National Institute for Health and Care Excellence

Final

Osteoarthritis in over 16s: diagnosis and management

[I] Evidence review for the clinical and cost effectiveness of oral, topical and transdermal medicines for the management of osteoarthritis

NICE guideline NG226

Evidence reviews underpinning recommendations 1.4.1 to 1.4.8 and research recommendations in the NICE guideline

October 2022

Final

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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	Inclusion: • Adults (age ≥16 years) with osteoarthritis affecting any joint Stratify by site of osteoarthritis for topical (local) interventions only: • Hip • Knee • Ankle • Foot • Toe • Shoulder • Elbow • Wrist • Hand • Thumb • Finger

	• Temporomandibular joint (TMJ) • Multisite 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. Exclusion: • 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	Oral medicines: • 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) Topical (local) medicines: • Capsaicin • Non-steroidal anti-inflammatory drug (including: ibuprofen, diclofenac) • Rubefacients • Local anaesthetic Topical (systemic, including transdermal) medicines: • Opioids (buprenorphine, fentanyl ect.)
Comparisons	• Compared to each other • Placebo
Outcomes	Primary outcomes: • 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 Secondary outcomes: • 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

	• 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

For full details see the review protocol in evidence review I2.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

One-hundred and eighty one (two-hundred and eleven papers) RCT studies were included in 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, 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 are summarised in Tables 2-26 below. Evidence from these studies is summarised in the clinical evidence summaries (Tables 31-53) and the summary matrices below (Tables 27-30).

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

- Paracetamol
  - Paracetamol compared to placebo (n=8)[4, 41, 90, 96, 140, 156, 158, 163]
- Non-steroidal anti-inflammatory drugs (NSAIDs)
  - NSAIDs compared to paracetamol (n=13)[17, 31, 32, 41, 64, 84, 90, 135, 156, 183, 196, 210, 219]
  - 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, 85-88, 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, 179-182, 185, 186, 188-190, 192, 194, 195, 203, 204, 214-218, 220, 222, 226]
- NSAIDs and gastroprotection
  - NSAIDs and gastroprotection compared to paracetamol (n=1)[157]
  - NSAIDs and gastroprotection compared to NSAIDs (n=6)[27, 29, 44, 55, 91, 139]
  - NSAIDs and gastroprotection compared to placebo (n=2)[27, 55]
- Weak opioids (for example: codeine, dihydrocodeine)
  - Weak opioids compared to placebo (n=1)[154]
- Strong opioids (for example: morphine, oxycodone, hydromorphone, tapentadol and tramadol. It was decided to include tramadol as a strong opioid to be consistent with the BNF[144]).
  - Strong opioids compared to NSAIDs (n=4)[14, 18, 60, 153]
  - Strong opioids compared to placebo (n=16)[2, 10, 37, 39, 48, 60, 73, 75, 82, 83, 134, 136, 187, 197, 211, 224]
- Anti-epileptic drugs
  - Anti-epileptic drugs compared to paracetamol (n=1)[66]
  - Anti-epileptic drugs compared to antidepressant drugs (n=1)[193]
  - Anti-epileptic drugs compared to placebo (n=1)[193]
- Antidepressant drugs
  - Antidepressant drugs compared to paracetamol (n=1)[66]
  - Antidepressant drugs compared to placebo (n=8)[1, 45, 46, 78, 100, 193, 206, 213]
- Glucosamine
  - Glucosamine compared to paracetamol (n=1)[96]
  - Glucosamine compared to NSAIDs (n=6)[49, 51, 129, 142, 149, 162]
  - Glucosamine compared to placebo (n=17)[5, 38, 50, 51, 79, 80, 89, 96, 98, 101, 115, 147, 152, 159, 164, 170, 225]

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

- Knee osteoarthritis
  - Topical capsaicin compared to placebo (n=1)[114]
  - Topical NSAIDs compared to oral NSAIDs (n=7)[53, 62, 168, 190, 198, 205, 209]

  - Topical NSAIDs compared to topical capsaicin (n=1)[155]
  - Topical NSAIDs compared to placebo (n=17)[11, 15, 16, 22, 30, 53, 59, 94, 112, 146, 166-169, 190, 202, 212]
- Hand osteoarthritis:
  - Topical capsaicin compared to placebo (n=1)[178]
  - Topical NSAIDs compared to placebo (n=1)[3]

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

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

- Transdermal opioids compared to oral strong opioids (n=1)[105]
- Transdermal opioids compared to placebo (n=3)[33, 120, 143]

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

- Rubefacients (topical local)
- Local anaesthetics (topical local)

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

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

See also the study selection flow chart in evidence review I2, study evidence tables in evidence review I2, forest plots in evidence review I3 and GRADE tables in evidence review I3.

