drugs	Risk difference with non-steroidal anti-inflammatory drugs and gastroprotection	
Serious adverse events 2: Cardiovascular adverse events at ≤3 months	2023 (2 RCT) follow up: mean 12 weeks	⊕⊕⊕○ MODERATE ^c	RR 2.52 (1.03 to 6.21)	6 per 1,000	9 more per 1,000 (0 fewer to 31 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 3: Hepatorenal adverse events at ≤3 months	481 (1 RCT) follow up: 6 weeks	⊕○○○ VERY LOW ^{a,c}	RR 1.18 (0.23 to 6.00)	13 per 1,000	2 more per 1,000 (10 fewer to 65 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 4: Central nervous system adverse events at ≤3 months	361 (1 RCT) follow up: 4 weeks	⊕⊕○○ LOW ^{a,c}	RR 0.62 (0.31 to 1.22)	109 per 1,000	41 fewer per 1,000 (75 fewer to 24 more)	MID (precision) = RR 0.8-1.25.

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

c. Downgraded by 1 or 2 increments because of population indirectness

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1 **1.1.6.1.6 Non-steroidal anti-inflammatory drugs and gastroprotection compared to placebo**

2 **Table 36: Clinical evidence summary: non-steroidal anti-inflammatory drugs and gastroprotection compared to placebo**

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with non-steroidal anti-inflammatory drugs and gastroprotection	
Pain (VAS, 0-10, high is poor, change score) at ≤3 months	418 (1 RCT) follow up: 6 weeks	⊕○○○ VERY LOW a,b	-	The mean pain was -1.3	MD 1.59 lower (2.29 lower to 0.89 lower)	MID = 0.5 SD (SMD)
Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months	418 (1 RCT) follow up: 6 weeks	⊕○○○ VERY LOW a,b	RR 2.04 (0.62 to 6.67)	33 per 1,000	34 more per 1,000 (13 fewer to 187 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months	736 (1 RCT) follow up: 12 weeks	⊕⊕○○ LOW _{b,c}	RR 0.89 (0.65 to 1.22)	199 per 1,000	22 fewer per 1,000 (70 fewer to 44 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 2: Cardiovascular adverse events at ≤3 months	736 (1 RCT) follow up: 12 weeks	⊕⊕○○ LOW _b	RR 2.51 (0.73 to 8.59)	12 per 1,000	18 more per 1,000 (3 fewer to 91 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 3: Hepatorenal adverse events at ≤3 months	418 (1 RCT) follow up: 6 weeks	⊕○○○ VERY LOW a,b	Peto OR 3.64 (0.43 to 30.72)	0 per 1,000	20 more per 1,000 (10 fewer to 40 more) ^d	MID (precision) = Peto OR 0.8-1.25.

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 1 or 2 increments because of outcome indirectness

d. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

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2 **1.1.6.1.7 Weak opioids compared to placebo**

3 **Table 37: Clinical evidence summary: weak opioids compared to placebo**

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with weak opioids	
Pain (WOMAC, 0-500, high is poor, change score) at ≤3 months	66 (1 RCT) follow up: 4 weeks	⊕○○○ VERY LOW ^{a,b}	-	The mean pain was -31.1	MD 86.9 lower (135.16 lower to 38.64 lower)	MID = 0.5 SD (SMD)
Physical function (WOMAC, 0-1700, high is poor, change score) at ≤3 months	66 (1 RCT) follow up: 4 weeks	⊕○○○ VERY LOW ^{a,b}	-	The mean physical function was -143.5	MD 300.7 lower (470.41 lower to 130.99 lower)	MID = 0.5 SD (SMD)

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

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5 **1.1.6.1.8 Strong opioids compared to oral non-steroidal anti-inflammatory drugs**

6 **Table 38: Clinical evidence summary: strong opioids compared to oral non-steroidal anti-inflammatory drugs**

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with oral non-steroidal anti-inflammatory drugs	Risk difference with strong opioids	
Quality of life (SF-36 physical component summary, 0-100, high is good, change score) at ≤3 months	801 (1 RCT) follow up: 12 weeks	⊕○○○ VERY LOW ^{a,b}	-	The mean quality of life was 5.2	MD 2.1 lower (3.46 lower to 0.74 lower)	MID = 2 (established value)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with oral non-steroidal anti-inflammatory drugs	Risk difference with strong opioids	
Quality of life (SF-36 mental component summary, 0-100, high is good, change score) at ≤3 months	801 (1 RCT) follow up: 12 weeks	⊕⊕○○ LOW ^a	-	The mean quality of life was -0.1	MD 0.4 lower (1.76 lower to 0.96 higher)	MID = 3 (established value)
Pain (WOMAC, 0-500, high is poor, change scores) at ≤3 months	898 (2 RCTs) follow up: mean 9 weeks	⊕⊕○○ LOW ^{a,b}	-	The mean pain was -105.1	MD 28.02 higher (9.75 higher to 46.29 higher)	MID = 48.1 (0.5 x median baseline control group SD)
Pain (VAS, 0-100, high is poor, final value) at ≤3 months	218 (1 RCT) follow up: 12 weeks	⊕○○○ VERY LOW ^{a,b}	-	The mean pain was 26.07	MD 0.95 lower (1.99 lower to 0.09 higher)	MID = 0.5 SD (SMD)
Physical function (WOMAC, 0-1700, high is poor, change scores) at ≤3 months	898 (2 RCTs) follow up: mean 9 weeks	⊕○○○ VERY LOW ^{a,b,c}	-	The mean physical function was 338.3	MD 75.68 higher (56.61 lower to 207.97 higher)	MID = 185.8 (0.5 x median baseline control group SD)
Serious adverse events 3: Hepatorenal adverse events at ≤3 months	218 (1 RCT) follow up: 12 weeks	⊕○○○ VERY LOW ^{a,b}	RR 1.02 (0.21 to 4.94)			
				27 per 1,000	1 more per 1,000 (21 fewer to 106 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 4: Central nervous system adverse events at ≤3 months	120 (1 RCT) follow up: 4 weeks	⊕○○○ VERY LOW ^{a,b}	Peto OR 7.39 (0.15 to 372.38)	0 per 1,000	20 fewer per 1,000 (30 fewer to 60 more) ^d	MID (precision) = Peto OR 0.8-1.25.

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

d. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

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2 **1.1.6.1.9 Strong opioids compared to placebo**

3 **Table 39: Clinical evidence summary: Strong opioids compared to placebo**

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with strong opioids	
Quality of life (EQ-5D, 0-1, high is good, change scores) at ≤3 months	2010 (2 RCTs) follow up: mean 12 weeks	⊕○○○ VERY LOW a,b,c	-	The mean quality of life was 0.15	MD 0 (0.11 lower to 0.11 higher)	MID = 0.03 (pragmatic value agreed between the NGC and NICE)
Quality of life (SF-36 physical component summary, 0-100, high is good, change scores) at ≤3 months	2059 (3 RCTs) follow up: mean 9 weeks	⊕⊕○○ LOW _a	-	The mean quality of life was 2.4	MD 0.91 higher (0.05 higher to 1.78 higher)	MID = 2 (established value)
Quality of life (SF-36 mental component summary, 0-100, high is good, change scores) at ≤3 months	2059 (3 RCTs) follow up: mean 9 weeks	⊕○○○ VERY LOW _{a,b}	-	The mean quality of life was 0.5	MD 0.61 lower (2.19 lower to 0.97 higher)	MID = 3 (established value)
Quality of life (SF-36 pain subscale, 0-100, high is good, final value and change score) at ≤3 months	453 (2 RCTs) follow up: mean 8 weeks	⊕○○○ VERY LOW _{a,c}	-	-	MD 2.07 higher (0.37 lower to 4.52 higher)	MID = 3 (established value)
Quality of life (SF-36 physical functioning subscale, 0-100, high is good, final value) at ≤3 months	276 (1 RCT) follow up: 12 weeks	⊕○○○ VERY LOW _{a,c}	-	The mean quality of life was 14.72	MD 1.13 lower (6.3 lower to 4.04 higher)	MID = 3 (established value)
Quality of life (SF-36 vitality subscale, 0-100, high is good, final value) at ≤3 months	182 (1 RCT) follow up: 4 weeks	⊕○○○ VERY LOW _{a,c}	-	The mean quality of life was 40.21	MD 2.93 higher (0.98 lower to 6.84 higher)	MID = 2 (established value)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with strong opioids	
Quality of life (SF-36 general health perception subscale, 0-100, high is good, final value) at ≤3 months	182 (1 RCT) follow up: 4 weeks	⊕○○○ VERY LOW _{a,c}	-	The mean quality of life was 44.39	MD 2.15 higher (1.17 lower to 5.47 higher)	MID = 2 (established value)
Quality of life (SF-36 social functioning subscale, 0-100, high is good, final value) at ≤3 months	276 (1 RCT) follow up: 12 weeks	⊕○○○ VERY LOW _{a,c}	-	The mean quality of life was 9.55	MD 2.26 lower (7.87 lower to 3.35 higher)	MID = 3 (established value)
Pain (WOMAC, VAS, NRS [different scale ranges], high is poor, change scores) at ≤3 months	5993 (13 RCTs) follow up: mean 10 weeks	⊕○○○ VERY LOW _{a,b,c}	-	-	SMD 0.35 SD lower (0.51 lower to 0.18 lower)	MID = 0.5 SD (SMD)
Pain (WOMAC, VAS [different scale ranges], high is poor, final values) at ≤3 months	464 (3 RCTs) follow up: mean 7 weeks	⊕○○○ VERY LOW _{a,c}	-	-	SMD 0.34 SD lower (0.52 lower to 0.15 higher)	MID = 0.5 SD (SMD)
Physical function (WOMAC [different scale ranges], high is poor, change scores) at ≤3 months	2915 (6 RCTs) follow up: mean 11 weeks	⊕⊕○○ LOW _{a,b}	-	-	SMD 0.2 SD lower (0.28 lower to 0.11 lower)	MID = 0.5 SD (SMD)
Physical function (WOMAC, VAS [different scale ranges], high is poor, final values) at ≤3 months	311 (2 RCTs) follow up: mean 9 weeks	⊕○○○ VERY LOW _{a,c}	-	-	SMD 0.29 SD lower (0.51 lower to 0.06 lower)	MID = 0.5 SD (SMD)
Psychological distress (negative affect scale, 0-10, high is poor, change score) at ≤3 months	107 (1 RCT) follow up: 2 weeks	⊕⊕○○ LOW _{a,c}	-	-	MD 0.2 lower (0.47 lower to 0.07 higher)	MID = 0.5 SD (SMD)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with strong opioids	
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months	2163 (3 RCTs) follow up: mean 9 weeks	⊕○○○ VERY LOW a,b,c	RR 1.63 (0.80 to 3.28)	447 per 1,000	282 more per 1,000 (89 fewer to 1,000 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 2: Cardiovascular adverse events at ≤3 months	1998 (2 RCTs) follow up: mean 12 weeks	⊕○○○ VERY LOW _{a,c}	RR 1.21 (0.54 to 2.70)	16 per 1,000	3 more per 1,000 (7 fewer to 27 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 4: Central nervous system adverse events at ≤3 months	2163 (3 RCTs) follow up: mean 9 weeks	⊕⊕○○ LOW _a	RR 1.93 (1.67 to 2.24)	228 per 1,000	212 more per 1,000 (152 more to 282 more)	MID (precision) = RR 0.8-1.25.

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

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2 **1.1.6.1.10 Anti-epileptic drugs compared to paracetamol**

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with paracetamol	Risk difference with anti-epileptic drugs	
Pain (WOMAC, 0-100, %, high is poor, change score) at ≤3 months	100 (1 RCT) follow-up: 3 months	⊕⊕○○ LOW _a	-	The mean pain was - 50.32%	MD 23.62 lower (28.26 lower to 18.98 lower)	MID = 0.5 SD (SMD)

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with paracetamol	Risk difference with anti-epileptic drugs	
Physical function (WOMAC, 0-100, %, high is poor, change score) at ≤3 months	100 (1 RCT) follow-up: 3 months	⊕⊕○○ LOW ^a	-	The mean physical function was -58.82%	MD 10.71 lower (14.12 lower to 7.3 lower)	MID = 0.5 SD (SMD)
Serious adverse events 4: Central nervous system adverse events at ≤3 months	100 (1 RCT) follow-up: 3 months	⊕○○○ VERY LOW ^{a,b}	Peto OR 7.87 (1.07 to 57.56)	0 per 1,000	80 more per 1,000 (0 fewer to 160 more) ^c	MID (precision) = Peto OR 0.8-1.25.

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

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- 2 **1.1.6.1.10 Anti-epileptic drugs compared to antidepressant drugs**

3 **Table 40: Clinical evidence summary: anti-epileptic drugs compared to antidepressants**

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with antidepressants	Risk difference with anti-epileptic drugs	
Pain (AUSCAN, 0-500, high is poor, change score) at ≤3 months	43 (1 RCT) follow up: 13 weeks	⊕⊕○○ LOW ^{a,b}	-	The mean pain was -35.8	MD 96.3 lower (193.56 lower to 0.96 higher)	MID = 0.5 SD (SMD)
Pain (WOMAC, 0-100, %, high is poor, change score) at ≤3 months	100 (1 RCT) follow up: 3 months	⊕○○○ VERY LOW ^{a,b}	-	The mean pain was -78.29%	MD 4.35 higher (0.16 lower to 8.86 higher)	MID = 0.5 SD (SMD)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with antidepressants	Risk difference with anti-epileptic drugs	
Physical function (AUSCAN, 0-900, high is poor, change scores) at < 3 months	43 (1 RCT) follow up: 13 weeks	⊕⊕○○ LOW _{a,b}	-	The mean physical function was -101.8	MD 144.6 lower (284.11 lower to 5.09 lower)	MID = 0.5 SD (SMD)
Physical function (WOMAC, 0-100, %, high is poor, change score) at ≤3 months	100 (1 RCT) follow up: 3 months	⊕⊕○○ LOW _a	-	The mean physical function was -68.36%	MD 1.17 lower (5.23 lower to 2.89 higher)	MID = 0.5 SD (SMD)
Psychological distress (HADS depression score, 0-21, high is poor, change score) at ≤3 months	43 (1 RCT) follow up: 13 weeks	⊕⊕○○ LOW _{a,b}	-	The mean psychological distress was -1.3	MD 0.48 higher (1.73 lower to 2.69 higher)	MID = 0.5 SD (SMD)
Psychological distress (HADS anxiety score, 0-21, high is poor, change score) at ≤3 months)	43 (1 RCT) follow up: 13 weeks	⊕⊕○○ LOW _{a,b}	-	The mean psychological distress was -0.3	MD 0.8 lower (2.66 lower to 1.06 higher)	MID = 0.5 SD (SMD)
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months	43 (1 RCT) follow up: 13 weeks	⊕⊕○○ LOW _a	RR 0.37 (0.20 to 0.70)	857 per 1,000	540 fewer per 1,000 (686 fewer to 257 fewer)	MID (precision) = RR 0.8-1.25.
Serious adverse events 2: Cardiovascular adverse events at ≤3 months	43 (1 RCT) follow up: 13 weeks	⊕○○○ VERY LOW _{a,b}	RR 1.43 (0.27 to 7.73)	95 per 1,000	41 more per 1,000 (69 fewer to 639 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 4: Central nervous system adverse events at ≤3 months	100 (1 RCT) follow up: 3 months	⊕○○○ VERY LOW _{a,b}	RR 0.57 (0.18 to 1.83)	140 per 1,000	60 fewer per 1,000 (115 fewer to 116 more)	MID (precision) = RR 0.8-1.25.

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with antidepressants	Risk difference with anti-epileptic drugs	
<p>a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias</p> <p>b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs</p>						

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2 **1.1.6.1.11 Anti-epileptic drugs compared to placebo**

3 **Table 41: Clinical evidence summary: anti-epileptic drugs compared to placebo**

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with anti-epileptic drugs	
Pain (AUSCAN, 0-500, high is poor, change score) at ≤3 months	44 (1 RCT) follow up: 13 weeks	⊕⊕○○ LOW _{a,b}	-	The mean pain was -46.61	MD 85.49 lower (153.7 lower to 17.28 lower)	MID = 0.5 SD (SMD)
Physical function (AUSCAN, 0-900, high is poor, change score) at ≤3 months	44 (1 RCT) follow up: 13 weeks	⊕⊕○○ LOW _{a,b}	-	The mean physical function was -67.3	MD 179.1 lower (295.82 lower to 62.38 lower)	MID = 0.5 SD (SMD)
Psychological distress (HADS anxiety score, 0-21, high is poor, change score) at ≤3 months	44 (1 RCT) follow up: 13 weeks	⊕⊕○○ LOW _{a,b}	-	The mean psychological distress was 0.5	MD 1.32 lower (2.91 lower to 0.27 higher)	MID = 0.5 SD (SMD)
Psychological distress (HADS depression score, 0-21, high is poor, change scores) at ≤3 months	44 (1 RCT) follow up: 13 weeks	⊕⊕○○ LOW _{a,b}	-	The mean psychological distress was 0.05	MD 1.15 lower (2.85 lower to 0.55 higher)	MID = 0.5 SD (SMD)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with anti-epileptic drugs	
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months	44 (1 RCT) follow up: 13 weeks	⊕○○○ VERY LOW ^{a,b}	RR 1.40 (0.52 to 3.74)	227 per 1,000	91 more per 1,000 (109 fewer to 622 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 2: Cardiovascular adverse events at ≤3 months	44 (1 RCT) follow up: 13 weeks	⊕○○○ VERY LOW ^{a,b}	RR 3.00 (0.34 to 26.66)	46 per 1,000	92 more per 1,000 (30 fewer to 1,000 more)	MID (precision) = RR 0.8-1.25.

^a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

^b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

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2 **1.1.6.1.12 Antidepressant drugs compared to paracetamol**

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with paracetamol	Risk difference with antidepressant drugs	
Pain (WOMAC, 0-100, %, high is poor, change score) at ≤3 months	100 (1 RCT) follow-up: 3 months	⊕⊕○○ LOW ^a	-	The mean pain was -50.32 %	MD 27.97 % lower (32.06 lower to 23.88 lower)	MID = 0.5 SD (SMD)
Physical function (WOMAC, 0-100, %, high is poor, change score) at ≤3 months	100 (1 RCT) follow-up: 3 months	⊕⊕○○ LOW ^a	-	The mean physical function was -58.82 %	MD 9.54% lower (13.55 lower to 5.53 lower)	MID = 0.5 SD (SMD)
Serious adverse events 4: Central nervous system adverse events at ≤3 months	100 (1 RCT)	⊕⊕○○ LOW ^a	Peto OR 8.41 (1.82 to 38.77)	0 per 1,000	140 more per 1,000 (40 more to 240 more) ^b	MID (precision) = Peto OR 0.8-1.25.

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with paracetamol	Risk difference with antidepressant drugs	
	follow-up: 3 months					
<p>a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias</p> <p>b. Absolute effect calculated by risk difference due to zero events in at least one arm of one study</p>						

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2 **1.1.6.1.12 Antidepressant drugs compared to placebo**

3 **Table 42: Clinical evidence summary: antidepressants compared to placebo**

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with antidepressant drugs	
Quality of life (EQ-5D, -0.11-1, high is good, change scores) at ≤3 months	815 (3 RCTs) follow up: mean 13 weeks	⊕○○○ VERY LOW a,b,c	-	The mean quality of life was 0.09	MD 0.05 higher (0.01 higher to 0.09 higher)	MID = 0.03 (pragmatic value agreed between the NGC and NICE)
Quality of life (SF-36 physical function, 0-100, high is good, change score) at ≤3 months	205 (1 RCT) follow up: 14 weeks	⊕⊕○○ LOW a,c	-	The mean quality of life was -0.6	MD 2.6 higher (0.02 higher to 5.18 higher)	MID = 3 (established value)
Quality of life (SF-36 bodily pain, 0-100, high is good, change score) at ≤3 months	205 (1 RCT) follow up: 14 weeks	⊕⊕○○ LOW a,c	-	The mean quality of life was -0.6	MD 2.7 higher (0.21 higher to 5.19 higher)	MID = 3 (established value)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with antidepressant drugs	
Quality of life (SF-36 role physical, 0-100, high is good, change score) at ≤3 months	205 (1 RCT) follow up: 14 weeks	⊕⊕○○ LOW _{a,c}	-	The mean quality of life was -0.6	MD 1.9 higher (1.3 lower to 5.1 higher)	MID = 3 (established value)
Quality of life (SF-36 vitality, 0-100, high is good, change score) at ≤3 months	205 (1 RCT) follow up: 14 weeks	⊕⊕○○ LOW _{a,c}	-	The mean quality of life was -0.6	MD 0.6 higher (1.3 lower to 5.1 higher)	MID = 2 (established value)
Quality of life (SF-36 general health, 0-100, high is good, change score) at ≤3 months	205 (1 RCT) follow up: 14 weeks	⊕⊕○○ LOW _{a,c}	-	The mean quality of life was -0.6	MD 0.5 lower (2.57 lower to 1.57 higher)	MID = 2 (established value)
Quality of life (SF-36 role emotional, 0-100, high is good, change score) at ≤3 months	205 (1 RCT) follow up: 14 weeks	⊕⊕○○ LOW _{a,c}	-	The mean quality of life was -0.6	MD 1.8 higher (1.73 lower to 5.33 higher)	MID = 3 (established value)
Quality of life (SF-36 mental health, 0-100, high is good, change score) at ≤3 months	205 (1 RCT) follow up: 14 weeks	⊕⊕⊕○ MODERATE _a	-	The mean quality of life was -0.6	MD 0.2 lower (2.75 lower to 2.35 higher)	MID = 4 (established value)
Quality of life (SF-36 social function, 0-100, high is good, change score) at ≤3 months	205 (1 RCT) follow up: 14 weeks	⊕⊕○○ LOW _{a,c}	-	The mean quality of life was -0.6	MD 2 higher (1.56 lower to 5.56 higher)	MID = 3 (established value)
Pain (WOMAC, AUSCAN [different scale ranges], high is poor, change scores) at ≤3 months	1955 (7 RCTs) follow up: mean 13 weeks	⊕⊕⊕○ MODERATE _a	-	-	SMD 0.34 SD lower (0.43 lower to 0.25 lower)	MID = 0.5 SD (SMD)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with antidepressant drugs	
Pain (WOMAC, 0-20, high is poor, final value) at >3 months	288 (1 RCT) follow up: 16 weeks	⊕⊕○○ LOW _{a,c}	-	The mean pain was 8.4	MD 2.4 lower (3.51 lower to 1.29 lower)	MID = 0.5 SD (SMD)
Physical function (WOMAC, AUSCAN [different scale ranges], high is poor, change scores) at ≤3 months	1510 (5 RCTs) follow up: mean 13 weeks	⊕⊕⊕○ MODERATE _a	-	-	SMD 0.35 SD lower (0.45 lower to 0.26 lower)	MID = 0.5 SD (SMD)
Physical function (WOMAC, 0-68, high is poor, final value) at >3 months	288 (1 RCT) follow up: 16 weeks	⊕⊕○○ LOW _{a,c}	-	The mean physical function was 30.3	MD 5.7 lower (7.81 lower to 3.59 lower)	MID = 0.5 SD (SMD)
Psychological distress (Beck depression Inventory, HADS depression score [different scale ranges], high is poor, change scores) at ≤3 months	216 (2 RCTs) follow up: mean 13 weeks	⊕⊕⊕○ MODERATE _a	-	-	SMD 0.07 SD lower (0.34 lower to 0.19 higher)	MID = 0.5 SD (SMD)
Psychological distress (HADS anxiety scale, 0-21, high is poor, change scores) at ≤3 months	216 (2 RCTs) follow up: mean 13 weeks	⊕○○○ VERY LOW _{a,c}	-	The mean psychological distress was -0.19	MD 0.63 lower (1.32 lower to 0.07 higher)	MID = 0.13 (0.5 x median baseline control group SD)
Psychological distress (Geriatric depression scale, 0-15, high is poor, final value) at >3 months	288 (1 RCT) follow up: 16 weeks	⊕⊕⊕○ MODERATE _a	-	The mean psychological distress was 9.7	MD 4.5 lower (4.95 lower to 4.05 lower)	MID = 0.5 SD (SMD)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with antidepressant drugs	
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months	823 (3 RCTs) follow up: mean 12 weeks	⊕○○○ VERY LOW ^{a,d}	RR 3.33 (1.70 to 6.49)	20 per 1,000	50 more per 1,000 (30 more to 70 more) ^e	MID (precision) = RR 0.8-1.25.
Serious adverse events 2: Cardiovascular adverse events at ≤3 months	1378 (5 RCTs) follow up: mean 13 weeks	⊕○○○ VERY LOW ^{a,c,d}	RR 3.04 (0.92 to 10.08)	3 per 1,000	10 more per 1,000 (0 fewer to 20 more) ^e	MID (precision) = RR 0.8-1.25.
Serious adverse events 3: Hepatic and renal adverse events at ≤3 months	981 (3 RCTs) follow up: mean 12 weeks	⊕○○○ VERY LOW ^{a,c,d}	Peto OR 0.52 (0.05 to 4.96)	4 per 1,000	0 fewer per 1,000 (10 fewer to 10 more) ^e	MID (precision) = Peto OR 0.8-1.25.
Serious adverse events 4: Central nervous system adverse events at ≤3 months	981 (3 RCTs) follow up: mean 12 weeks	⊕○○○ VERY LOW ^{a,b,d}	RR 1.02 (0.33 to 3.19)	61 per 1,000	1 more per 1,000 (41 fewer to 134 more)	MID (precision) = RR 0.8-1.25.

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

e. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

1 **1.1.6.1.13 Glucosamine compared to paracetamol**

2 **Table 43: Clinical evidence summary: glucosamine compared to paracetamol**

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with paracetamol	Risk difference with glucosamine	
Pain (WOMAC, 0-20, high is poor, change score) at >3 months	214 (1 RCT) follow up: 26 weeks	⊕⊕○○ LOW _a	-	The mean pain was -2.4	MD 0.3 lower (1.16 lower to 0.56 higher)	MID = 0.5 SD (SMD)
Physical function (WOMAC, 0-68, high is poor, change score) at >3 months	214 (1 RCT) follow up: 26 weeks	⊕⊕○○ LOW _a	-	The mean physical function was -8.7	MD 0.5 lower (3.26 lower to 2.26 higher)	MID = 0.5 SD (SMD)
Serious adverse events 2: Cardiovascular adverse events at >3 months	214 (1 RCT) follow up: 26 weeks	⊕○○○ VERY LOW _{a,b}	Peto OR 0.14 (0.00 to 6.95)	9 per 1,000	10 fewer per 1,000 (30 fewer to 20 more) _c	MID (precision) = Peto OR 0.8-1.25.
Serious adverse events 3: Hepatorenal adverse events at >3 months	214 (1 RCT) follow up: 26 weeks	⊕⊕○○ LOW _a	RR 0.10 (0.02 to 0.40)	194 per 1,000	175 fewer per 1,000 (190 fewer to 116 fewer)	MID (precision) = RR 0.8-1.25.

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

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1 **1.1.6.1.14 Glucosamine compared to oral non-steroidal anti-inflammatory drugs**

2 **Table 44: Clinical evidence summary: Glucosamine compared to oral non-steroidal anti-inflammatory drugs**

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with oral non-steroidal anti-inflammatory drugs	Risk difference with glucosamine	
Pain (WOMAC [different scale ranges], high is poor, change scores) at >3 months	855 (2 RCTs) follow up: mean 24 weeks	⊕○○○ VERY LOW a,b,c	-	-	SMD 0.72 SD higher (0.4 lower to 1.84 higher)	MID = 0.5 SD (SMD)
Physical function (WOMAC [different scale ranges], high is poor, change scores) at >3 months	855 (2 RCTs) follow up: mean 24 weeks	⊕⊕○○ LOW a,b	-	-	SMD 0.06 SD higher (0.23 lower to 0.34 higher)	MID = 0.5 SD (SMD)
Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months	199 (1 RCT) follow up: 4 weeks	⊕○○○ VERY LOW a,c	Peto OR 0.13 (0.00 to 6.75)	10 per 1,000	10 fewer per 1,000 (40 fewer to 20 more) ^d	MID (precision) = Peto OR 0.8-1.25.
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months	455 (4 RCTs) follow up: mean 7 weeks	⊕○○○ VERY LOW a,b,c	RR 0.39 (0.16 to 0.95)	150 per 1,000	92 fewer per 1,000 (126 fewer to 8 fewer)	MID (precision) = RR 0.8-1.25.
Serious adverse events 2: Cardiovascular adverse events at ≤3 months	218 (2 RCTs) follow up: mean 8 weeks	⊕○○○ VERY LOW a,c,e	RR 0.55 (0.02 to 14.10)	22 per 1,000	20 fewer per 1,000 (100 fewer to 70 more) ^d	MID (precision) = RR 0.8-1.25.
Serious adverse events 2: Cardiovascular adverse events at >3 months	635 (1 RCT) follow up: 24 weeks	⊕⊕○○ LOW ^c	RR 1.00 (0.06 to 15.97)	3 per 1,000	0 fewer per 1,000 (3 fewer to 45 more)	MID (precision) = RR 0.8-1.25.

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with oral non-steroidal anti-inflammatory drugs	Risk difference with glucosamine	
Serious adverse events 3: Hepatorenal adverse events at ≤3 months	178 (1 RCT) follow up: 4 weeks	⊕⊕○○ LOW ^{a,c}	Peto OR 0.14 (0.00 to 6.98)	11 per 1,000	10 fewer per 1,000 (40 fewer to 20 more) ^d	MID (precision) = Peto OR 0.8-1.25.
Serious adverse events 3: Hepatorenal adverse events at >3 months	213 (1 RCT) follow up: mean 24 weeks	⊕○○○ VERY LOW ^{a,c}	RR 1.94 (0.36 to 10.39)	19 per 1,000	18 more per 1,000 (12 fewer to 179 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 4: Central nervous system adverse events at ≤3 months	256 (3 RCTs) follow up: mean 8 weeks	⊕○○○ VERY LOW ^{a,c}	RR 0.30 (0.06 to 1.39)	50 per 1,000	40 fewer per 1,000 (80 fewer to 10 more) ^d	MID (precision) = RR 0.8-1.25.

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

e. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

1 **1.1.6.1.15 Glucosamine compared to placebo**

2 **Table 45: Clinical evidence summary: glucosamine compared to placebo**

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with glucosamine	
Quality of life (EQ-5D, 0-1, high is good, change score) at >3 months	137 (1 RCT) follow up: 26 weeks	⊕○○○ VERY LOW _{a,b}	-	The mean quality of life was -0.04	MD 0.01 higher (0.05 lower to 0.07 higher)	MID = 0.03 (established value)
Quality of life (SF-12 physical component summary, 0-100, high is good, final value) at >3 months	303 (1 RCT) follow up: 24 months	⊕⊕○○ LOW _{a,b}	-	The mean quality of life was 44.2	MD 0.3 lower (2.45 lower to 1.85 higher)	MID = 0.5 SD (SMD)
Quality of life (SF-12 mental component summary, 0-100, high is good, final value) at >3 months	303 (1 RCT) follow up: 24 months	⊕⊕○○ LOW _{a,b}	-	The mean quality of life was 51.6	MD 1.5 higher (0.79 lower to 3.79 higher)	MID = 0.5 SD (SMD)
Pain (WOMAC, VAS, 0-100, final values and change scores, high is poor) at ≤3 months	770 (8 RCTs) follow up: mean 10 weeks	⊕○○○ VERY LOW _{a,b,c}	-	The mean pain was 20.5	MD 6.66 lower (14.62 lower to 1.31 higher)	MID = 8.3 (0.5 x median baseline control group SD)
Pain (WOMAC, 0-20, high is poor, final value) at ≤3 months	118 (1 RCT) follow up: 8 weeks	⊕⊕○○ LOW _a	-	The mean pain was 7.65	MD 0.51 lower (1.98 lower to 0.96 higher)	MID = 0.5 SD (SMD)
Pain (WOMAC [different scale ranges], high is poor, change scores) at >3 months	1602 (6 RCTs) follow up: mean 60 weeks	⊕⊕⊕○ MODERATE _a	-	-	SMD 0.03 SD lower (0.13 lower to 0.07 higher)	MID = 0.5 SD (SMD)
Pain (WOMAC [different scale ranges], high is poor, final values) at >3 months	513 (4 RCTs) follow up: mean 19.5 months	⊕⊕⊕○ MODERATE _a	-	-	SMD 0.15 SD lower (0.33 lower to 0.02 higher)	MID = 0.5 SD (SMD)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with glucosamine	
Physical function (WOMAC, 0-100, high is poor, final value and change scores) at ≤3 months	551 (5 RCTs) follow up: mean 11 weeks	⊕⊕○○ LOW _{a,b}	-	The mean physical function was 19.0	MD 6.17 lower (12.84 lower to 0.49 higher)	MID = 9.8 (0.5 x median baseline control group SD)
Physical function (WOMAC, 0-68, high is poor, final value) at ≤3 months	118 (1 RCT) follow up: 8 weeks	⊕⊕○○ LOW _a	-	The mean physical function was 37.17	MD 1.19 lower (6.39 lower to 4.01 higher)	MID = 0.5 SD (SMD)
Physical function (WOMAC [different scale ranges], high is poor, change scores) at >3 months	1602 (6 RCTs) follow up: mean 60 weeks	⊕⊕○○ LOW _{a,c}	-	-	SMD 0.09 SD lower (0.25 lower to 0.07 higher)	MID = 0.5 SD (SMD)
Physical function (WOMAC [different scale ranges], high is poor, final values) at >3 months	441 (3 RCTs) follow up: mean 51 weeks	⊕⊕⊕○ MODERATE _a	-	-	SMD 0 SD (0.18 lower to 0.19 higher)	MID = 0.5 SD (SMD)
Osteoarthritis flares at >3 months	137 (1 RCT) follow up: 26 weeks	⊕⊕○○ LOW _b	RR 1.06 (0.73 to 1.55)	424 per 1,000	25 more per 1,000 (114 fewer to 233 more)	MID (precision) = RR 0.8-1.25.
				76 per 1,000	25 more per 1,000 (114 fewer to 233 more) _f	
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months	464 (4 RCTs) follow up: mean 8 weeks	⊕○○○ VERY LOW _{a,d,e}	RR 1.37 (0.71 to 2.01)	76 per 1,000	25 more per 1,000 (114 fewer to 233 more) _f	MID (precision) = RR 0.8-1.25.
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at >3 months	90 (1 RCT) follow up: 6 months	⊕○○○ VERY LOW _{a,b}	Peto OR 9.73 (0.59 to 160.85)	0 per 1,000	50 more per 1,000 (30 fewer to 130 more) _f	MID (precision) = Peto OR 0.8-1.25.

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with glucosamine	
Serious adverse events 2: Cardiovascular adverse events at ≤3 months	287 (2 RCTs) follow up: mean 8 weeks	⊕○○○ VERY LOW ^{a,e}	RR 0.01 (-1.84 to 1.71)	8 per 1,000	10 fewer per 1,000 (40 fewer to 10 more) ^f	MID (precision) = RR 0.8-1.25.
Serious adverse events 2: Cardiovascular adverse events at >3 months	1345 (4 RCTs) follow up: mean 76 weeks	⊕○○○ VERY LOW ^{a,d,e}	RR 1.08 (0.65 to 1.80)	8 per 1,000	1 more per 1,000 (3 fewer to 6 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 3: Hepatorenal adverse events at >3 months	211 (1 RCT) follow up: 26 weeks	⊕○○○ VERY LOW ^{a,b}	RR 0.33 (0.07 to 1.60)	57 per 1,000	38 fewer per 1,000 (53 fewer to 34 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 4: Central nervous system adverse events at ≤3 months	367 (4 RCTs) follow up: mean 9 weeks	⊕○○○ VERY LOW ^{a,d,e}	RR 0.41 (0.11 to 1.56)	33 per 1,000	19 fewer per 1,000 (29 fewer to 18 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 4: Central nervous system adverse events at >3 months	90 (1 RCT) follow up: 6 months	⊕○○○ VERY LOW ^{a,b}	Peto OR 9.73 (0.59 to 160.85)	0 per 1,000	50 more per 1,000 (30 fewer to 130 more) ^f	MID (precision) = Peto OR 0.8-1.25.