1.1.4.2 Excluded studies

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

See the excluded studies list in evidence review I3.

1.1.5 Summary of studies included in the effectiveness evidence

1.1.5.1 Oral

1.1.5.1.1 Paracetamol compared to placebo

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]	**Paracetamol** (n=318) Paracetamol ER 1950/day or 3900mg/day in three divided doses for 16 weeks **Placebo** (n=165) **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	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 62.2 (10.8) years N = 483 Definition: Symptomatic idiopathic osteoarthritis of the hip or knee with radiographic features Severity: Equivalent to Kellgren Lawrence grade 2-3 Duration of symptoms: At least 6 months Presence of multimorbidities: Not stated/unclear	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	Study design classification: 1) Including only responders
Case 2003[41]	**Paracetamol** (n=29) Paracetamol 1000mg four times daily with matching placebo twice daily for 12 weeks **Oral non-steroidal anti-inflammatory drugs** (n=25)	**Knee osteoarthritis** Mean age (SD): 62.2 (9.6) years N = 82 Definition: Unilateral symptomatic osteoarthritis of	Pain at ≤3 months Physical function at ≤3 months	Study design classification: 1) Including only responders

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

Study	Intervention and comparison	Population	Outcomes	Comments
	Glucosamine (n=106) Glucosamine 1500mg oral powder for solution per day and matching placebo for 26 weeks Glucosamine purity: Purity not stated **Placebo** (n=104) **Concomitant therapy:** Ibuprofen 400mg was permitted for rescue medication	Definition: Primary symptomatic knee osteoarthritis according to the clinical and radiographic American College of Rheumatology criteria Severity: Kellgren Lawrence grade 2-3 Duration of symptoms (mean [SD]): 7.0 (5.7) years Presence of multimorbidities: Not stated/unclear	Serious adverse events 2: cardiovascular adverse events at >3 months Serious adverse events 3: hepatorenal adverse events at >3 months	
Miceli-richard 2004[140]	**Paracetamol** (n=405) Paracetamol 1 gram four times a day for 6 weeks **Placebo** (n=374) **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	**Knee osteoarthritis** Mean age (SD): 70 (11) years N = 779 Definition: Symptomatic osteoarthritis of the knee for at least 3 months Severity: Kellgren Lawrence grade 2-4 Duration of symptoms (mean [SD]): 46 (47) months Presence of multimorbidities: Not stated/unclear	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	Study design classification: 4) Unclear

Study	Intervention and comparison	Population	Outcomes	Comments
Pincus 2004[156] (PACES trial)	**Paracetamol** (n=631) Paracetamol 1000mg four times a day for 6 weeks **Non-steroidal anti-inflammatory drugs** (n=723) Celecoxib 200mg/day for 6 weeks **Placebo** (n=562) **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	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 63.45 (10.03) years N = 1916 Definition: Radiographic and clinical osteoarthritis Severity: Kellgren Lawrence mean grade 2-3 Duration of symptoms (mean [SD]): 9.36 (8.99) years 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 4: central nervous system adverse events at ≤3 months	Study design classification: 4) Unclear Pooled analysis of two trials Crossover trial
Prior 2014[158]	**Paracetamol** (n=267) Paracetamol extended release 1300mg 3 times a day for 12 weeks **Placebo** (n=275) **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.	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 61.7 (10.1) years N = 542 Definition: Clinical and radiographic osteoarthritis Severity: Kellgren Lawrence grades 2-3. ACR class 1-3. Duration of symptoms: At least 6 months	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	Study design classification: 1) Including only responders

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]	**Paracetamol** (n=471) Sustained release paracetamol 2000mg twice a day or extended release paracetamol 1330mg three times a day for 12 weeks **Placebo** (n=237) **Concomitant therapy:** People were permitted to take oral ibuprofen 2x200mg as rescue medication.	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 60.8 (8.4) years N = 708 Definition: Clinical and radiographic diagnosis of osteoarthritis Severity: Kellgren Lawrence grade 2-4 Duration of symptoms: More than 6 months Presence of multimorbidities: Not stated/unclear	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	Study design classification: 4) Unclear