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis

d. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)

e. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

f. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

1 **1.1.6.2 Topical (local) (including comparisons to oral formulations)**

2 **1.1.6.2.1 Capsaicin compared to placebo for people with knee osteoarthritis**

3 **Table 46: Clinical evidence summary: capsaicin compared to placebo in knee osteoarthritis**

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with capsaicin	
Pain (WOMAC, 0-20, high is poor, change score) at ≤3 months	198 (1 RCT) follow up: 4 weeks	⊕⊕⊕○ MODERATE _a	-	The mean pain was -1.24	MD 3.42 lower (4.49 lower to 2.35 lower)	MID = 0.5 SD (SMD)
Physical function (WOMAC, 0-68, high is poor, change score) at ≤3 months	198 (1 RCT) follow up: 4 weeks	⊕⊕○○ LOW _{a,b}	-	The mean physical function was -5.56	MD 8.98 lower (12.4 lower to 5.56 lower)	MID = 0.5 SD (SMD)
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months	198 (1 RCT) follow up: 4 weeks	⊕⊕○○ LOW _{a,c}	RR 0.00 (-0.02 to 0.02)	0 per 1,000	0 fewer per 1,000 (20 fewer to 20 more) _d	MID (precision) = RR 0.8-1.25.
Serious adverse events 2: Cardiovascular adverse events at ≤3 months	198 (1 RCT) follow up: 4 weeks	⊕⊕○○ LOW _{a,c}	RR 0.00 (-0.02 to 0.02)	0 per 1,000	0 fewer per 1,000 (20 fewer to 20 more) _d	MID (precision) = RR 0.8-1.25.
Serious adverse events 3: Hepatorenal adverse events at ≤3 months	198 (1 RCT) follow up: 4 weeks	⊕⊕○○ LOW _{a,c}	RR 0.00 (-0.02 to 0.02)	0 per 1,000	0 fewer per 1,000 (20 fewer to 20 more) _d	MID (precision) = RR 0.8-1.25.

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with capsaicin	
Serious adverse events 4: Central nervous system adverse events at ≤3 months	198 (1 RCT) follow up: 4 weeks	⊕⊕○○ LOW _{a,c}	RR 0.00 (-0.02 to 0.02)	0 per 1,000	0 fewer per 1,000 (20 fewer to 20 more) _d	MID (precision) = RR 0.8-1.25.
<p>a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias</p> <p>b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs</p> <p>c. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size</p> <p>d. Absolute effect calculated by risk difference due to zero events in at least one arm of one study</p>						

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2 **1.1.6.2.2 Capsaicin compared to placebo for people with hand osteoarthritis**

3 **Table 47: Clinical evidence summary: capsaicin compared to placebo in hand osteoarthritis**

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with capsaicin	
Pain (visual analogue scale, 0-100, high is poor, final value) at ≤3 months	41 (1 RCT) follow up: 9 weeks	⊕○○○ VERY LOW _{a,b}	-	The mean pain was 37.7	MD 4.3 lower (16.2 lower to 7.6 higher)	MID = 0.5 SD (SMD)
<p>a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias</p> <p>b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs</p>						

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1 **1.1.6.2.3 Topical non-steroidal anti-inflammatory drugs compared to oral non-steroidal anti-inflammatory drugs for people with knee**
2 **osteoarthritis**

3 **Table 48: Clinical evidence summary: Topical non-steroidal anti-inflammatory drugs compared to oral non-steroidal anti-inflammatory**
4 **drugs in knee osteoarthritis**

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with oral non-steroidal anti-inflammatory drugs	Risk difference with topical non-steroidal anti-inflammatory drugs	
Quality of life (SF-36 physical component summary, SF-12 physical component summary, 0-100, high is good, change scores) at ≤3 months	301 (2 RCTs) follow up: mean 7 weeks	⊕⊕⊕○ MODERATE _a	-	-	MD 0.1 lower (1.7 lower to 1.5 higher)	MID = 4.25 (0.5 x median baseline SD)
Quality of life (SF-36 mental component summary, SF-12 mental component summary, 0-100, high is good, change scores) at ≤3 months	301 (2 RCTs) follow up: mean 7 weeks	⊕⊕⊕○ MODERATE _a	-	-	MD 1.2 lower (3.3 lower to 0.9 higher)	MID = 5.4 (0.5 x median baseline SD)
Quality of life (SF-36 physical component summary, 0-100, high is good, change score) at >3 months	282 (1 RCT) follow up: 24 months	⊕○○○ VERY LOW _{a,b}	-	-	MD 0.7 lower (2.5 lower to 1.1 higher)	MID = 2 (established value)
Quality of life (SF-36 mental component summary, 0-100, high is good, change score) at >3 months	282 (1 RCT) follow up: 24 months	⊕⊕○○ LOW _a	-	-	MD 0.5 lower (2.6 lower to 1.6 higher)	MID = 3 (established value)
Pain (WOMAC pain subscale [different scale ranges], high is poor, change scores) at ≤3 months	2064 (6 RCTs) follow up: mean 9 weeks	⊕⊕⊕○ MODERATE _a	-	-	SMD 0.03 SD higher (0.06 lower to 0.12 higher)	MID = 0.5 SD (SMD)
Pain (WOMAC pain subscale, 0-100, high is poor, change score) at >3 months	282 (1 RCT) follow up: 24 months	⊕⊕○○ LOW _a	-	-	MD 5 higher (0 to 10 higher)	MID = 0.5 SD (SMD)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with oral non-steroidal anti-inflammatory drugs	Risk difference with topical non-steroidal anti-inflammatory drugs	
Physical function (WOMAC physical function subscale [different scale ranges], high is poor, change scores) at ≤3 months	1368 (5 RCTs) follow up: mean 9 weeks	⊕⊕○○ LOW _{a,c}	-	-	SMD 0 SD (0.11 lower to 0.1 higher)	MID = 0.5 SD (SMD)
Physical function (WOMAC physical function subscale, 0-100, high is poor, change score) at >3 months	282 (1 RCT) follow up: 24 months	⊕⊕○○ LOW _a	-	-	MD 3 higher (2 lower to 8 higher)	MID = 0.5 SD (SMD)
Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months	305 (1 RCT) follow up: 12 weeks	⊕○○○ VERY LOW _{a,b}	Peto OR 7.25 (0.14 to 365.27)	0 per 1,000	10 more per 1,000 (10 fewer to 20 more) _d	MID (precision) = Peto OR 0.8-1.25.
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months	2122 (4 RCTs) follow up: mean 9 weeks	⊕○○○ VERY LOW _{a,b,c}	RR 0.56 (0.31 to 1.00)	209 per 1,000	92 fewer per 1,000 (144 fewer to 0 fewer)	MID (precision) = RR 0.8-1.25.
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at >3 months	282 (1 RCT) follow up: 24 months	⊕⊕○○ LOW _{a,b}	RR 1.06 (0.80 to 1.41)	396 per 1,000	24 more per 1,000 (79 fewer to 162 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 2: Cardiovascular adverse events at ≤3 months	1170 (2 RCTs) follow up: mean 8 weeks	⊕○○○ VERY LOW _{a,b,e}	Peto OR 0.24 (0.05 to 1.07)	10 per 1,000	20 fewer per 1,000 (30 fewer to 0 fewer) _d	MID (precision) = Peto OR 0.8-1.25.
Serious adverse events 4: Central nervous system adverse events at ≤3 months	1440 (3 RCTs) follow up: mean 7 weeks	⊕○○○ VERY LOW _{a,b,e}	RR 0.57 (0.25 to 1.34)	18 per 1,000	8 fewer per 1,000 (14 fewer to 6 more) _d	MID (precision) = RR 0.8-1.25.

^a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with oral non-steroidal anti-inflammatory drugs	Risk difference with topical non-steroidal anti-inflammatory drugs	
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs c. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis d. Absolute effect calculated by risk difference due to zero events in at least one arm of one study e. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)						

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2 **1.1.6.2.4 Topical non-steroidal anti-inflammatory drugs compared to capsaicin for people with knee osteoarthritis**

3 **Table 49: Clinical evidence summary: topical non-steroidal anti-inflammatory drugs compared to capsaicin in knee osteoarthritis**

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with capsaicin	Risk difference with topical non-steroidal anti-inflammatory drugs	
Pain (NRS, 0-10, high is poor, change score) at <3 months	44 (1 RCT) follow-up: 12 weeks	⊕⊕○○ LOW ^{a,b}	-	The mean pain was -1.6	MD 0.4 higher (0.61 lower to 1.41 higher)	MID = 0.5 SD (SMD)
a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs						

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1 **1.1.6.2.4 Topical non-steroidal anti-inflammatory drugs compared to placebo for people with knee osteoarthritis**

2 **Table 50: Clinical evidence summary: topical non-steroidal anti-inflammatory drugs compared to placebo in knee osteoarthritis**

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with topical non-steroidal anti-inflammatory drugs	
Pain (WOMAC, VAS, 0-100, high is poor, final values and change scores) at ≤3 months	3135 (9 RCTs) follow up: mean 6 weeks	⊕○○○ VERY LOW _{a,b,c}	-	The mean pain was 24.1	MD 6.01 lower (9.87 lower to 2.16 lower)	MID = 5.8 (0.5 x median baseline control group SD)
Pain (WOMAC pain subscale, 0-20, high is poor, change scores) at ≤3 months	2458 (8 RCTs) follow up: mean 9 weeks	⊕⊕⊕○ MODERATE _a	-	The mean pain was 5.3	MD 1.32 lower (1.93 lower to 0.7 lower)	MID = 1.6 (0.5 x median baseline control group SD)
Physical function (WOMAC physical function subscale [different scale ranges], high is poor, change scores) at ≤3 months	3643 (12 RCTs) follow up: mean 8 weeks	⊕⊕○○ LOW _{a,b}	-	-	SMD 0.32 SD lower (0.47 lower to 0.18 lower)	MID = 0.5 SD (SMD)
Physical function (WOMAC physical function subscale, 0-100, high is poor, final value) at ≤3 months	828 (1 RCT) follow up: 12 weeks	⊕⊕⊕○ MODERATE _a	-	The mean physical function was 33.16	MD 2.91 lower (6.4 lower to 0.58 higher)	MID = 0.5 SD (SMD)
Serious adverse events 1A: Gastrointestinal (bleeding or perforation) adverse events at ≤3 months	1014 (3 RCTs) follow up: mean 10 weeks	⊕○○○ VERY LOW _{a,c,d}	Peto OR 0.43 (0.06 to 3.12)	9 per 1,000	0 fewer per 1,000 (10 fewer to 10 more) _e	MID (precision) = Peto OR 0.8-1.25.
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months	3895 (9 RCTs) follow up: mean 8 weeks	⊕○○○ VERY LOW _{a,d,f}	RR 0.91 (0.70 to 1.30)	33 per 1,000	0 fewer per 1,000 (10 fewer to 10 more) _e	MID (precision) = RR 0.8-1.25.
Serious adverse events 2: Cardiovascular adverse events at ≤3 months	3644 (7 RCTs) follow up:	⊕○○○ VERY LOW _{a,d,f}	RR 1.70 (1.00 to 2.57)	4 per 1,000	0 fewer per 1,000 (0 fewer to 10 more) _e	MID (precision) = RR 0.8-1.25.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with topical non-steroidal anti-inflammatory drugs	
	mean 10 weeks					
Serious adverse events 3: Hepatorenal adverse events at ≤3 months	1247 (4 RCTs) follow up: mean 5 weeks	⊕○○○ VERY LOW _{a,d,f}	RR 1.65 (0.29 to 2.41)	3 per 1,000	10 more per 1,000 (10 fewer to 20 more) _e	MID (precision) = RR 0.8-1.25.
Serious adverse events 4: Central nervous system adverse events at ≤3 months	3340 (8 RCTs) follow up: mean 11 weeks	⊕○○○ VERY LOW _{a,d,f}	RR 0.83 (0.53 to 1.16)	18 per 1,000	10 fewer per 1,000 (30 fewer to 10 more) _e	MID (precision) = RR 0.8-1.25.

- a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
- b. Downgraded by 1 or 2 increments because heterogeneity, unexplained by subgroup analysis
- c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
- d. Downgraded for heterogeneity due to conflicting number of events in different studies (zero events in one or more studies)
- e. Absolute effect calculated by risk difference due to zero events in at least one arm of one study
- f. Downgraded by 1 to 2 increments for imprecision due to zero events and small sample size

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2 **1.1.6.2.5 Topical non-steroidal anti-inflammatory drugs compared to placebo for people with hand osteoarthritis**

3 **Table 51: Clinical evidence summary: topical non-steroidal anti-inflammatory drugs compared to placebo in hand osteoarthritis**

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with topical non-steroidal anti-inflammatory drugs	
Pain (AUSCAN pain index, 0-100, high is poor, change score) at ≤3 months	385 (1 RCT)	⊕⊕⊕○ MODERATE _a	-	The mean pain was 22.5	MD 4.7 higher (0.77 lower to 10.17 higher)	MID = 0.5 SD (SMD)

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with topical non-steroidal anti-inflammatory drugs	
	follow up: 8 weeks					
Physical function (AUSCAN functional index, 0-100, high is poor, change score) at ≤3 months	385 (1 RCT) follow up: 8 weeks	⊕⊕⊕○ MODERATE ^a	-	The mean physical function was 19.2	MD 7.3 higher (1.74 higher to 12.86 higher)	MID = 0.5 SD (SMD)
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months	385 (1 RCT) follow up: 8 weeks	⊕○○○ VERY LOW ^{a,b}	RR 2.02 (0.84 to 4.85)	37 per 1,000	38 more per 1,000 (6 fewer to 142 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 4: Central nervous system adverse events at ≤3 months	385 (1 RCT) follow up: 8 weeks	⊕○○○ VERY LOW ^{a,b}	RR 1.09 (0.61 to 1.95)	102 per 1,000	9 more per 1,000 (40 fewer to 97 more)	MID (precision) = RR 0.8-1.25.
^a . Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias ^b . Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs						

1 **1.1.6.3 Topical (systemic) (including comparisons to oral formulations)**

2 **1.1.6.3.1 Transdermal strong opioids compared to oral strong opioids**

3 **Table 52: Clinical evidence summary: transdermal strong opioids compared to oral strong opioids**

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with oral strong opioids	Risk difference with transdermal strong opioids	
Pain (NRS, 0-10, high is poor, final value) at ≤3 months	134 (1 RCT) follow up: 12 weeks	⊕⊕○○ LOW ^a	-	The mean pain was 4.1	MD 0.18 lower (0.9 lower to 0.54 higher)	MID = 0.5 SD (SMD)
Serious adverse events 2: Cardiovascular adverse events at ≤3 months	134 (1 RCT) follow up: 12 weeks	⊕○○○ VERY LOW ^{a,b}	RR 8.49 (0.47 to 154.58)	0 per 1,000	60 more per 1,000 (0 fewer to 120 more) ^c	MID (precision) = RR 0.8-1.25.

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

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5 **1.1.6.3.2 Transdermal strong opioids compared to placebo**

6 **Table 53: Clinical evidence summary: transdermal strong opioids compared to placebo**

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with transdermal strong opioids	
Quality of life (SF-36 pain index, 0-100, high is good, change score) at ≤3 months	399 (1 RCT) follow up: 6 weeks	⊕○○○ VERY LOW ^{a,b}	-	The mean quality of life was 7.1	MD 4.3 higher (0.42 higher to 8.18 higher)	MID = 3 (established value)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with transdermal strong opioids	
Quality of life (SF-36 physical functioning, 0-100, high is good, change score) at ≤3 months	399 (1 RCT) follow up: 6 weeks	⊕○○○ VERY LOW _{a,b}	-	The mean quality of life was 2.9	MD 1.9 higher (1.58 lower to 5.38 higher)	MID = 3 (established value)
Quality of life (SF-36 role physical, 0-100, high is good, change score) at ≤3 months	399 (1 RCT) follow up: 6 weeks	⊕○○○ VERY LOW _{a,b}	-	The mean quality of life was 7.8	MD 2.5 lower (9.73 lower to 4.73 higher)	MID = 3 (established value)
Quality of life (SF-36 vitality, 0-100, high is good, change score) at ≤3 months	399 (1 RCT) follow up: 6 weeks	⊕○○○ VERY LOW _{a,b}	-	The mean quality of life was 3.1	MD 1.2 lower (5.22 lower to 2.82 higher)	MID = 2 (established value)
Quality of life (SF-36 general health, 0-100, high is good, change score) at ≤3 months	399 (1 RCT) follow up: 6 weeks	⊕○○○ VERY LOW _{a,b}	-	The mean quality of life was 3.4	MD 1 lower (4.19 lower to 2.19 higher)	MID = 2 (established value)
Quality of life (SF-36 mental health, 0-100, high is good, change score) at ≤3 months	399 (1 RCT) follow up: 6 weeks	⊕○○○ VERY LOW _{a,b}	-	The mean quality of life was 0.7	MD 1.1 lower (4.71 lower to 2.51 higher)	MID = 3 (established value)
Quality of life (SF-36 role emotional, 0-100, high is good, change score) at ≤3 months	399 (1 RCT) follow up: 6 weeks	⊕○○○ VERY LOW _{a,b}	-	The mean quality of life was 6	MD 8.4 lower (17.74 lower to 0.94 higher)	MID = 4 (established value)
Quality of life (SF-36 social functioning, 0-100, high is good, change score) at ≤3 months	399 (1 RCT) follow up: 6 weeks	⊕○○○ VERY LOW _{a,b}	-	The mean quality of life was 6.3	MD 3.1 lower (9.1 lower to 2.9 higher)	MID = 3 (established value)
Pain (WOMAC, NRS [different scale ranges], high is poor, change scores) at ≤3 months	710 (2 RCTs)	⊕○○○ VERY LOW _{a,b}	-	-	SMD 0.34 SD lower (0.66 lower to 0.01 lower)	MID = 0.5 SD (SMD)

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with transdermal strong opioids	
	follow up: 5 weeks					
Pain (WOMAC, 0-20, high is poor, change score) at >3 months	194 (1 RCT) follow up: 24 weeks	⊕⊕○○ LOW _{a,b}	-	The mean pain was -2.3	MD 0.9 lower (1.96 lower to 0.16 higher)	MID = 0.5 SD (SMD)
Physical function (WOMAC, unclear scale range, high is poor, change score) at ≤3 months	399 (1 RCT) follow up: 6 weeks	⊕⊕○○ LOW _a	-	The mean physical function was -0.7	MD 0.4 lower (0.67 lower to 0.13 lower)	MID = 0.5 SD (SMD)
Physical function (WOMAC, 0-68, high is poor, change score) at >3 months	190 (1 RCT) follow up: 24 weeks	⊕⊕○○ LOW _{a,b}	-	The mean physical function was -6.5	MD 3.5 lower (6.79 lower to 0.21 lower)	MID = 0.5 SD (SMD)
Serious adverse events 1B: Gastrointestinal (non-bleeding or perforation) adverse events at >3 months	199 (1 RCT) follow up: 24 weeks	⊕⊕○○ LOW _a	RR 2.26 (1.54 to 3.30)	253 per 1,000	319 more per 1,000 (137 more to 582 more)	MID (precision) = RR 0.8-1.25.
Serious adverse events 4: Central nervous system adverse events at >3 months	199 (1 RCT) follow up: 24 weeks	⊕⊕○○ LOW _a	RR 2.48 (1.55 to 3.96)	182 per 1,000	269 more per 1,000 (100 more to 539 more)	MID (precision) = RR 0.8-1.25.
<p>a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias</p> <p>b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs</p>						

1 See [Evidence review I OTT- appendices E-L](#) for full GRADE tables.

1 **1.1.7 Economic evidence**

2 **1.1.7.1 Included studies**

3 Seven health economic studies with relevant comparisons were included in this review:

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- 1 comparing NSAIDs to NSAIDs with gastroprotection⁴⁷;
 - 1 comparing paracetamol, NSAIDs, NSAIDs with gastroprotection and no treatment¹²¹;
 - 1 comparing paracetamol, NSAIDs, NSAIDs with gastroprotection, fixed-dose NSAIDs with gastroprotection and no treatment (NICE osteoarthritis clinical guidelines [CG177] 2014 – Consultation draft only)¹⁴⁵
 - 1 comparing topical NSAIDs and oral NSAIDs⁴²;
 - 2 comparing glucosamine with no treatment^{26, 36} and
 - 1 comparing glucosamine with no treatment and paracetamol¹⁸⁴.