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

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
Batlle-gualda 2007[17]	**Non-steroidal anti-inflammatory drugs** (n=82) Aceclofenac 100mg twice a day with matching placebo for 6 weeks **Paracetamol** (n=86)	**Knee osteoarthritis** Mean age (SD): 62.4 (6.8) years N = 168 Definition: Primary knee osteoarthritis diagnosed with radiographic and clinical features	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	Study design classification: 2) Excluding non-responders

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

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

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

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

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)	**Paracetamol** (n=631) Paracetamol 1000mg four times a day for 6 weeks **Non-steroidal anti-inflammatory drugs** (n=723) Celecoxib 200mg/day for 6 weeks **Placebo** (n=562) **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	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 63.45 (10.03) years N = 1916 Definition: Radiographic and clinical osteoarthritis Severity: Kellgren Lawrence mean grade 2-3 Duration of symptoms (mean [SD]): 9.36 (8.99) years 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 4: central nervous system adverse events at ≤3 months	Study design classification: 4) Unclear Pooled analysis of two trials Crossover trial
Schnitzer 2005[183] VACT trial	**Non-steroidal anti-inflammatory drugs** (n=523) Celecoxib 200mg/day for 6 weeks **Paracetamol** (n=269) Paracetamol 1000mg four times a day for 6 weeks A third group (n=786) was not included in the analysis due to	**Knee osteoarthritis** Mean age (SD): 62.1 (10.34) years N = 1578 Definition: Symptomatic osteoarthritis of the knee defined by clinical diagnosis Severity: Functional class 1-3	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	Study design classification: 1) Including only responders Pooled analysis of 2 trials. One trial was Geba 2002 [84], which is analysed separately.

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

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

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

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

Study	Intervention and comparison	Population	Outcomes	Comments
	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	of Rheumatology clinical criteria Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 10 (8) years Presence of multimorbidities: Not stated/unclear	and perforation) adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months	
Berry 1982[20]	**Non-steroidal anti-inflammatory drugs** (n=30) Diclofenac 50mg three times daily or piroxicam 20mg once daily for 4 weeks **Placebo** (n=30) **Concomitant therapy:** People were withdrawn from all anti-inflammatory/analgesic preparations on the first day of the study period	**Mixed osteoarthritis (knee or hip)** Mean age (range): 67.3 (51-82) years N = 30 Definition: Clinical evidence of osteoarthritis Severity: Not stated Duration of symptoms (mean): 7 years Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months	Study design classification: 4) Unclear Crossover trial
Berry 1983[21]	**Non-steroidal anti-inflammatory drugs** (n=24) Naproxen 750mg per day (250mg in the morning, 500mg at night) for 2 weeks **Placebo** (n=24) A third group (n=24) was not included in the analysis due to the medication not being	**Knee osteoarthritis** Mean age (SD): 62.3 (1.8) years N = 24 Definition: Osteoarthritis confirmed by radiography Severity: Not stated	Pain at ≤3 months	Study design classification: 4) Unclear Crossover trial

Study	Intervention and comparison	Population	Outcomes	Comments
	licensed for use in the UK (antrafenine). **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.	Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear		
Bingham 2007[23]	**Non-steroidal anti-inflammatory drugs** (n=963) Etoricoxib 30mg or celecoxib 200mg once a day for 12 weeks **Placebo** (n=244) **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.	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 62.1 (9.6) years N = Definition: A diagnosis of osteoarthritis for at least 6 months Severity: Functional class 1-3 Duration of symptoms: At least 6 months Presence of multimorbidities: People with multimorbidities excluded	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 Pooled analysis of 2 trials
Birbara 2006[25]	**Non-steroidal anti-inflammatory drugs** (n=326) Celecoxib 200mg once a day for 6 weeks **Placebo** (n=163)	**Knee osteoarthritis** Mean age (SD): 60.7 (10.6) years N = 808 Definition: A clinical diagnosis for at least 6 months	Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months	Study design classification: 1) Including only responders Pooled analysis of 2 trials