13 These are summarised in the health economic evidence profiles below (**Table 54, Table 55**
14 and **Table 56**) and the health economic evidence tables in Appendix H.

15 No health economic studies were included that relate to weak or strong opioids (oral or
16 transdermal), anti-epileptics, antidepressants, capsaicin cream, rubefacients, and topical
17 local anaesthetics.

18 **1.1.7.2 Excluded studies**

19 One economic study relating to this review question was identified but excluded due to the
20 availability of more applicable evidence.³⁴ This is listed in Appendix C, with reasons for
21 exclusion given.

22 See also the health economic study selection flow chart in Appendix G.

1 **1.1.8 Summary of included economic evidence**

2 **Table 54: Health economic evidence profile: Oral analgesics**

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Chen 2009 ⁴⁷ UK	Directly applicable ^(a)	Potentially serious limitations ^(b)	<p>Probabilistic model based on meta-analysis of RCTs</p> <p>Cost-utility analysis (QALYs)</p> <p>Population: People with arthritis (majority osteoarthritis)</p> <p>Comparators:</p> <p>NSAIDs (ibuprofen, diclofenac, low and high dose celecoxib, branded and generic etodolac, etoricoxib, lumiracoxib, low and high dose meloxicam, rofecoxib, valdecoxib)</p> <p>NSAIDs with gastroprotection (ibuprofen + PPI, diclofenac + PPI)</p> <p>Time horizon: 5 years</p>	For full incremental analysis of all 14 treatments please see the full evidence table in Appendix H.		The most cost-effective treatment at the £20,000 per QALY gained is low dose meloxicam (ICER: £12,557 per QALY gained compared to ibuprofen)	<p>Multiple deterministic sensitivity analyses were undertaken in which low dose meloxicam remains the most cost-effective option.</p> <p>Diclofenac with gastroprotection was found to be the most cost effective treatment in a scenario analysis undertaken for populations with increased risk of GI events.</p>
Latimer 2009 ¹²¹ UK	Directly applicable ^(c)	Potentially serious limitations ^(d)	<p>Probabilistic model based on meta-analysis of RCTs</p> <p>Cost-utility analysis (QALYs)</p> <p>Population: People with symptomatic osteoarthritis</p> <p>Comparators:</p> <p>No treatment</p> <p>Paracetamol</p>	For full incremental analysis of all 12 treatments please see the full evidence table in Appendix H.		Celecoxib with gastroprotection found to be the most cost effective treatment (ICER: £10,724 per QALY gained compared to etoricoxib with gastroprotection).	<p>Celecoxib plus gastroprotection remains most cost effective option for a number of sensitivity analyses.</p> <p>Etoricoxib plus gastroprotection becomes the most cost effective option when</p>

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			<p>NSAIDs (diclofenac, naproxen, ibuprofen, etoricoxib, celecoxib)</p> <p>NSAIDs with gastroprotection (diclofenac + PPI, naproxen + PPI, ibuprofen + PPI, etoricoxib + PPI, celecoxib + PPI)</p> <p>Time horizon: Lifetime</p>			All treatments without the addition of gastro-protection were found to accumulate fewer QALYs and similar costs to those with gastroprotection. Therefore it was considered that the addition of gastroprotection is highly cost effective.	the same stroke risk for etoricoxib as celecoxib is assumed.
NICE Osteoarthritis clinical guidelines 2014 (consultation draft only)	Directly applicable ^(e)	Potentially serious limitations ^(f)	<p>Probabilistic model based on meta-analysis of RCTs</p> <p>Cost-utility analysis (QALYs)</p> <p>Population: People with osteoarthritis</p> <p>Comparators:</p> <p>No treatment</p> <p>Paracetamol</p> <p>NSAIDs (diclofenac, naproxen, ibuprofen, etoricoxib, celecoxib)</p> <p>NSAIDs with gastroprotection (diclofenac + PPI, naproxen + PPI, ibuprofen + PPI, etoricoxib + PPI, celecoxib + PPI)</p> <p>Fixed-dose NSAID with gastroprotection</p>	For full incremental analysis of all 15 treatments please see the full evidence table in Appendix H.		Etoricoxib with gastroprotection found to be the most cost effective treatment (ICER: £13,214 per QALY gained compared to diclofenac with gastroprotection).	<p>Etoricoxib + PPI remained the most cost effective option when the treatment duration was increased from 3 months to 2 years and also when the starting age was increased to 65 years to reflect the population with greater baseline gastrointestinal and cardiovascular risk.</p> <p>However the results of probabilistic analysis highlighted the overall uncertainty about which drug is the most</p>

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			(diclofenac 150mg + misoprostol 400mg, Naproxen 1000mg + esomeprazole 40mg, Ketoprofen 200mg + omeprazole 20mg) Time horizon: Lifetime				cost effective: etoricoxib + PPI (10.3%), diclofenac + PPI (34.5%), celecoxib + PPI (6.1%), naproxen + PPI (23.5%), ibuprofen +PPI (6.1%).

Abbreviations: ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life years; NSAID = non-steroidal anti-inflammatory drugs; PPI = proton pump inhibitor; RCT= randomised controlled trial

(a) Study does not include all comparators being assessed in the review. 2009 units costs may not reflect the current NHS context.

(b) Mixed arthritis population in RCTs used for derive treatment effect, although the majority of people have osteoarthritis.

(c) Study does not include all comparators being assessed in the review. 2008 units costs may not reflect the current NHS context. Utilities were not derived directly from EQ-5D questionnaire in line with NICE reference case, but from mapping from WOMAC.

(d) Further RCTs have been published for some of the comparators and therefore treatment effects may not reflect the full body of evidence. Unclear source of estimates for resource use.

(e) Study does not include all comparators being assessed in the review. Unit costs from 2012 may not reflect the current NHS context. Utilities were not derived directly from EQ-5D questionnaire but were mapped from WOMAC.

(f) Further RCTs have been published for some of the comparators and therefore treatment effects may not reflect the full body of evidence. Unclear source of estimates for resource use in dyspepsia, symptomatic ulcer and complicated GI events.

1 **Table 55: Health economic evidence profile: Oral vs topical NSAID**

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Castelnuovo 2008/Underwood 2008 ⁴² UK	Partially applicable ^(a)	Potentially serious limitations ^(b)	<ul style="list-style-type: none"> • Within-RCT analysis (Underwood 2008²⁰⁸) • Cost-utility analysis (QALYs) • Population: People aged 50 years and over who had troublesome pain in or around the knee on most days for at least a month as well as knee pain for >3 months in the preceding year. Radiological diagnosis was not required. • Comparators: <ol style="list-style-type: none"> 1. Topical ibuprofen 2. Oral ibuprofen Time horizon: 12 months	£191 ^(c)	0.021 QALYs	£9,114 per QALY gained	Probability oral ibuprofen cost effective (£30K threshold): 80% Oral ibuprofen remains cost effective in multiple sensitivity analyses.

2 Abbreviations: ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life years; RCT= randomised controlled trial

3 (a) Resource use (2003-2005) and inflated unit costs (2006) may not reflect current UK NHS practice.

4 (b) Within-trial analysis and so may not reflect full body of available evidence for this comparison; 1 of X studies included in the clinical review for topical versus oral NSAID. A
5 longer time horizon may be preferable given that glucosamine seems to become less cost effective over time.

6 (c) 2006 costs. Cost components incorporated: prescriptions, consultations, diagnostic tests, hospital admissions, equipment and aids.

7

1 **Table 56: Health economic evidence profile: Glucosamine**

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental QALYs	Cost effectiveness	Uncertainty
Black 2009 ²⁶ UK	Partially applicable ^(a)	Potentially serious limitations ^(b)	<ul style="list-style-type: none"> • Probabilistic model based on progression to total knee replacement. • Cost-utility analysis (QALYs) • Population: People with knee osteoarthritis • Comparators: <ol style="list-style-type: none"> 1. Usual care 2. Glucosamine sulphate plus usual care • Lifetime horizon 	£2,405 ^(c)	0.11	£21,335 per QALY gained	<p>Probability glucosamine sulphate in addition to usual care cost effective (£20/£30K threshold): 43%</p> <p>Results robust to one-way sensitivity analyses on key parameters.</p>
Bruyere 2019 ³⁶ Belgium	Partially applicable ^(d)	Potentially serious limitations ^(e)	<ul style="list-style-type: none"> • Individual patient data simulation • Cost-utility analysis (QALYs) • Population: People with osteoarthritis • Comparators: <ol style="list-style-type: none"> 1. No treatment (placebo) 2. Prescription crystalline glucosamine sulphate 3. Other forms of glucosamine • Time horizon: 3, 6 & 36 months 	<p>3 months: ^(f)</p> <p>2 – 1: £124 3 – 1: £44</p> <p>6 months:</p> <p>2 – 1: £247 3 – 1: £88</p> <p>36 months:</p> <p>2 – 1: £1,484</p>	<p>3 months:</p> <p>2 – 1: 0.026 3 – 1: 0.001</p> <p>6 months:</p> <p>2 – 1: 0.058 3 – 1: -0.003</p> <p>36 months:</p> <p>2 – 1: 0.145</p>	<p>3 months:</p> <p>2 – 1: £4,730 per QALY gained 3 – 1: £43,990 per QALY gained</p> <p>6 months:</p> <p>2 – 1: £4,252 per QALY gained 3 – 1: Int 1 dominates 3</p> <p>36 months:</p> <p>2 – 1: £10,203 per QALY gained</p>	<p>Probability interventions cost effective (£20/£30K threshold): NR</p> <p>Sensitivity analysis undertaken adjusting for the fact that different studies used different time points. In this case, longer study data was used at all time points. In this case, prescription crystalline glucosamine sulphate no longer cost effective, and other forms of glucosamine are dominated by no treatment at all time points.</p>

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental QALYs	Cost effectiveness	Uncertainty
Scholtissen 2010 ¹⁸⁴ Spain	Partially applicable ^(g)	Potentially serious limitations ^(h)	<ul style="list-style-type: none"> • Deterministic decision analytic model • Cost-utility analysis (QALYs) • Population: People with symptomatic osteoarthritis • Comparators: <ol style="list-style-type: none"> 1. No treatment (placebo) 2. Paracetamol 3. Glucosamine • Time horizon: 6 months 	2-1: £44 3-2: saves £9	3-1: 0.01 3-2: 0.01	Intervention 3 dominates intervention 2. 3 vs 1: £3,488 per QALY gained (da)	Probability 3 cost effective (£19K threshold): 71%

1 Abbreviations: ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life years

2 (a) Study does not include all comparators being assessed in the review. Resource use (1999) and unit costs (2008) may not reflect current NHS practice. Utilities were not derived
3 directly from EQ-5D questionnaire in line with NICE reference case, but from mapping from WOMAC to HUI3.

4 (b) Further RCTs have been published for reporting quality of life and so treatment effects may not reflect the full body of evidence .

5 (c) 2008 costs. Cost components incorporated: GP visits, medications, outpatient visits, inpatient care, professions allied to medicine consultations, complementary therapist and
6 X-ray procedures

7 (d) Study does not include all comparators being assessed in the review. Utilities were not derived directly from EQ-5D questionnaire in line with NICE reference case, but from
8 mapping from WOMAC.

9 (e) Only incorporates the cost of glucosamine and not other resource use and therefore costs may not be fully represented.

10 (f) 2017 Euros converted to UK pounds.¹⁵⁰. Cost components incorporated: glucosamine costs

11 (g) Study does not include all comparators being assessed in the review. Spanish resource use and unit costs (2009) may not reflect current UK NHS practice. Utilities not derived
12 from EQ-5D in line with NICE reference case.

13 (h) Time horizon may not capture the change in benefit over time. Treatment effects determined from one trial and so may not reflect the full body of evidence. No analysis of
14 uncertainty undertaken.

15 (i) 2009 costs. Cost components incorporated: Drug costs only adjusted for compliance. Other healthcare costs were assumed to be comparable between treatment groups.

1 1.1.9 Economic model

2 1.1.9.1 Population and strategies evaluated

3 The modelled population were adults with osteoarthritis. The strategies compared were:

4 1. No treatment: patients do not have drug treatment for their osteoarthritis.

5 2. Paracetamol

6 3. Oral NSAIDs plus PPIs

7 4. Oral NSAIDs alone

8 5. Topical NSAIDs

9 6. Oral strong opioids

10 7. Transdermal buprenorphine.

11 Patients take one drug for a treatment duration of three months.

12 1.1.9.2 Methods and data sources (Summary)

13 Baseline adverse event probabilities

- 14 • The probability of gastrointestinal (GI) bleeds with no treatment was taken from all
15 relevant trials between oral NSAIDs alone and no treatment, oral NSAIDs with PPIs
16 and no treatment and oral NSAIDs with PPI and oral NSAIDs alone.
- 17 • The probability of GI non-bleeding adverse events with no treatment were based on
18 those most frequently observed during clinical trials and taken from all relevant trials.
19 Constipation, nausea and vomiting were most frequently reported with oral strong
20 opioids and transdermal buprenorphine, while dyspepsia and symptomatic ulcer were
21 most frequently reported with oral NSAIDs with and without PPIs.
- 22 • There were eight health states linked to cardiovascular (CV) events: stable angina
23 (SA), unstable angina (UA), myocardial infarction (MI), transient ischaemic attack
24 (TIA), non-fatal stroke, death resulting from coronary heart disease (CHD) and death
25 resulting from cerebrovascular disease (CVD). The overall rate of CV events was
26 taken from literature and the distribution of CV events were taken from the QRISK2.
- 27 • The incidence of acute kidney injury (AKI), progression from AKI to chronic kidney
28 disease (CKD) stages 3-4 and further progression to CKD stage 5 were all taken from
29 literature.
- 30 • The incidence of acute liver failure (ALF) and the proportion of patients with ALF who
31 subsequently have a liver transplant were also taken from literature.
- 32 • Vertigo was a commonly reported adverse event of the central nervous system with
33 oral strong opioids and transdermal buprenorphine and its probability of occurring
34 was based reported cases from all relevant trials.

35 Treatment effects - adverse events

- 36 • Adverse events data associated with drug treatment were taken from the clinical
37 review and applied to each cycle of the model for the relevant drug treatment.

38 Mortality

- 39 • Transition probabilities for mortality in the no treatment arm were based on the Office
40 of National Statistics (ONS) life tables for England 2018-20.
- 41 • Excess mortality from GI bleeding, CV events, AKI, ALF and liver transplant were
42 taken from literature. It was assumed there was no excess mortality with constipation,
43 nausea, vomiting and vertigo.

- 1 • Standardised mortality ratios associated with chronic health states (CV events, CKD
2 stages 3-4, CKD stage 5 and post-liver transplant) were taken from literature.

3 **Treatment effects – utilities**

- 4 • EQ-5D scores were not directly available for all interventions and in many instances
5 were mapped from SF-36 or WOMAC scores.
- 6 • The incremental EQ-5D gain versus no treatment were as follows:
7 ○ paracetamol (0.035)
8 ○ oral NSAIDs plus PPI and oral NSAIDs alone
9 ○ (0.051), topical NSAIDs (0.102),
10 ○ oral strong opioids (0.009) and
11 ○ transdermal buprenorphine (0.061).
- 12 • Utility multipliers or utility decrements were applied in the case of an adverse event.
13 These were taken from literature.

14 **1.1.9.3 Resource use and costs**

- 15 • The cost of the different drug treatments were obtained from the Drug Tariff⁷¹, with
16 doses based on Average Daily Quantities (ADQs) for the relevant indication taken
17 from the online BNF.⁶³ A weighted average of drug class costs was used based on
18 prescription usages data between 2020/21 released by the NHS.⁷²
- 19 • It was assumed that all people with osteoarthritis attended annual follow-ups with
20 their GP. Patients receiving NSAIDs or opioids were also assumed to attend an
21 additional appointment with their GP during the year, with patients receiving NSAIDs
22 also having an annual biochemistry test.
- 23 • The costs of hospital resources (e.g., endoscopy) were taken from the NHS
24 Reference Costs 2019/20.⁷³ Staff costs were taken from the PSSRU unit costs
25 2020.²⁷
- 26 • Resource use associated with gastrointestinal (GI) bleeds, dyspepsia and
27 symptomatic ulcer were based on a decision tree, following assumptions made in the
28 2006 HTA paper on gastroprotection (Brown 2006).{Brown, 2006 #4185} Costs of
29 each branch in the decision tree were calculated using HRG codes from the NHS
30 reference costs 2019/20.{NHS England and NHS Improvement, 2020 #4188}
- 31 • For the remaining non-bleeding GI adverse events (constipation, nausea, vomiting
32 and vertigo), a single GP consultation along with a prescription for 14 days treatment
33 was assumed.
- 34 • For cardiovascular (CV) adverse events, costs for stroke were taken from Xu 2016⁶⁰,
35 costs for transient ischaemic attack (TIA), unstable angina (UA) and heart failure (HF)
36 were taken from Danese 2016{Danese, 2016 #4169}, while the cost of treating stable
37 angina (SA) was taken from NHS Reference costs 2019/20.⁷⁴ All costs were inflated
38 to 2019/20 costs.
- 39 • The cost of treating acute kidney injury was taken from NHS Reference Costs
40 2019/20.⁷⁴ The cost of treating chronic kidney disease were also based on NHS
41 Reference costs and further calculations were based on assumptions made in the
42 NICE acute kidney injury guideline [CG169,NG148]{National Institute for, 2013
43 #4289}{National Institute for, 2019 #4291}
- 44 • The cost of acute liver failure (ALF) and liver transplant were taken from the NHS
45 Reference costs 2019/20.⁷⁴
- 46 • For vertigo, a single GP consultation along with a prescription for 14 days treatment
47 was assumed.

1 **1.1.9.4 Computations**

2 The key outcomes were mean NHS cost per patient and mean QALYs per patient. These
3 were calculated using a state-transition (Markov) model structure. Costs and QALYs
4 occurring in the future were discounted at 3.5% per year to be consistent with the NICE
5 reference case. The results were calculated both:

- 6 • Deterministically, based on the point estimates of each input parameter
- 7 • Probabilistically, based on a distribution for each input parameter (estimated using its
8 standard error) and sampling the results 10,000 times before calculating a mean (Monte
9 Carlo simulation).

10 **1.1.9.5 Results**

11 The base case results can be found in Table 57 and Figure 1. They show that all
12 interventions are cost effective compared with no treatment except for oral NSAIDs plus PPI
13 (cost per QALY gained of £28,190) and oral strong opioids (cost per QALY gained of
14 £32,916). A comparison of probabilistic incremental net health benefit shows that there were
15 four treatments ranked higher than no treatment. Topical NSAIDs are the optimal treatment
16 strategy, followed by oral NSAIDs alone, followed by paracetamol and lastly buprenorphine.

17 Results of sensitivity analysis are presented in Table 58. When the treatment duration was
18 extended over a lifetime with the assumption that adverse events occur in the first cycle only,
19 all interventions were cost effective versus no treatment. The addition of falls and fractures
20 from drug treatment into the analysis resulted in transdermal buprenorphine no longer being
21 cost effective versus no treatment (cost per QALY gained of £26,120). Co-prescribing
22 laxatives with opioids did not significantly alter base case results for oral strong opioids and
23 transdermal buprenorphine. NSAIDs plus PPIs were cost effective versus no treatment when
24 certain assumptions around cardiovascular adverse events were relaxed; specifically when
25 the adverse events of stable angina, unstable angina and transient ischaemic attack were
26 removed from the model, when the relative risk of cardiovascular events was the same as
27 that of NSAIDs alone, when acute mortality associated with cardiovascular events were
28 removed and when the long-term relative risk of mortality after a cardiovascular event was
29 the same as the general population. NSAIDs plus PPIs were also cost effective versus no
30 treatment when utilities were mapped using the Barton and Price algorithms instead of the
31 Walioo algorithm. The inclusion of trials that reported VAS pain scores during mapping led to
32 two significant changes versus base case results; paracetamol was dominated by no
33 treatment and oral strong opioids became cost effective versus no treatment (cost per QALY
34 gained of £18,852). Strong oral opioids were also cost effective when the morphine-
35 equivalent daily dose was less than or equal to 40mg (cost per QALY gained of £16,332) but
36 not when it was greater than 40mg.

Table 57. Cost effectiveness (probabilistic base case results)

	No treatment	Paracetamol	Oral NSAIDs + PPIs	Oral NSAIDs alone	Topical NSAIDs	Oral strong opioids	Transdermal buprenorphine
Total costs	£5,867	£5,891	£5,983	£5,904	£5,906	£5,927	£5,956
Life years (undiscounted)	22.82	22.82	22.79	22.81	22.82	22.82	22.82
QALYs	5.5683	5.5756	5.5724	5.5791	5.5818	5.5701	5.5777
Incr. cost (vs no treatment)	£0	£24	£116	£37	£38	£60	£89
Incr. QALYs (vs no treatment)	-	0.0073	0.0041	0.0108	0.0135	0.0018	0.0094
ICER (n versus no treatment)	-	£3,301	£28,190	£3,449	£2,847	£32,916	£9,454
NHB @20k threshold	5.27	5.28	5.27	5.28	5.29	5.27	5.28
Rank of NHB	5	3	7	2	1	6	4

Figure 1. Cost effectiveness plane (probabilistic base case results)

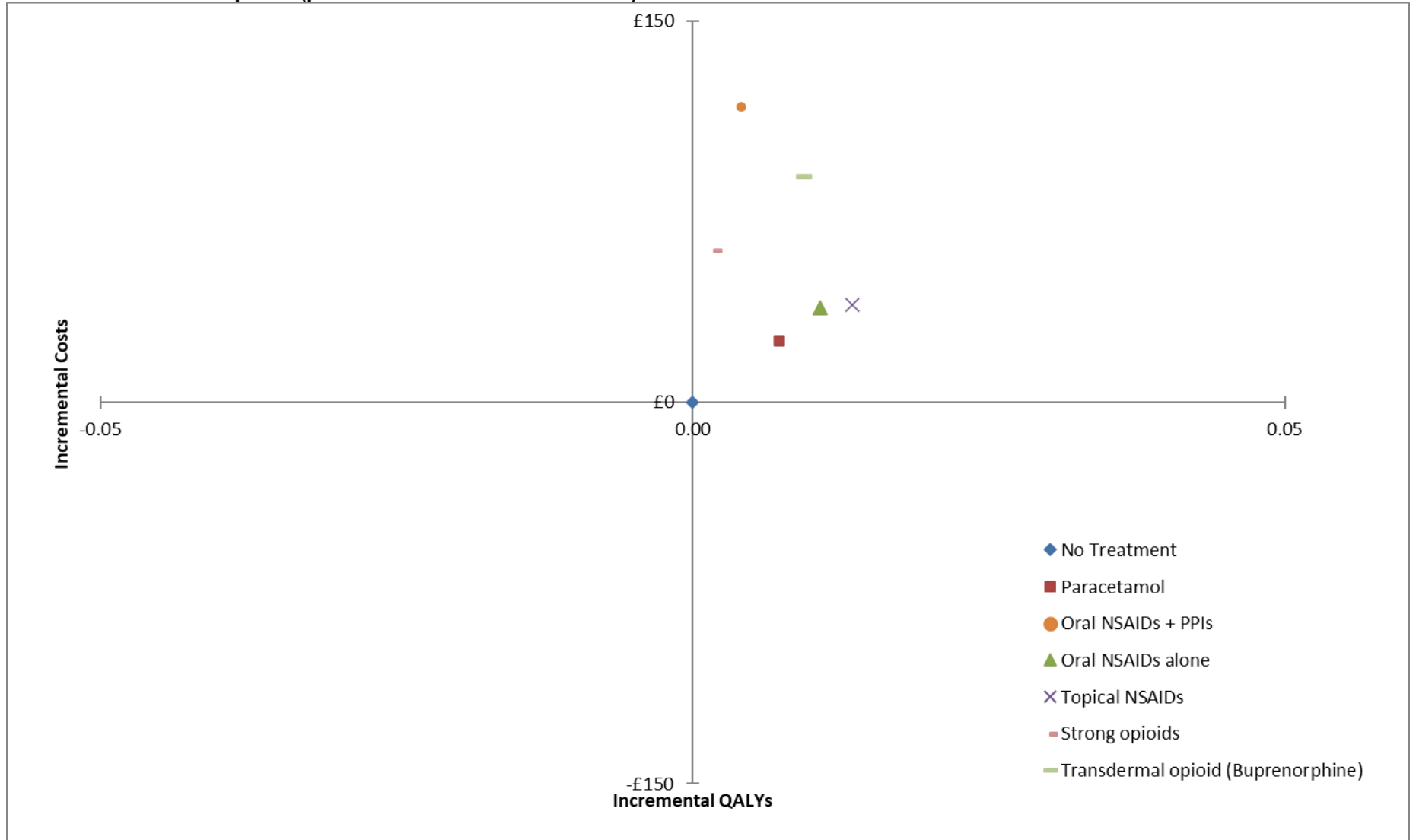


Table 58. Rank of net health benefit (£20,000 per QALY gained) (probabilistic sensitivity analyses)

Analysis	Costs						
	No treatment	Paraceta mol	Oral NSAIDs + PPIs	Oral NSAIDs alone	Topical NSAIDs	Oral strong opioids	Buprenorp hine
Base case results	5	3	6	2	1	7	4
Treatment duration							
Lifetime treatment duration with some AEs in the first cycle only	7	3	6	2	1	5	4
Adverse events							
Add falls and hip fractures	5	3	4	2	1	7	6
Add laxatives with opioids	6	3	5	2	1	7	4
Remove SA, UA, TIA	6	3	4	2	1	7	5
NSAID+PPI CV event RR same as NSAID alone	6	4	3	2	1	7	5
Use NSAIDs plus PPI RR for CV events from NMA	5	3	7	2	1	6	4
Exclude sudden CV deaths	6	3	5	2	1	7	4
Only short-term CV impact of treatment	6	3	4	2	1	7	5
Utilities							
Oral opioids QoL equal to transdermal opioids	6	4	7	2	1	3	5
Utilities: Barton algorithm	6	3	5	2	1	7	4
Utilities: Price algorithm	6	3	5	2	1	7	4
Utilities: Lawrence algorithm	5	3	6	2	1	7	4
Utilities: Maund algorithm	6	2	7	4	1	5	3
Costs							
Use drug cost from trials	5	3	7	2	1	6	4
Other							
Including all VAS trials	5	7	6	2	1	4	3
Oral strong opioids =<40mg MMED trials	6	3	7	2	1	5	4

Oral strong opioids >40mg MMED trials	5	3	6	2	1	7	4
Paracetamol best case scenario	5	3	7	2	1	6	4
Paracetamol worst case scenario	5	7	6	2	1	4	3
Oral NSAIDs plus PPI best case	6	4	3	2	1	7	5

1 1.1.11 Economic evidence statements

2 In a comparison of paracetamol and no treatment

- 3 • One cost utility analysis reported that paracetamol was cost effective versus no
4 treatment (£12,771), however, in a full incremental analysis it was extendedly
5 dominated by oral NSAIDs plus PPIs. This analysis was assessed as directly
6 applicable with potentially serious limitations.{Latimer, 2009 #160}
- 7 • One cost utility analysis reported that paracetamol dominated by no treatment. This
8 analysis was assessed as directly applicable with minor limitations.{National Institute
9 for Health and Care Excellence, 2014 #3138}
- 10 • One original cost utility analysis from this guideline review reported that paracetamol
11 was cost effective compared with no treatment (£3,301). This analysis was assessed
12 as directly applicable with minor limitations.

13 In a comparison of oral NSAIDs alone and no treatment

- 14 • One cost utility analysis reported that diclofenac, ibuprofen, naproxen and COX-2
15 inhibitors celecoxib and etoricoxib were dominated by no treatment. This analysis
16 was assessed as directly applicable with potentially serious limitations.{Latimer, 2009
17 #160}
- 18 • One cost utility analysis reported that diclofenac, ibuprofen and naproxen were
19 dominated by no treatment. However, COX-2 inhibitors celecoxib and etoricoxib were
20 cost effective. This analysis was assessed as directly applicable with minor
21 limitations.{National Institute for Health and Care Excellence, 2014 #3138}
- 22 • One original cost utility analysis from this guideline review reported that oral NSAIDs
23 alone were cost effective compared with no treatment (£3,449). This analysis was
24 assessed as directly applicable with minor limitations.

25 In a comparison of oral NSAIDs plus PPIs and no treatment

- 26 • One cost utility analysis reported that oral NSAIDs plus PPIs were cost effective
27 compared with no treatment. This analysis was assessed as directly applicable with
28 potentially serious limitations.{Latimer, 2009 #160}
- 29 • One cost utility analysis reported that oral NSAIDs plus PPIs were cost effective
30 compared with no treatment. This analysis was assessed as directly applicable with
31 minor limitations.{National Institute for Health and Care Excellence, 2014 #3138}
- 32 • One original cost utility analysis from this guideline review reported that oral NSAIDs
33 plus PPIs were not cost effective compared with no treatment (£28,190). This
34 analysis was assessed as directly applicable with minor limitations.

35 In a comparison of oral NSAIDs plus PPIs and oral NSAIDs alone

- 36 • One cost utility analysis reported that meloxicam alone was the most cost-effective
37 strategy in a full incremental analysis. It was assessed as directly applicable with
38 potentially serious limitations.{Chen, 2009 #157}
- 39 • One cost utility analysis reported that celecoxib 200mg plus PPI was the most cost-
40 effective strategy in a full incremental analysis (£12,557). It was assessed as directly
41 applicable with potentially serious limitations.{Latimer, 2009 #160}
- 42 • One cost utility analysis reported that etoricoxib 200mg plus PPI was the most cost-
43 effective strategy in a full incremental analysis (13,160). Fixed-dose combinations
44 (ketoprofen 200mg/omeprazole 20mg, diclofenac 150mg/misoprostol 400mg and
45 naproxen 1000mg/esomeprazole 40mg) were also dominated by NSAIDs plus PPI.
46 This analysis was assessed as directly applicable with minor limitations.{National
47 Institute for Health and Care Excellence, 2014 #3138}

- 1 • One original cost utility analysis from this guideline review reported that oral NSAIDs
2 plus PPIs were dominated by oral NSAIDs alone. This analysis was assessed as
3 directly applicable with minor limitations.
- 4 In a comparison of topical NSAIDs and no treatment
- 5 • One original cost utility analysis reported that topical NSAIDs were cost effective
6 compared with no treatment (£2,847). This analysis was assessed as directly
7 applicable with minor limitations.
- 8 In a comparison of oral NSAIDs and topical NSAIDs
- 9 • One cost utility analysis reported that oral ibuprofen was cost effective compared with
10 topical ibuprofen (£9,114). This analysis was assessed as partially applicable with
11 potentially serious limitations.{Castelnuovo, 2008 #150}
- 12 • One original cost utility analysis from this guideline review reported that oral NSAIDs
13 with and without PPIs were dominated by topical NSAIDs. This analysis was
14 assessed as directly applicable with minor limitations.
- 15 In a comparison of oral strong opioids and no treatment
- 16 • One original cost utility analysis from this guideline review reported that oral strong
17 opioids were not cost effective compared with no treatment (£32,916). This analysis
18 was assessed as directly applicable with minor limitations.
- 19 In a comparison of transdermal buprenorphine and no treatment
- 20 • One original cost utility analysis from this guideline review reported that the
21 transdermal opioid buprenorphine was cost effective compared with no treatment
22 (£9,454). This analysis was assessed as directly applicable with minor limitations.
- 23 In a comparison of glucosamine with no treatment or paracetamol
- 24 • One cost utility analysis reported that glucosamine was not cost effective compared
25 with no treatment (£21,335). This analysis was assessed as directly applicable with
26 minor limitations.{Black, 2009 #155}
- 27 • One cost utility reported that prescription crystalline glucosamine sulphate was cost
28 effective compared to no treatment (£10,203), but that other forms of glucosamine
29 were dominated by no treatment. This analysis was assessed as partially applicable
30 with potentially serious limitations.{Bruyere, 2019 #253}
- 31 • One cost utility analysis reported that glucosamine was cost effective compared with
32 no treatment (£3,488). It also reported that that glucosamine dominated paracetamol.
33 This analysis was assessed as partially applicable with potentially serious limitations.

34 **1.1.12 The committee's discussion and interpretation of the evidence**

35 **1.1.12.1. The outcomes that matter most**

36 The critical outcomes were quality of life, pain and physical function. These were considered
37 critical due to their relevance to people with osteoarthritis. The Osteoarthritis Research
38 Society International (OARSI) consider that pain and physical function were the most
39 important outcomes for evaluating interventions. Quality of life gives a broader perspective
40 on the person's wellbeing, allowing for examination of the biopsychosocial impact of
41 interventions. The important outcomes were psychological distress, osteoarthritis flare and
42 serious treatment adverse events, which was split into five categories: gastrointestinal
43 (bleeding or perforation) events, gastrointestinal (non-bleeding or perforation) events,
44 cardiovascular events, renal and hepatic events, and central nervous system events.

1 The committee considered osteoarthritis flares to be important in the lived experience and
2 management of osteoarthritis. However, these were also considered difficult to measure with
3 no clear consensus on their definition. The Flares in OA OMERACT working group have
4 proposed an initial definition and domains of OA flares through a consensus exercise; “it is a
5 transient state, different from the usual state of the condition, with a duration of a few days,
6 characterized by onset, worsening of pain, swelling, stiffness, impact on sleep, activity,
7 functioning, and psychological aspects that can resolve spontaneously or lead to a need to
8 adjust therapy.”. However this has been considered to have limitations and has not been
9 widely adopted. Therefore, the committee included the outcome accepting any reasonable
10 definition provided by any studies..

11 Mortality was included as a treatment adverse events rather than as a discreet outcome and
12 categorised as an important outcome. Osteoarthritis as a disease process is not considered
13 to cause mortality by itself and mortality is an uncommon outcome from osteoarthritis
14 interventions. There was evidence available for all outcomes. However, while the critical
15 outcomes were reported frequently for all comparisons, other outcomes were reported less
16 frequently (of note osteoarthritis flares, which was only reported in one study).

17 **1.1.12.2 The quality of the evidence**

18 One-hundred and seventy three studies were included in the review. The comparisons where
19 evidence was identified are below:

- 20 • Comparisons to placebo
 - 21 ○ Oral medicines
 - 22 – Paracetamol
 - 23 – Non-steroidal anti-inflammatory drugs
 - 24 – Non-steroidal anti-inflammatory drugs with gastroprotection
 - 25 – Weak opioids
 - 26 – Strong opioids
 - 27 – Anti-epileptic drugs
 - 28 – Antidepressant drugs
 - 29 – Glucosamine
 - 30 ○ Topical (local) medicines
 - 31 – Capsaicin for knee osteoarthritis
 - 32 – Non-steroidal anti-inflammatory drugs for knee osteoarthritis
 - 33 – Non-steroidal anti-inflammatory drugs for hand osteoarthritis
 - 34 ○ Topical (systemic) medicines
 - 35 – Transdermal opioids
- 36 • Interventions compared to other interventions
 - 37 ○ Oral medicines
 - 38 – Non-steroidal anti-inflammatory drugs compared to paracetamol
 - 39 – Non-steroidal anti-inflammatory drugs with gastroprotection compared to
40 paracetamol
 - 41 – Non-steroidal anti-inflammatory drugs with gastroprotection compared to non-
42 steroidal anti-inflammatory drugs
 - 43 – Strong opioids compared to non-steroidal anti-inflammatory drugs
 - 44 – Anti-epileptic drugs compared to antidepressant drugs
 - 45 – Glucosamine compared to paracetamol
 - 46 – Glucosamine compared to non-steroidal anti-inflammatory drugs

- 1 ○ Topical (local) medicines (including comparisons to oral medicines)
- 2 – Topical non-steroidal anti-inflammatory drugs compared to oral non-steroidal anti-
- 3 inflammatory drugs for knee osteoarthritis
- 4 ○ Topical (systemic) medicines (including comparisons to oral medicines)
- 5 – Transdermal opioids compared to oral strong opioids

6 There were no relevant clinical studies comparing the following interventions:

- 7 • Rubefacients
- 8 • Local anaesthetic

9
10 For the topical (local) medicines, where the trials were stratified by the site of osteoarthritis,
11 the only sites of osteoarthritis included in the review were knee and hand.