Study	Intervention and comparison	Population	Outcomes	Comments
	A third group (n=319) was not included in the analysis due to the medication not being licensed for use in the UK (rofecoxib). **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.	Severity: Functional class 1-3 Duration of symptoms: At least 6 months Presence of multimorbidities: Not stated/unclear	Serious adverse events 2: cardiovascular adverse events at ≤3 months	
Bocanegra 1998[27]	**Non-steroidal anti-inflammatory drugs** (n=154) Diclofenac 75mg twice a day for 6 weeks **Non-steroidal anti-inflammatory drugs and gastroprotection** (n=327) Diclofenac 50mg with misoprostol 200 microgram	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 62.5 (10.4) years N = 572 Definition: Symptomatic osteoarthritis with a functional classification of 1-3	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	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	three times a day or diclofenac 75mg wth misoprostol 200 microgram two times a day for 6 weeks **Placebo** (n=91) **Concomitant therapy:** No additional information - all antiinflammatory drugs were not permitted (with the exception of aspirin ≤325mg/day).	Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 11.2 (8.7) years Presence of multimorbidities: Not stated/unclear		
Caroit 1976[40]	**Non-steroidal anti-inflammatory drugs** (n=9) Ketoprofen 50mg three times a day for 2 weeks **Placebo** (n=9) **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	**Hip osteoarthritis** Mean age (range): 63 (54-72) years N = 9 Definition: Osteoarthritis based on classical criteria associated with presence of radiological signs Severity: Not stated Duration of symptoms (mean): 9 years Presence of multimorbidities: Not stated/unclear	Serious adverse events 3: hepatorenal adverse events at ≤3 months	Study design classification: 1) Including only responders Crossover trial
Case 2003[41]	**Paracetamol** (n=29) Paracetamol 1000mg four times daily with matching placebo twice daily for 12 weeks	**Knee osteoarthritis** Mean age (SD): 62.2 (9.6) years N = 82	Pain at ≤3 months Physical function at ≤3 months	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	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 **Placebo** (n=28) **Concomitant therapy:** Use of nonstudy pain medications during the trial was prohibited	Definition: Unilateral symptomatic osteoarthritis of the knee based on clinical and radiological criteria Severity: Kellgren Lawrence grade 2 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear		
Clegg 2006[51] GAIT trial Subsidiary papers: Hochberg 2008[97] Sawitzke 2008[174] Sawitzke 2010[175]	**Non-steroidal anti-inflammatory drugs** (n=318) Celecoxib 200mg daily for 24 weeks **Glucosamine** (n=317) Glucosamine hydrochloride 500mg three times daily for 24 weeks **Placebo** (n=313) 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).	**Knee osteoarthritis** Mean age (SD): 58.6 (10.4) years N = 1583 Definition: Clinical and radiographic evidence of osteoarthritis Severity: Kellgren Lawrence grade 2-3. Functional class 1-3. Duration of symptoms (mean [SD]): 10.0 (9.8) years Presence of multimorbidities: Not stated/unclear	Pain at >3 months Physical function at >3 months Serious adverse events 2: cardiovascular adverse events at >3 months	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
	Glucosamine purity: Statement regarding purity **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.			
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 **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	**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
	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]	**Non-steroidal anti-inflammatory drugs** (n=428) Naproxen 220mg two to three times per day for 1 week **Placebo** (n=419) **Concomitant therapy:** Use of aspirin ≤325mg/day was permitted	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 60.7 (12.9) years N = 847 Definition: Radiographic evidence of osteoarthritis Severity: Kellgren Lawrence grade 1-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	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: 4) Unclear Pooled analysis of 4 studies
Cryer 2011[55]	**Non-steroidal anti-inflammatory drugs** (n=494) Celecoxib 200mg once daily for 12 weeks **Non-steroidal anti-inflammatory drugs with gastroprotection** (n=492) Naproxen 500mg and esomeprazole 20mg twice daily for 12 weeks **Placebo** (n=248)	**Knee osteoarthritis** Mean age (range): 61.9 (49-90) years N = 1234 Definition: Symptomatic, clinically diagnosed osteoarthritis Severity: Functional class I-III Duration of symptoms: Not stated	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 Pooled analysis of 2 trials