12 There was minimal moderate evidence and only one outcome with high quality evidence
13 included in this review. Outcomes were commonly downgraded for inconsistency, risk of bias
14 and imprecision. Inconsistent results were not explained by subgroup analysis or resolved by
15 sensitivity analyses. Risk of bias concerns were common, with the most common problems
16 being due to problems with allocation concealment and participant dropout. The number of
17 participants varied between comparisons, which some comparisons having a large sample
18 size (including oral non-steroidal anti-inflammatory drugs compared to placebo) while others
19 had very small sample sizes (including anti-epileptic drugs compared to placebo). More detail
20 about each class of medicine is listed below:

21 ***Paracetamol***

22 Evidence was available comparing paracetamol to placebo, oral non-steroidal anti-
23 inflammatory drugs (with and without gastroprotection) and glucosamine.

- 24 • When compared to placebo, evidence was generally of low quality, but ranged from
25 moderate to very low quality. Where downgrading occurred, this was often for risk of bias
26 (in particular selection and attrition bias) and imprecision.
- 27 • When compared to oral non-steroidal anti-inflammatory drugs (without gastroprotection),
28 evidence was generally of very low quality, but ranged from moderate to very low. Where
29 downgrading occurred, this was often for risk of bias (in particular selection and attrition
30 bias) and imprecision.
- 31 • When compared to oral non-steroidal anti-inflammatory drugs with gastroprotection,
32 evidence was generally of very low quality, but ranged from low to very low quality. When
33 downgrading occurred, this was often for risk of bias (in particular selection and attrition
34 bias) and imprecision.
- 35 • When compared to glucosamine, evidence was generally of low quality, but ranged from
36 low to very low. Where downgrading occurred, this was mainly due to risk of bias (in
37 particular selection and attrition bias).

38 ***Oral non-steroidal anti-inflammatory drugs***

39 Studies comparing oral non-steroidal anti-inflammatory drugs to placebo, paracetamol, oral
40 non-steroidal anti-inflammatory drugs with gastroprotection, strong opioids, glucosamine and
41 topical non-steroidal anti-inflammatory drugs were included in the analysis.

- 42 • When compared to placebo, evidence was generally of very low quality, but ranged from
43 high to very low quality. Where downgrading occurred, this was often for risk of bias (in
44 particular selection and attrition bias) and imprecision. Some outcomes were downgraded
45 for inconsistency (where subgroup analysis did not resolve the heterogeneity).

- 1 • When compared to paracetamol, evidence was generally of very low quality, but ranged
2 from moderate to very low. Where downgrading occurred, this was often for risk of bias (in
3 particular selection and attrition bias) and imprecision.
- 4 • When compared to oral non-steroidal anti-inflammatory drugs with gastroprotection,
5 evidence was generally of low quality, but ranged from moderate to very low quality.
6 Where downgrading occurred, this was for risk of bias (in particular selection and attrition
7 bias), imprecision or indirectness (namely population indirectness where 10-20% of the
8 population of one study had rheumatoid arthritis).
- 9 • When compared to strong opioids, evidence was generally of very low quality, but ranged
10 from low to very low quality. Where downgrading occurred, this was often for risk of bias
11 (in particular selection and attrition bias) or imprecision.
- 12 • When compared to glucosamine, evidence was generally of very low quality, but ranged
13 from low to very low quality. Where downgrading occurred, this was often for risk of bias
14 (in particular selection and attrition bias) or inconsistency (where subgroup analysis did
15 not resolve the heterogeneity).
- 16 • When compared to topical non-steroidal anti-inflammatory drugs, evidence was generally
17 of low quality, but ranged from moderate to very low quality. Where downgrading
18 occurred, this was often for risk of bias and imprecision. Some outcomes were
19 downgraded for inconsistency (where subgroup analysis did not resolve the
20 heterogeneity).

21 ***Oral non-steroidal anti-inflammatory drugs with gastroprotection***

22 Studies comparing oral non-steroidal anti-inflammatory drugs with gastroprotection to
23 placebo, paracetamol and oral non-steroidal anti-inflammatory drugs without gastroprotection
24 were included in the analysis.

- 25 • When compared to placebo, evidence was generally of very low quality, but ranged from
26 low to very low quality. Where downgrading occurred, this was for risk of bias and
27 imprecision. In one cases the outcome was downgraded for outcome indirectness (due to
28 only using data where there were withdrawals due to adverse events for an adverse event
29 outcome).
- 30 • When compared to paracetamol, evidence was generally of very low quality, but ranged
31 from low to very low quality. When downgrading occurred this was often for risk of bias (in
32 particular selection and attrition bias) and imprecision.
- 33 • When compared to oral non-steroidal anti-inflammatory drugs (without gastroprotection),
34 evidence was generally of low quality, but ranged from moderate to very low quality.
35 Where downgrading occurred, this was for risk of bias (in particular selection and attrition
36 bias), imprecision or indirectness (namely population indirectness where 10-20% of the
37 population of one study had rheumatoid arthritis).

38 ***Opioids: Strong opioids, weak opioids and transdermal opioids***

39 Studies comparing strong opioids to placebo, oral non-steroidal anti-inflammatory drugs
40 (without gastroprotection) and transdermal opioids were included in the analysis.

- 41 • When compared to placebo, evidence was generally of very low quality, but ranged from
42 low to very low quality. When downgrading occurred, this was often due to risk of bias (in
43 particular attrition bias) and imprecision. Some outcomes were downgraded for
44 inconsistency (where subgroup analysis did not resolve the heterogeneity).
- 45 • When compared to oral non-steroidal anti-inflammatory drugs (without gastroprotection),
46 evidence was generally of very low quality, but ranged from low to very low quality. Where
47 downgrading occurred, this was often for risk of bias (in particular selection and attrition
48 bias) or imprecision.

- 1 • When compared to transdermal opioids, evidence was of low to very low quality.
2 Outcomes were downgraded for risk of bias (in particular attrition bias) and imprecision.
- 3 Whereas only one study comparing weak opioids to placebo was included. The quality of
4 evidence was very low. Downgrading occurred due to risk of bias and imprecision.
- 5 Finally, studies compared transdermal opioids (which included buprenorphine and fentanyl)
6 to placebo and oral strong opioids were included.
- 7 • When compared to placebo, evidence was of low to very low quality. Outcomes were
8 downgraded for risk of bias (in particular selection and attrition bias) and imprecision.
- 9 • When compared to oral strong opioids, evidence was of low to very low quality. Outcomes
10 were downgraded for risk of bias (in particular attrition bias) and imprecision.

11 ***Anti-epileptic drugs***

12 Two studies were included that compared anti-epileptic drugs (namely gabapentinoids) to
13 antidepressant drugs and placebo or paracetamol respectively. Quality was generally low or
14 very low. Outcomes were downgraded for risk of bias (in particular attrition bias) and
15 imprecision.

16 ***Antidepressant drugs***

17 Studies comparing antidepressant drugs to placebo and anti-epileptic drugs were included in
18 the analysis.

- 19 • When compared to placebo, the evidence was of moderate quality, ranging from
20 moderate to very low quality. Outcome were downgraded for risk of bias (in particular
21 attrition bias), inconsistency (where subgroup analysis did not resolve the heterogeneity)
22 and imprecision.
- 23 • When compared to anti-epileptic drugs, the evidence was of low or very low quality.
24 Outcomes were downgraded for risk of bias (in particular attrition bias) and imprecision.

25 ***Glucosamine***

26 Studies comparing glucosamine to placebo, paracetamol and oral non-steroidal anti-
27 inflammatory drugs (without gastroprotection) were included in the analysis.

- 28 • When compared to placebo, evidence was generally of low quality, ranging from moderate
29 to very low. Where downgrading occurred, this was mainly due to risk of bias or
30 imprecision. In some cases this was due to inconsistency (where subgroup analysis did
31 not resolve the heterogeneity).
- 32 • When compared to paracetamol, evidence was generally of low quality, but ranged from
33 low to very low. Where downgrading occurred, this was mainly due to risk of bias (in
34 particular selection and attrition bias).
- 35 • When compared to oral non-steroidal anti-inflammatory drugs (without gastroprotection),
36 evidence was generally of very low quality, but ranged from low to very low quality. Where
37 downgrading occurred, this was often for risk of bias (in particular selection and attrition
38 bias) or inconsistency (where subgroup analysis did not resolve the heterogeneity).

39 ***Topical capsaicin***

40 Studies comparing topical capsaicin to placebo (in knee or hand osteoarthritis) were included
41 in the analysis. There was one study included for each of the osteoarthritis joint sites.

- 42 • When compared to placebo in people with knee osteoarthritis, the quality was either
43 moderate or low. Where downgraded this was due to risk of bias (in particular selection
44 bias) and imprecision.

- 1 • When compared to placebo in people with hand osteoarthritis, the quality was very low.
2 This was downgraded for risk of bias and imprecision.

3 **Topical non-steroidal anti-inflammatory drugs**

4 Studies comparing topical non-steroidal anti-inflammatory drugs to oral non-steroidal anti-
5 inflammatory drugs (without gastroprotection) in people with knee osteoarthritis, or placebo in
6 people with knee or hand osteoarthritis were included in the analysis. There was 1 study
7 included for people with hand osteoarthritis, while there were more studies including people
8 with knee osteoarthritis.

- 9 • When compared to oral non-steroidal anti-inflammatory drugs in people with knee
10 osteoarthritis, evidence was generally of low quality, but ranged from moderate to very low
11 quality. Where downgrading occurred, this was often for risk of bias and imprecision.
12 Some outcomes were downgraded for inconsistency (where subgroup analysis did not
13 resolve the heterogeneity).
- 14 • When compared to placebo in people with knee osteoarthritis, evidence was generally of
15 very low quality, but ranged from moderate to very low. Where downgrading occurred, this
16 was often due to risk of bias (in particular selection bias), inconsistency (that was not
17 resolved by subgroup analysis) or imprecision.
- 18 • When compared to placebo in people with hand osteoarthritis, evidence was of moderate
19 to very low quality. Where outcomes were downgraded, this was due to risk of bias (in
20 particular selection and attrition bias) and imprecision.

21 Where there was no evidence (rubefacients and local anaesthetics) and where there was
22 very little evidence (weak opioids, anti-epileptic drugs and antidepressant drugs other than
23 duloxetine) the committee were not confident in making recommendations and the committee
24 recommended further research (see research recommendations RR1, 2, 3, 4 and 6).

25 **1.1.12.3 Benefits and harms**

26 **Key uncertainties**

27 There was very limited evidence for specific interventions, including the use of topical
28 capsaicin and anti-epileptic drugs. For the topical analgesics there was no or limited
29 evidence for their use in sites other than knee osteoarthritis. The committee agree that in
30 some cases this is reasonable, as studies have shown that it is unlikely that these
31 formulations will be able to penetrate for more proximal, deep joints (for example: hip
32 osteoarthritis). However, there is insufficient evidence to state whether topical medicines will
33 have the same or a different effect when compared to knee osteoarthritis, and so should be
34 considered when prescribing topical medicines.

35 The majority of trials making up the evidence was conducted for periods of time less than 3
36 months, with only specific interventions conducting longer term trials (the main intervention
37 that was studied for longer periods of time being glucosamine). This, added with limitations in
38 the results of randomised controlled trials for reporting safety data, provides uncertainty into
39 the long-term risks of using these medicines and whether they retain any benefits or lose
40 efficacy after prolonged exposure.

41 Some trials included in this analysis were enrichment trials, where the population selected
42 may have had features that made the analysis more difficult to interpret. This included trials
43 that included people who responded to the medication class previously, trials that excluded
44 people who did not respond to the medication class previously and selection of specific
45 populations (including people who had not responded to other medications or fulfilled specific
46 response criteria). These criteria could lead to more favourable conditions for the active
47 medicine arm of the trial and so could lead to artificially increased effects. The inclusion

1 criteria were considered against this for all studies. In general, enrichment designs were
2 more common in papers investigating the use of non-steroidal anti-inflammatory drugs
3 (including oral and topical formulations) and strong opioids. Studies investigating the use of
4 paracetamol were inconsistent, with some using enriched designs while others did not use
5 specific response criteria. Studies investigating other medications generally did not use
6 response criteria. Due to this, sensitivity analyses were conducted to investigate the effect of
7 enrichment trials and to see if the results from enrichment design trials led to an important
8 difference in the meta-analysis. These analyses found that where heterogeneity was present,
9 the sensitivity analysis did not lead to a resolution of the heterogeneity in most cases and
10 therefore, the enrichment designs likely did not contribute to this. The committee noted that
11 for trials involving non-steroidal anti-inflammatory drugs the effect sizes were generally larger
12 in trials that included enriched populations but not by a clinically important amount. The
13 committee considered this when making their recommendations.

14 The committee acknowledged that evidence examining the use of the interventions may be
15 present for other populations. This review specifically investigated the use of the medicines
16 for people with osteoarthritis. However, some evidence for other conditions may provide
17 additional information about the effect of the medicine (for example: for people with pain for
18 other reasons). The committee considered this when examining the evidence and used their
19 expert knowledge in conjunction with the evidence identified while making recommendations.

20

21 ***Paracetamol***

22 Studies comparing paracetamol to placebo, oral non-steroidal anti-inflammatory drugs (with
23 and without gastroprotection) and glucosamine were included in the analysis and none
24 demonstrated a clinical benefit of paracetamol. This evidence came from populations with
25 either knee osteoarthritis or mixed (knee or hip) osteoarthritis. This included different
26 formulations of paracetamol, including extended released formulations, which are not
27 commonly used in clinical practice.

28 The results when compared to placebo showed no clinically important difference in quality of
29 life at less than 3 months, pain and physical function at less than and greater than 3 months,
30 gastrointestinal (bleeding or perforation and non-bleeding or perforation), hepatorenal and
31 central nervous system adverse events at less than 3 months and cardiovascular adverse
32 events at less than and greater than 3 months. However, there was a clinically important
33 harm of paracetamol in hepatorenal adverse events at greater than 3 months in 1 moderately
34 sized study. These findings concurred/were complemented by comparisons with oral non-
35 steroidal anti-inflammatory drugs (with and without gastroprotection) and glucosamine. Oral
36 non-steroidal anti-inflammatory drugs with gastroprotection were more effective than
37 paracetamol although they also showed more hepatorenal events at less than 3 months..

38 The committee noted the effect size for pain reduction with paracetamol when compared to
39 placebo was particularly small compared to the other interventions (0.05 standard deviations
40 lower, from 0.11 lower to 0.02 higher) and agreed that paracetamol was unlikely to have any
41 noticeable benefit for the majority of people with osteoarthritis. Taking into account the
42 potential hepatic adverse events that can come from longer term paracetamol use, and the
43 lack of clinical efficacy the committee agreed that paracetamol should not be routinely used
44 for people with osteoarthritis. The committee agreed that the amount of evidence was
45 sufficient and therefore a research recommendation was not required.

46

1 **Oral non-steroidal anti-inflammatory drugs**

2 Studies comparing oral non-steroidal anti-inflammatory drugs to placebo, paracetamol, oral
3 non-steroidal anti-inflammatory drugs with gastroprotection, strong opioids, glucosamine and
4 topical non-steroidal anti-inflammatory drugs were included in the analysis. This evidence
5 came from populations with mostly knee osteoarthritis, with some including mixed joint site
6 osteoarthritis (knee or hip, with some cases where hand osteoarthritis was included). This
7 included a range of different types of non-steroidal anti-inflammatory drugs (including non-
8 selective non-steroidal anti-inflammatory drugs, such as ibuprofen and diclofenac, and COX-
9 2 selective non-steroidal anti-inflammatory drugs, such as etoricoxib and celecoxib). The
10 studies generally included participants with a mean age less than 75 years.

11 Most studies were classified as enrichment trials, where selection criteria may reduce the
12 number of non-responders and/or increase the number of responders to the medicines. This
13 included 'flare' design studies, where participants were included if they had an increase in
14 pain after their previous non-steroidal anti-inflammatory drug was stopped. The committee
15 decided to conduct a sensitivity analysis for this if heterogeneity was present. 4 outcomes
16 had statistical heterogeneity and of these 1 outcome had statistical heterogeneity that was
17 resolved by a sensitivity analysis removing every enrichment study (pain [WOMAC, VAS
18 [different scale ranges], high is poor, change scores] at ≤ 3 months). However, on looking at
19 the analysis the committee agreed that this was unlikely to be a true solution to the source of
20 the heterogeneity as the sensitivity analysis removed all but 3 studies (when the original
21 analysis included 45 studies), while the main contributors to the heterogeneity were 5 outlier
22 study results. In removing studies in the sensitivity analysis, this removed many studies that
23 reported similar results to the 3 remaining studies. Given these factors, the committee
24 decided to use the original analysis, therefore including the enrichment studies in their
25 decision making.

26 The results when compared to placebo showed a mixed effect on quality of life (including 7
27 GRADE outcomes showing a clinically important benefit, and 3 showing no clinically
28 important difference) and no clinically important difference for pain, physical function,
29 gastrointestinal (bleeding or perforation and non-bleeding or perforation), cardiovascular,
30 hepatorenal and central nervous system adverse events at less than 3 months. Additionally,
31 the evidence showed no clinically important difference for pain, gastrointestinal (non-bleeding
32 or perforation), cardiovascular and hepatorenal adverse events at more than 3 months.
33 These results were mostly consistent when compared to paracetamol, with the exception of
34 gastrointestinal (non-bleeding or perforation) events, where a clinically important harm was
35 seen in 1 very low quality outcome with 178 participants. This harm was also seen when
36 compared to glucosamine and topical non-steroidal anti-inflammatory drugs. This was also
37 true when compared to non-steroidal anti-inflammatory drugs and gastroprotection apart
38 from for gastrointestinal (bleeding or perforation) events where a clinically important benefit
39 of non-steroidal anti-inflammatory drugs with gastroprotection was seen at less than 3
40 months, but not at more than 3 months. Similar results were also seen when compared to
41 strong opioids, glucosamine (apart from a clinically important benefit of non-steroidal anti-
42 inflammatory drugs for pain at more than 3 months) and topical non-steroidal anti-
43 inflammatory drugs. The adverse events differences were not reflected by the committee's
44 experiences where they would have expected higher levels of gastrointestinal adverse
45 events in clinical practice, in particular gastrointestinal (bleeding or perforation) events.

46 The committee wanted to emphasise that the aim of this review question was not to conduct
47 a full safety analysis of the medicines included and that randomised controlled trial evidence
48 risks being unable to capture safety events that other types of evidence may detect better
49 (such as cohort studies and registry data). Therefore, the committee included their
50 knowledge of safety warnings from other organisations (including the MHRA) while making
51 their decision. In particular, they noted the potential risk of gastrointestinal bleeding or

1 perforation, cardiovascular and renal adverse events due to non-steroidal anti-inflammatory
2 drug use.