Study	Intervention and comparison	Population	Outcomes	Comments
	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.	Presence of multimorbidities: Not stated/unclear		
Delemos 2011[60]	**Non-steroidal anti-inflammatory drugs** (n=203) Celecoxib 200mg once a day for 12 weeks **Strong opioids** (n=606) Tramadol 100mg once to three times a day for 12 weeks **Placebo** (n=202) **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.	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 59.92 (10.96) years N = 1011 Definition: Radiologically confirmed osteoarthritis Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 8.1 (7.9) years Presence of multimorbidities: Not stated/unclear	Quality of life at ≤3 months Pain at ≤3 months Physical function at ≤3 months Psychological distress at ≤3 months	Study design classification: 1) Including only responders
Dieppe 1993[63]	**Non-steroidal anti-inflammatory drugs** (n=45)	**Knee osteoarthritis**	Serious adverse events 1B: gastrointestinal (non-bleeding	Study design classification: 4) Unclear

Study	Intervention and comparison	Population	Outcomes	Comments
	Diclofenac 100mg/day (slow release formulation) for 2 years **Placebo** (n=44) **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.	Mean age (range): 63.1 (40-82) years N = 89 Definition: Symptomatic knee osteoarthritis with radiological confirmation Severity: Kellgren Lawrence grades 1-4 Duration of symptoms (mean): 9.8 years Presence of multimorbidities: Not stated/unclear	and perforation) adverse events at >3 months Serious adverse events 3: hepatorenal adverse events at >3 months	
Dore 1995[65]	**Non-steroidal anti-inflammatory drugs** (n=168) Naproxen 500mg twice daily or Etodolac 400mg twice daily for 4 weeks **Placebo** (n=86) **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	**Knee osteoarthritis** Mean age: 63.7 years N = 254 Definition: Symptomatic, radiologically confirmed osteoarthritis of the knee that required NSAID treatment Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	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	Study design classification: 2) Excluding non-responders
Esselinckx 1990[67]	**Non-steroidal anti-inflammatory drugs** (n=258) Diclofenac retard 100mg or tenoxicam 20mg or 40mg once a day for 4 weeks	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 62.5 (10.1) years N = 347	Serious adverse events 2: cardiovascular adverse events at ≤3 months	Study design classification: 3) Selection of specific population

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo (n=89) **Concomitant therapy:** No additional information	Definition: Painful osteoarthritis with radiological confirmation Severity: Not stated Duration of symptoms: median between 1 and 5 years Presence of multimorbidities: Not stated/unclear		
Essex 2012[69]	**Non-steroidal anti-inflammatory drugs** (n=255) Naproxen 500mg twice a day or celecoxib 200mg once daily for 6 weeks **Placebo** (n=67) **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.	**Knee osteoarthritis** Mean age (SD): 58.0 (8.5) years N = 322 Definition: Osteoarthritis in a flare state according to the American College of Rheumatology guidelines Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 5.4 (5.8) years Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding or perforation) adverse events at ≤3 months	Study design classification: 1) Including only responders
Essex 2014[68]	**Non-steroidal anti-inflammatory drugs** (n=256)	**Knee osteoarthritis**	Pain at ≤3 months	Study design classification: 1) Including only responders

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

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

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo (n=232) A third group (n=930) was not included in the analysis due to the medication not being licensed for use in the UK (lumiracoxib). **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, sucralphate (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)	Definition: Primary osteoarthritis of the knee with symptoms for at least 3 months Severity: Not stated Duration of symptoms (mean [SD]): 6.4 (7.4) years Presence of multimorbidities: Not stated/unclear	and perforation) adverse events at ≤3 months	
Ghosh 2007[85]	**Non-steroidal anti-inflammatory drugs** (n=304)	**Knee osteoarthritis** Mean age (range): 54.9 (40-64) years N = 427	Pain at ≤3 months Serious adverse events 1A: gastrointestinal (bleeding and	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	Diclofenac 75mg once a day or etoricoxib 90mg once a day for 4 weeks **Placebo** (n=123) **Concomitant therapy:** Paracetamol (up to 2g/day for a maximum of 3 days but not before assessment of arthritis) was permitted	Definition: Osteoarthritis with symptoms for at least 6 months and radiological evidence Severity: Functional class 1-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	perforation) adverse events 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	
Giansiracusa 1977[86]	**Non-steroidal anti-inflammatory drugs** (n=437) Ibuprofen 150mg four times daily or aspirin 300mg four times daily **Placebo** (n=437) **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	**Mixed osteoarthritis (knee, hip or shoulder)** Mean age: 64.4 years N = 437 Definition: Clinical diagnosis with roentgenograms confirming the diagnosis in most cases Severity: Not stated Duration of symptoms (mean): 11.6 years Presence of multimorbidities: Not stated/unclear	Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months	Study design classification: 4) Unclear Crossover trial
Gibofsky 2003[88]	**Non-steroidal anti-inflammatory drugs** (n=189) Celecoxib 200mg once a day **Placebo** (n=96)	**Knee osteoarthritis** Mean age (SD): 62.9 (10.3) years N = 475 Definition: Osteroarthritis in a flare state diagnosed	Pain at ≤3 months Physical function at ≤3 months	Study design classification: 1) Including only responders