3 While they noted there was no clinically important benefit for pain and physical function, they
4 agreed that there was a consistent direction/signal of small benefits for these outcomes.
5 Given this it is possible that the effect could be clinically important in this population. The
6 committee considered evidence from clinical practice alongside the evidence from trials.
7 Given this, the potential for harm and evidence from clinical practice, the committee agreed
8 that they could be considered for people in whom topical medicines are ineffective or
9 unsuitable. They emphasised that, as with all drug therapy (1.4.1, non-steroidal anti-
10 inflammatory drugs should only be used for the shortest time period possible as a way to
11 minimise the potential harms that could occur from using the medicine.

12

13 ***Oral non-steroidal anti-inflammatory drugs with gastroprotection***

14 Studies comparing oral non-steroidal anti-inflammatory drugs with gastroprotection to
15 placebo, paracetamol and oral non-steroidal anti-inflammatory drugs without gastroprotection
16 were included in the analysis. This evidence came from populations with mainly mixed joint
17 site osteoarthritis (knee or hip). The gastroprotection agents used included synthetic
18 prostaglandin analogues (misoprostol) and proton pump inhibitors (omeprazole and
19 esomeprazole). While proton pump inhibitors are commonly used in current clinical practice,
20 prostaglandin analogues are not. It was agreed that this evidence could still be relevant
21 showing the effect of a medicine that could reduce gastrointestinal bleeding and perforation
22 events, and so evidence including prostaglandin analogues were not downgraded for
23 indirectness. However, the committee agreed that this evidence could be extrapolated to this
24 support their decision making. .

25 When compared to placebo, oral non-steroidal anti-inflammatory drugs with gastroprotection
26 was shown to cause a clinically important benefit for pain at less than 3 months in 1 outcome
27 (n=1 , 418 participants), while showing no clinically important difference for gastrointestinal
28 (bleeding or perforation and non-bleeding or perforation) and cardiovascular adverse events
29 at less than 3 months. However, there was a clinically important harm for hepatorenal
30 adverse events at less than 3 months in the same study. These results were consistent when
31 compared to paracetamol, but were different when compared to oral non-steroidal anti-
32 inflammatory drugs without gastroprotection where there was no clinically important different
33 in pain and hepatorenal adverse events at less than 3 months in 1 outcome including 1 study
34 with 481 participants, and a clinically important benefit in gastrointestinal (bleeding or
35 perforation) adverse events at less than 3 months. However, this benefit was not retained at
36 greater than 3 months with 1 outcome containing 1 study with 4484 participants showing no
37 clinically important difference. Other adverse events showed no clinically important difference
38 as with the other comparisons. The committee agreed that this was consistent with their
39 experiences.

40 There was limited evidence for this comparison (with at most 3 studies informing any
41 outcomes). The results are consistent with those for oral non-steroidal anti-inflammatory
42 drugs without gastroprotection and show a potential benefit of adding gastroprotection for
43 reducing gastrointestinal (bleeding or perforation) events. However, this was associated with
44 an increase in cardiovascular adverse events which, while not a clinically important
45 difference, was a larger increase than with oral non-steroidal anti-inflammatory drugs alone.
46 The committee considered that this may be unrelated to the addition of gastroprotection. As
47 previously stated, given that randomised controlled trial evidence may not be the best
48 method for looking for safety evidence, the committee complemented this evidence with
49 clinical experience and guidance from other organisations, including the MHRA. Given this
50 and evidence from clinical practice, the committee agreed the gastroprotection may be

1 helpful for someone people. On balancing this with the cost-effectiveness evidence, the
2 committee decided that gastroprotection may not be required by all people with osteoarthritis,
3 but may be useful for people at risk of gastrointestinal bleeding events. Therefore, the
4 committee agreed a recommendation agreeing that gastroprotection should be considered
5 when assessing whether non-steroidal anti-inflammatory drugs are an appropriate treatment.

6

7 ***Opioids: Oral strong opioids, oral weak opioids and transdermal opioids***

8 1 small study (including 66 participants) compared an oral weak opioid (codeine) to placebo
9 in people with mixed joint site (knee or hip) osteoarthritis. Two outcomes were reported, pain
10 and physical function at less than 3 months, which both showed a clinically important benefit
11 of weak opioids.

12 The evidence is limited, the committee noted that codeine containing products are commonly
13 prescribed in current practice. There was no evidence identified regarding adverse events.
14 Therefore, the committee used their clinical experience to inform their decision making.

15 Studies comparing oral strong opioids to placebo, oral non-steroidal anti-inflammatory drugs
16 and transdermal opioids were included in the analysis. These studies included populations
17 with mainly mixed joint site osteoarthritis (knee or hip) or knee osteoarthritis. The medicines
18 included morphine, oxycodone, tramadol, tapentadol, oxymorphone and hydromorphone,
19 including standard release and extended release formulations for some of these medicines.

20 When compared to placebo, oral strong opioids showed a mixed effect on quality of life at
21 less than 3 months (with 2 outcomes based on 1 study with 182 participants showing a
22 clinically important benefit, and 6 outcomes based on 7 studies with 4762 participants
23 showing no clinically important difference), no clinically important difference in pain, physical
24 function, psychological distress and cardiovascular adverse events at less than 3 months,
25 and a clinically important harm of oral strong opioids for gastrointestinal (non-bleeding or
26 perforation) and central nervous system adverse events at less than 3 months. These
27 findings were mostly consistent when compared to oral non-steroidal anti-inflammatory drugs
28 varying only for quality of life (instead showing no clinically important different in 1 outcome,
29 and a clinically important harm in 1 outcome) and showing no clinically important difference
30 in central nervous system adverse events. When compared to transdermal opioids, there
31 was no clinically important difference in pain, but clinically important harms of transdermal
32 opioids for gastrointestinal (non-bleeding or perforation), cardiovascular events and central
33 nervous system events at less than 3 months, based on limited evidence (1 study). The
34 committee agreed that this was consistent with their experiences.

35 Studies comparing transdermal opioids to placebo and oral strong opioids were included in
36 the analysis. The studies included a population with mixed joint site (knee or hip)
37 osteoarthritis. The committee agreed that the doses used were representative of clinical
38 practice, except for Langford 2006¹²⁰, where the dose was significantly larger than what
39 would be used. In this case, the population were not opioid naïve. However, in current
40 practice clinicians would be more likely to stop the opioid medication, as the pain is deemed
41 to be opioid non-respondent, rather than to further titrate the dose up.

42 The results showed that transdermal opioids, when compared to placebo, had a mixed effect
43 on quality of life at less than 3 months (with a clinically important benefit in the pain subscale
44 of SF-36, no clinically important difference for the physical functioning, role physical, vitality,
45 general health and mental health subscales, and a clinically important harm for the role
46 emotional and social functioning subscales) based on 1 study with 399 participants.
47 Additionally, it showed no clinically important difference in the effect on pain and physical
48 function at less than and greater than 3 months. However, they showed a clinically important
49 harm in gastrointestinal (non-bleeding or perforation) adverse events and central nervous

1 system adverse events at greater than 3 months. The effect on pain was also observed at
2 less than 3 months when transdermal opioids were compared to oral strong opioids.
3 Additionally, they showed clinically important harms in gastrointestinal (non-bleeding or
4 perforation) adverse events, cardiovascular adverse events and central nervous system
5 adverse events.

6 The committee debated the terminology of weak and strong opioids. The definition agreed for
7 this review included tramadol in the oral strong opioid classification, as stated in the BNF.
8 However, when looking at opioid receptor activity, tramadol is defined as an oral weak opioid.
9 The committee discussed the morphine equivalent doses of different opioids when
10 considering their recommendation. This is an area of debate in the wider medical community
11 with no clear consensus.

12 The committee noted that the studies, of particular note for transdermal opioids, did not
13 investigate the medicine in populations where the majority of participants were over the age
14 of 75 years and specific populations where transdermal preparations may be more beneficial
15 (for example: people with dementia who may find it difficult to use oral medicines). There was
16 only one study investigating the route of administration, which included 134 participants. This
17 study showed increased adverse events. However, this may be explained by the dose of
18 medication, as the morphine equivalence was different between the two interventions
19 (buprenorphine initiated at 5 micrograms [equivalent to 12mg per day] compared to tramadol
20 initiated at 150mg per day [equivalent to 15mg per day]). Ultimately, they agreed that
21 clinicians should ensure the route of administration is tailored to the patients' needs and
22 preferences. However, they cautioned that there was little data to guide the benefits and
23 harms of different routes of opioids, particularly among the oldest population and those with
24 cognitive impairment.

25 Overall, in this discussion, the committee agreed that, given the adverse events and clinical
26 knowledge that the risk of adverse events increase with an increasing dose of opioids, if an
27 opioid has to be used because of pain that is not controlled by other means, then the lowest
28 possible dose should be used for as little time as possible. The committee acknowledged
29 that some adverse events, such as addiction, were not identified in this review and can have
30 a significant effect. Given all of these factors, the committee recommended that weak opioids
31 should not be routinely used and that strong opioids should not be used for people with
32 osteoarthritis. When considering prescribing opioids NICE's guideline on Medicines
33 associated with dependence or withdrawal symptoms: safe prescribing and withdrawal
34 management for adults should be consulted. The committee also made a research
35 recommendation to investigate the effect of oral weak opioids given the limited evidence for
36 this comparison.

37

38 ***Anti-epileptic drugs***

39 1 small study (n=65) compared an anti-epileptic drug (pregabalin) to an antidepressant drug
40 (duloxetine) and placebo while another small study investigated the use of the a different
41 anti-epileptic drug (gabapentin) and the same antidepressant drug compared to paracetamol.
42 The population included people with hand and knee osteoarthritis respectively. The studies
43 reported outcomes for pain and physical function at less than 3 months, which when
44 compared to placebo or paracetamol showed a clinically important benefit of antiepileptic
45 drugs. When compared to placebo, no clinically important difference was seen in
46 psychological distress at less than 3 months. When compared to placebo, clinically important
47 harms in gastrointestinal (non-bleeding or perforation) and cardiovascular adverse events
48 were observed. When compared to paracetamol, clinically important harms in central
49 nervous system adverse events were seen. When compared to antidepressant drugs, there
50 was no clinically important difference in gastrointestinal (non-bleeding or perforation) adverse

1 events and a clinically important benefit of anti-epileptic drugs in cardiovascular adverse
2 events.

3 Anti-epileptic drugs are not licensed for use in osteoarthritis in the United Kingdom, but may
4 have been used off-label by clinicians. The committee agreed that the evidence available
5 was very limited data, with only 1 small study with a small number of participants, and that it
6 was not possible to draw any conclusions from this. Given that there was limited evidence
7 the committee recommended further research (see research recommendations).

8

9 ***Antidepressant drugs***

10 Studies comparing antidepressant drugs to placebo and anti-epileptic drugs were included in
11 the analysis. The population mostly included people with knee osteoarthritis, although one
12 study included people with hand osteoarthritis. In these studies, the type of antidepressant
13 used was duloxetine, with only one study being available reporting other antidepressants
14 (nortriptyline).

15 The evidence showed a clinically important benefit for quality of life at less than 3 months
16 and psychological distress at more than 3 months. However, the effect on psychological
17 distress at less than 3 months was mixed, with a clinically important benefit in 1 outcome
18 reporting the HADS anxiety scale results for 2 studies, and no clinically important difference
19 in 1 outcome reporting the HADS depression scale results for 2 studies. There was a
20 clinically important benefit in pain and physical function at more than 3 months based on 1
21 study (reporting outcomes at 16 weeks) with a limited number of participants (288 people).
22 There was no clinically important difference in pain (in 7 studies with 1955 participants) and
23 physical function (in 5 studies with 1510 participants) at less than 3 months. Additionally,
24 there was no clinically important difference in cardiovascular and hepatorenal adverse
25 events, but clinically important harms in gastrointestinal (non-bleeding or perforation) and
26 central nervous system adverse events at less than 3 months.

27 Antidepressant drugs are not licensed for use in osteoarthritis in the United Kingdom but may
28 have been used off-label by clinicians. The committee noted that when this is used for people
29 with osteoarthritis, it is more common that tricyclic antidepressants (such as amitriptyline) are
30 prescribed. Given the limited evidence for any other types of antidepressants the committee
31 were unsure about the applicability of the evidence to current practice in the United Kingdom.
32 They noted that duloxetine at the dose prescribed would provide a dual antidepressant effect
33 as well as treating pain, which would not be the case for tricyclic antidepressants at the
34 doses prescribed in clinical practice. This added additional uncertainty into the results.

35 Given the limited data of efficacy with potential harms and the lack of applicability to current
36 practice in the United Kingdom, the committee did not recommend the use of antidepressant
37 drugs but suggested further research into other types of antidepressants (such as tricyclic
38 antidepressants) and their long term effectiveness in a research recommendation.

39

40 ***Glucosamine***

41 Studies comparing glucosamine to placebo, paracetamol and oral non-steroidal anti-
42 inflammatory drugs were included in the analysis. The population mostly included people
43 with knee osteoarthritis with one study including people with hip osteoarthritis and one
44 including people with temporomandibular joint osteoarthritis. When examined next to the
45 BNF, none of the formulations that are reported in the formulary had trial data reporting their
46 use in people with osteoarthritis. However, we included any study with a dose of
47 glucosamine greater than 1176mg/day (as the ruling from the MHRA review on glucosamine

1 was that a dose above this amount would be classified as a medicine). This included
2 glucosamine hydrochloride, glucosamine sulfate and other formulations of glucosamine
3 (including potassium salts).

4 When compared to placebo, the results showed no clinically important difference in
5 gastrointestinal (non-bleeding or perforation) and central nervous system adverse events at
6 less than 3 months, quality of life, osteoarthritis flares and hepatorenal adverse events at
7 more than 3 months, pain and physical function and pain, physical function and
8 cardiovascular adverse events at both less than and more than 3 months. These results
9 were similar when compared to paracetamol, with the exception that glucosamine showed a
10 clinically important benefit in hepatorenal adverse events at more than 3 months. When
11 compared to oral non-steroidal anti-inflammatory drugs, glucosamine showed a clinically
12 important benefit in gastrointestinal (non-bleeding or perforation) adverse events at less than
13 3 months; no clinically important difference in gastrointestinal (bleeding or perforation) and
14 central nervous system events at less than 3 months, physical function at more than 3
15 months, and cardiovascular and hepatorenal adverse events at less than and more than 3
16 months, with a clinically important harm in pain at more than 3 months. This was consistent
17 with the experiences of the committee members.

18 The committee noted that the effect size for pain reduction and physical function with
19 glucosamine when compared to placebo was small. On examination of the forest plots the
20 committee noted that the effect size was similar to that of oral non-steroidal anti-inflammatory
21 drugs. However, this effect size was amplified by three studies, of which two of these had a
22 smaller number of participants. The committee agreed that the results for oral non-steroidal
23 anti-inflammatory drugs were more consistent with a larger number of participants
24 contributing to the value. In this way, they justified that the results for glucosamine were less
25 certain and could have been more influenced by the studies with a positive value. To this
26 end, the committee concluded that glucosamine was unlikely to have a benefit for the
27 majority of people with osteoarthritis.

28 This was more evident in long term studies with the mean time over 1 year, where the effects
29 were minimal for pain and physical function. The committee explained that one of the
30 reasons why glucosamine is prescribed is for long term effects on maintaining function. The
31 studies included in this review did not show any evidence to support this.

32 Therefore, based on the lack of evidence of benefits the committee recommended to
33 glucosamine should not be routinely used for people with osteoarthritis. Due to the significant
34 amount of evidence available, the committee agreed that a research recommendation was
35 not required.

36

37 ***Topical capsaicin***

38 Studies comparing topical capsaicin to placebo in people with knee and hand osteoarthritis
39 were included. The evidence for this comparison was limited, with one study each of the joint
40 sites (including 198 people with knee osteoarthritis, and 41 people with hand osteoarthritis
41 respectively). The evidence for knee osteoarthritis showed clinical important benefits for pain
42 and physical function, and no clinically important difference for adverse events. In
43 comparison, the evidence for hand osteoarthritis showed no clinically important difference for
44 pain.

45 The committee noted the limited evidence available. Given the limited evidence and the
46 increased cost from capsaicin compared to topical non-steroidal anti-inflammatory drugs, the
47 committee recommended that capsaicin should not be routinely offered for people with
48 osteoarthritis. However, they recommended further research to further investigate the effect.

1

2 Topical non-steroidal anti-inflammatory drugs

3 Studies comparing topical non-steroidal anti-inflammatory drugs to placebo in people with
4 knee and hand osteoarthritis, and oral non-steroidal anti-inflammatory drugs in people with
5 knee osteoarthritis were included. The active ingredients included ibuprofen, diclofenac,
6 ketoprofen and piroxicam, which was agreed to be representative of the different types of
7 topical non-steroidal anti-inflammatory drugs used in current clinical practice.

8 Most studies were classified as enrichment trials, where selection criteria may reduce the
9 number of non-responders and/or increase the number of responders to the medicines. This
10 included 'flare' design studies, where participants were included if they had an increase in
11 pain after their previous non-steroidal anti-inflammatory drug was stopped. The committee
12 decided to conduct a sensitivity analysis for this if heterogeneity was present. 2 outcomes
13 had statistical heterogeneity and of these 1 outcome had statistical heterogeneity that was
14 resolved by a sensitivity analysis removing only the most selective enrichment studies
15 (Physical function [WOMAC physical function subscale [different scale ranges], high is poor,
16 change scores] at ≤ 3 months). However, on looking at the analysis the committee agreed
17 that this was unlikely to be a true solution to the source of the heterogeneity as the sensitivity
18 analysis removed all but 3 studies (when the original analysis included 11 studies), while the
19 main contributors to the heterogeneity were 2 outlier study results. In removing studies in the
20 sensitivity analysis, this removed many studies that reported similar results to the 3
21 remaining studies. Given these factors, the committee decided to use the original analysis,
22 therefore including the enrichment studies in their decision making.

23 When compared to placebo for knee osteoarthritis, 1 outcome (including 9 studies with 3135
24 people of very low quality) showed a clinically important benefit of topical non-steroidal anti-
25 inflammatory drugs for pain reduction at less than 3 months, while 1 outcome (including 8
26 studies with 2458 people of moderate quality) showed no clinically important difference.
27 Additionally, there was no clinically important difference in physical function, gastrointestinal
28 (bleeding and perforation and non-bleeding and perforation), cardiovascular, hepatorenal
29 and central nervous system adverse events at less than 3 months. In hand osteoarthritis the
30 results were similar, with no clinically important difference being seen in pain, physical
31 function, gastrointestinal (non-bleeding or perforation) and central nervous system adverse
32 events at less than 3 months. When compared to oral non-steroidal anti-inflammatory drugs,
33 topical medicines showed no clinically important difference in quality of life, pain and physical
34 function outcomes at less than and more than 3 months, while showing a clinically important
35 benefit for gastrointestinal (non-bleeding or perforation) adverse events at less than 3
36 months which was not retained at more than 3 months. Otherwise, they showed similar
37 safety results with no clinically important difference in gastrointestinal (bleeding or
38 perforation), cardiovascular and central nervous system adverse events at less than 3
39 months. This was consistent with the experiences of the committee members.

40 While they noted that that there was no clinically important difference for pain and physical
41 function, they agreed that the outcomes were close to the default minimally important
42 difference used in the analysis. Given that the minimally important difference were default
43 values rather than those specific to a population with osteoarthritis, it is possible that the
44 effect could be clinically important in this population. When compared to oral non-steroidal
45 anti-inflammatory drugs it appeared that topical non-steroidal anti-inflammatory drugs may
46 lead to less gastrointestinal (non-bleeding and perforation) adverse events. Given this and
47 evidence from clinical practice, the committee agreed that topical non-steroidal anti-
48 inflammatory drugs should be offered for people with knee osteoarthritis, and considered for
49 people with osteoarthritis affects other joints. While acknowledging that there was sufficient
50 evidence for people with knee osteoarthritis, the evidence for hand osteoarthritis was limited
51 and further evidence was required before recommending confidently for other joint sites. The

1 committee agreed that topical non-steroidal anti-inflammatory drugs could be considered for
2 people with osteoarthritis affecting other joint sites due to the possibility that they could be
3 effective while having minimal adverse effects. The committee made a research
4 recommendation in order to gain further information about use for osteoarthritis affecting
5 other joint sites to support future recommendations.

6

7 ***Other topical treatments: Rubefaciants and local anaesthetics***

8 There was plenty of data for specific interventions (for example: oral non-steroidal anti-
9 inflammatory drugs) but limited data for others, with no information on topical rubefaciants
10 and local anaesthetics. The findings of this review regarding rubefaciants was different from
11 the previous version of the guideline. This is because the evidence for topical rubefaciants
12 was based on studies using trolamine salicylate, which is not licensed for use in the United
13 Kingdom, and so was excluded in this review. Current formulations of rubefaciants (including
14 diethylamine salicylate, methyl salicylate, salicylic acid [including combinations with
15 mucopolysaccharides], choline salicylate and tetrahydrofurfuryl salicylate) that are licensed
16 for use in the United Kingdom have not had randomised controlled trials reported for their
17 use for people with osteoarthritis.

18 Local anaesthetic patches may be used rarely by people for osteoarthritis. However, there
19 were no studies that were included in this review that reported their use. Due to the limited
20 evidence for both medicines, the committee recommended further research to investigate the
21 use of local anaesthetic patches and so agreed a research recommendation. A research
22 recommendation was not made regarding rubefaciants as these are no longer regularly used
23 in clinical practice due to a lack of efficacy, being previously recommended to not be used for
24 people with osteoarthritis in previous versions of the guideline, and the committee agreed
25 that there was likely no benefit to completing additional research in this area.

26

27 **1.1.12.4 Cost effectiveness and resource use**

28 The review identified eight economic evaluations reporting on the uses of one or more of:

- 29 • paracetamol,
- 30 • oral or topical non-steroidal anti-inflammatory drugs (with and without
31 gastroprotection),
- 32 • oral opioids and
- 33 • glucosamine.

34 An original cost-utility analysis was developed to compare:

- 35 • paracetamol
- 36 • oral or topical non-steroidal anti-inflammatory drugs (with and without
37 gastroprotection),
- 38 • oral or topical opioids.

39 ***Paracetamol***

40 Two studies compared paracetamol to no treatment. These were the original models from
41 previous NICE clinical guidelines for osteoarthritis; CG59 and CG177. The latter was in the
42 consultation version but along with the review of oral drugs was removed from the final
43 version. They both took a UK perspective and were therefore deemed directly applicable.
44 Both studies used EQ-5D to determine health outcomes, which were mapped from the
45 WOMAC index. CG59 provided an incomplete description of resource use. Although this was
46 addressed in CG177, there remained unclear sources of resource use for some health

1 states. The CG59 model was therefore considered to have potentially serious limitations,
2 while the CG177 model was considered to have minor limitations.

3 CG59 reported that paracetamol was cost effective versus no treatment with a cost per
4 QALY of £12,771. However, CG177 reported that paracetamol was dominated by no
5 treatment; being more costly and less effective. However, in that model it had been assumed
6 that paracetamol had a similar adverse event profile to NSAIDs, which was not the
7 conclusion of the new guideline review. The new guideline clinical review reported that the
8 only relevant adverse event for paracetamol was hepatorenal events. For modelling
9 purposes, this was attributed as acute liver failure.

10 The new guideline model found paracetamol to be cost effective at £3,301 per QALY gained.
11 However, the quality-of-life improvement was smaller than for the other drugs and the
12 committee were not convinced that the trials showed a meaningful improvement over
13 placebo.

14 ***Oral non-steroidal anti-inflammatory drugs***

15 **Oral NSAIDs versus no treatment**

16 Two studies compared oral NSAIDs alone to no treatment. These were the original models
17 from the previous NICE clinical guidelines for osteoarthritis; CG59 and CG177 – see
18 Paracetamol versus no treatment, above.

19 Both studies reported that no treatment dominated diclofenac, naproxen and ibuprofen. In
20 the case of COX-2 inhibitors without PPIs, CG59 reported that they were cost effective
21 versus no treatment whereas CG177 reported that they were dominated by no treatment.

22 The new guideline model found that oral NSAIDs alone were cost effective versus no
23 treatment with a cost per QALY gained of £3,449. This differed from the previous analyses
24 because of the greater utility gain reported in the new guideline model compared with
25 previous models (0.058 in the new guideline model versus 0.035 and 0.033 in CG59 and
26 CG177, respectively).

27 ***Oral non-steroidal anti-inflammatory drugs with gastroprotection***

28 **Oral NSAIDs with PPI versus no treatment**

29 Two studies compared oral NSAIDs (with or without PPIs) to no treatment. These were the
30 original models from the previous NICE clinical guidelines for osteoarthritis; CG59 and
31 CG177 – see Paracetamol versus no treatment, above. The CG177 model differed from the
32 CG59 model in that it introduced fixed-dose combinations of NSAIDs + PPI into the
33 comparison as a sensitivity analysis.

34 Both studies reported that oral NSAIDs with PPIs were cost effective versus no treatment in
35 the base case.

36 The new guideline model however reported that oral NSAIDs with PPIs were not cost
37 effective versus no treatment at a cost per QALY gained threshold of 20,000. This change
38 was mainly driven by an increased risk of cardiovascular adverse events with the addition of
39 PPIs. During sensitivity analysis, oral NSAIDs plus PPI were cost effective versus no
40 treatment when the Barton and Price algorithms were used instead of the Willoo algorithm
41 and when certain assumptions regarding adverse events were relaxed (the removal of SA,
42 UA and TIA from CV adverse events, where the relative risk of CV events was the same as
43 NSAIDs alone, when acute mortality associated with CV events were excluded and where
44 only the short-term cost of CV events were included). The committee acknowledged that
45 there is an increased risk of cardiovascular-related adverse events with PPIs but given that

1 treatment durations were likely for short, intermittent periods, the risk is likely to be lower
2 than that observed with their continuous use.

3 **Oral NSAIDs with PPI versus oral NSAIDs alone**

4 Three studies compared oral NSAIDs with PPIs versus oral NSAIDs alone. All took a UK
5 perspective and contained original modelling, and all were considered directly applicable.

6 One study contained a mixed population of rheumatoid arthritis and osteoarthritis. The
7 sources for resource use associated with adverse events were unclear, as was the source
8 and method of capturing QALYs. Probabilistic analysis was also not conducted. This study
9 was deemed therefore to have potentially serious limitations.

10 The remaining two studies were models from previous NICE osteoarthritis clinical guidelines
11 in 2008 (CG59) and 2014 (CG177) – see Paracetamol versus no treatment, above.

12 The most cost-effective option varied across studies, the first study reported that low dose
13 meloxicam was the most cost-effective option with a cost per QALY of £12,557, whilst the
14 other two studies reported that a combination of an NSAID plus PPI was the most cost
15 effective option (celecoxib 200mg + PPI in CG57 with a cost per QALY of £10,724 and
16 etoricoxib + PPI in CG177 with a cost per QALY of £13,160). Fixed-dose combinations were
17 dominated by NSAIDs plus PPI, with ketoprofen 200mg/omeprazole 20mg dominated by
18 diclofenac + PPI and diclofenac 150mg/misoprostol 400mg and naproxen
19 1000mg/esomeprazole 40mg both dominated by etoricoxib + PPI.

20 The new guideline model found that oral NSAIDs alone dominated oral NSAIDs with PPIs,
21 being cheaper and more effective. During sensitivity analysis, oral NSAIDs alone always
22 ranked higher than oral NSAIDs plus PPIs. The previous guideline model (CG177) reported
23 that the addition of PPIs to NSAIDs was more costly but also more effective. However, it
24 should be noted that in the previous model, the relative risk of gastrointestinal,
25 cardiovascular and renal adverse events were lower with oral NSAIDs plus PPI than with oral
26 NSAIDs alone. This was not the case in the new guideline model where the relative risk of
27 cardiovascular and renal adverse events were actually higher with oral NSAIDs plus PPI than
28 with oral NSAIDs alone.

29

30 **Oral versus topical NSAIDs**

31 One study was identified that compared oral ibuprofen with topical ibuprofen. The economic
32 evaluation was based on an RCT and took a UK perspective. A clinical diagnosis of
33 osteoarthritis was not a requirement with the patient population comprising of individuals with
34 knee pain on most days in a month for more than 3 months in the past year. The study was
35 therefore graded as being partially applicable. Patients were followed up during the trial via
36 postal questionnaire at 3, 6, 12, and 24 months. A 12-month time horizon was used in the
37 base case with a 24-month horizon explored during sensitivity analysis. The sensitivity
38 analysis found that oral ibuprofen became less cost-effective over time. The use of dated
39 resource use and costing data as well as the use of a single clinical trial to obtain efficacy
40 data were other study limitations. It was therefore assessed as having potentially serious
41 limitations. Overall, the study reported that oral ibuprofen was cost effective compared to
42 topical ibuprofen with a cost per QALY of £9,114.

43 Topical NSAIDs are the main first-line treatment for OA of the knee and have been
44 recommended since the first NICE guideline but there was no economic evidence comparing
45 it with no treatment. Although the price is more expensive than oral NSAIDs, the published
46 economic evaluation shows it to be less costly than oral NSAIDs. Oral vs topical was below
47 £20k per QALY, which might suggest prioritising oral. However, as topical is safer and less
48 costly, for those patients in whom it is effective, it will be cost effective.

1 The new guideline model found that topical NSAIDs dominated oral NSAIDs (with and
2 without PPIs), being cheaper and more effective than both. The difference in results
3 between the new guideline model and the study identified during review can be attributed to
4 the difference in incremental QALY gains between the two interventions. In the new guideline
5 model, the incremental QALY gain with topical NSAIDs compared with oral NSAIDs was
6 0.051. In the study identified during evidence review, there was a loss of 0.021 QALYs with
7 topical ibuprofen versus oral ibuprofen.

8 ***Opioids: Oral strong opioids, oral weak opioids and transdermal opioids***

9 The new guideline model found that the transdermal opioid buprenorphine was cost effective
10 versus no treatment with a cost per QALY gained of £9,454. During sensitivity analysis, it
11 ranked between third and sixth in a comparison of incremental net health benefit and only
12 ranked lower than no treatment when falls and hip fractures were included. Oral strong
13 opioids were not cost effective at a willingness-to-pay threshold of £20,000 with a cost per
14 QALY gained of £32,916. During sensitivity analysis, oral strong opioids only ranked higher
15 than no treatment when VAS trials were included in the analysis and where the morphine-
16 equivalent daily dose was less than or equal to 40mg. However, opioids are addictive and
17 the risk of addiction has not been captured by the model.

18 Oral weak opioids were not included in the model due to insufficient evidence.

19 ***Topical non-steroidal anti-inflammatory drugs***

20 The new guideline model found that topical NSAIDs were cost effective versus no treatment
21 with a cost per QALY gained of £2,847. Topical NSAIDs were the most cost-effective
22 treatment in the model and during sensitivity never fell below second in a comparison of
23 incremental net health benefit. Therefore the committee prioritised topical NSAIDs as the
24 first line of medicine for osteoarthritis.

25 ***Glucosamine***

26 **Glucosamine versus no treatment**

27 Three studies comparing glucosamine to usual care or no treatment were identified. All
28 calculated QALYs by mapping from the WOMAC index to HUI3.

29 One study compared glucosamine with usual care in patients with knee OA. It took a UK
30 NHS perspective and was graded as being directly applicable. Although the study used a
31 lifetime horizon, the use of dated sources for unit costs and resource use meant it was also
32 graded as having minor limitations. The cost per QALY gained for glucosamine compared
33 with usual care was greater than the cost effectiveness threshold of £20,000 per QALY and
34 usual care was therefore considered the optimal strategy.

35 The second study compared two intervention arms to no treatment: prescription crystalline
36 glucosamine sulphate and other forms of glucosamine. It did not specify which perspective
37 was taken and for these reasons was graded as being partially applicable. Moreover, it only
38 included the actual cost of glucosamine in its analysis, which was calculated by pooling
39 costing data from multiple countries. It was therefore deemed to hold potentially serious
40 limitations. Prescription crystalline glucosamine sulphate was cost effective versus no
41 treatment with a cost per QALY of £10,203. However, the 'other forms of glucosamine'
42 intervention arm was dominated by no treatment.

43 The final study compared glucosamine to no treatment as well as paracetamol. It took a
44 Spanish perspective and was therefore assessed as being partially applicable. Additionally, it
45 was based on a single trial and had a time horizon of six months. The use of Spanish
46 resourcing and costing data may not be indicative of UK NHS practice. For these reasons,

1 this study was assessed to have potentially serious limitations. The study reported that
2 glucosamine was cost effective compared to no treatment with a cost per QALY of £3,488.

3 Overall, the clinical and cost effectiveness evidence was insufficient to support a
4 recommendation.

5 **Glucosamine versus paracetamol**

6 One study compared glucosamine to paracetamol. It took a Spanish perspective and
7 calculated QALYs by mapping from the WOMAC index to HUI3. It was assessed as partially
8 applicable. It was also based on a single trial and had a time horizon of six months. The use
9 of Spanish resourcing and costing data may not be indicative of UK NHS practice. For these
10 reasons, this study was judged to have potentially serious limitations. The study reported that
11 glucosamine dominated paracetamol (being cheaper and more effective). The committee
12 queried the cheaper cost of glucosamine compared with paracetamol and subsequently, the
13 applicability of the cost effectiveness results to the UK NHS setting.

14 The committee concluded that the evidence of glucosamine's cost effectiveness was
15 unreliable due to either small trial sample size or study methodology. It did not think original
16 modelling to ascertain the cost effectiveness of glucosamine would be helpful, given the lack
17 of good quality clinical evidence.

18 **Other drugs**

19 There was no economic evidence for other drugs including anti-epileptics, anti-depressants,
20 topical capsaicin and other topical treatments. The committee made research
21 recommendations for anti-epileptics, anti-depressants and topical capsaicin.

22 **Key uncertainties**

23 The main limitations of the new guideline model were:

- 24 • The trials that informed treatment effects were in different populations. For example,
25 patients taking opioids in the trials having already tried NSAIDs. This meant that a
26 like-for-like comparison of the different drug classes could not be conducted for
27 treatment effectiveness.
- 28 • Drug treatments in the trials were heterogeneous. Since the model looked at drug
29 classes rather than individual drugs, the treatment effectiveness and adverse event
30 profiles for each drug class were dependent on the individual drugs selected in the
31 clinical trials. It was assumed in the model that the results observed with individual
32 drugs were a fair representation of the overall drug class.
- 33 • EQ-5D scores were not directly available and had to be mapped from various health
34 outcomes. Additionally, baseline scores had to be imputed where only change scores
35 were reported.
- 36 • The adverse events reported in clinical trials were sometimes minor outcomes, but
37 the relative risks from these were taken and applied to more rare and serious adverse
38 events. For example, the most frequently reported hepatic adverse event with
39 paracetamol was altered liver function tests, but its relative risk was applied to acute
40 liver failure. However, since the incidence of acute liver failure in the general
41 population is so low in the first instance, it is unlikely that drug-related liver failure has
42 been over-estimated.
- 43 • The adverse event costs and utilities were taken from various sources and may not
44 have always been up to date.

1 1.1.12.5 Other factors the committee took into account

2 The committee considered when medication should be prescribed. They agreed that
3 pharmacological treatments should be used at the lowest effective dose for the shortest time
4 possible and should be used to support people to complete effective treatments for
5 osteoarthritis, such as therapeutic exercise. They agreed that medications should be
6 reviewed before offering repeat prescriptions, but agreed that the form of this review could be
7 flexible including a range of methods such as: text messaging, e-mails, online consultation
8 software, telephone, face to face and video calls. If the discussion about the need for review
9 before a repeat prescription takes place when first prescribing the medication, then the most
10 appropriate method for follow up can be agreed between the person with osteoarthritis and
11 the healthcare professional. The committee made recommendations accordingly to support
12 good practice in prescribing medication for people with osteoarthritis.

13 The committee observed that the majority of evidence was in a populations under the age of
14 75 years and that there was limited evidence documented in people with multimorbidity. In
15 these populations medicines may react differently. The committee wanted to emphasise
16 caution to people prescribing these medicines to people in these populations.

17 Other NICE guidance should be considered when offering these medicines, including the
18 safe prescribing and withdrawal management of prescribed drugs associated with
19 dependence and withdrawal for opioids and gabapentinoids.

20 The committee noted that the research identified does not appear to represent the diverse
21 population of people with osteoarthritis. They agreed that any further research should be
22 representative of the population, including people from different family backgrounds, and
23 socioeconomic backgrounds, disabled people, and people of different ages and genders.
24 Future work should be done to consider the different experiences of people from diverse
25 communities to ensure that the approach taken can be made equitable for everyone. With
26 this in mind the committee subgrouped their research recommendation by these protected
27 characteristics where appropriate while suggesting that people from each group should be
28 included in the research to ensure that it is applicable to the entire population.

29 1.1.13 Recommendations supported by this evidence review

30 This evidence review supports recommendations 1.4.1 to 1.4.9. Other evidence supporting
31 these recommendations can be found in evidence review I.
32

1 1.1.14 References

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