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

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

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

Study	Intervention and comparison	Population	Outcomes	Comments
	Ketoprofen 50mg three times a day for 2 weeks **Placebo** (n=9) **Concomitant therapy:** No additional information	Definition: Painful osteoarthritis with positive radiological signs Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	and perforation) adverse events at ≤3 months Serious adverse events 3: hepatorenal adverse events at ≤3 months	Crossover trial
Kageyama 1973[103]	**Non-steroidal anti-inflammatory drugs** (n=74) Naproxen 500mg daily for 2 weeks **Placebo** (n=43) 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). **Concomitant therapy:** Other anti-arthritis agents were not allowed. Any pre-established physical therapy program was permitted to continue.	**Mixed osteoarthritis (knee, hip, fingers or polyarticular)** Mean age: Unclear N = 178 Definition: Clinical and radiological diagnosis Severity: Not stated Duration of symptoms: Unclear Presence of multimorbidities: Not stated/unclear	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: 4) Unclear
Karakaya 1977[104]	**Non-steroidal anti-inflammatory drugs** (n=20) Indomethacin 25mg three times a day for 4 weeks	**Knee osteoarthritis** Mean age: Not stated/unclear N = 60	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
	Placebo (n=20) A third group (n=20) was not included in the analysis due to the medication not being licensed for use in the UK (proquazone). **Concomitant therapy:** No additional information	Definition: Clinical and radiological diagnosis Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear		
Kivitz 2001[110]	**Non-steroidal anti-inflammatory drugs** (n=82) Ibuprofen 400mg once daily for 2 weeks **Placebo** (n=160) A third group (n=249) was not included in the analysis due to the medication not being licensed for use in the UK (oxaprozin). **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.	**Knee osteoarthritis** Mean age (range): 59.8 (28-91) years N = 491 Definition: Osteoarthritis for at least 6 months confirmed by weightbearing radiograph Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Serious adverse events 4: central nervous system adverse events at ≤3 months	Study design classification: 1) Including only responders In Forest plots this study is referred to as Kivitz 2001A

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

Study	Intervention and comparison	Population	Outcomes	Comments
	following specified times before the baseline endoscopy: NSAIDs (including full dose aspirin at a dosage ≥325mg/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.			
Kivitz 2004[109]	**Non-steroidal anti-inflammatory drugs** (n=410) Nabumetone 100mg once daily for 6 weeks **Placebo** (n=208) A third group (n=423) was not included in the analysis due to the medication not being licensed for use in the UK (rofecoxib). **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	**Knee osteoarthritis** Mean age (SD): 63.2 (10.2) years N = 1041 Definition: Osteoarthritis with a positive history of response to NSAIDs Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 6.1 (7.3) years 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: 1) Including only responders

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

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]	**Non-steroidal anti-inflammatory drugs** (n=145) Celecoxib 200mg once daily for 6 weeks **Placebo** (n=71) A third group (n=146) was not included in the analysis due to the medication not being licensed for use in the UK (polmacoxib). **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.	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 62.4 (7.8) years N = 362 Definition: Clinical diagnosis according to clinical and imaging criteria from the American College of Rheumatology guidelines Severity: Functional class 1-3 Duration of symptoms: At least 3 months Presence of multimorbidities: High comorbidity score	Pain at ≤3 months Physical function at ≤3 months	Study design classification: 4) Unclear
Lehmann 2005[124]	**Non-steroidal anti-inflammatory drugs** (n=420) Celecoxib 200mg once a day for 13 weeks **Placebo** (n=424)	**Knee osteoarthritis** Mean age (SD): 62.4 (10.1) years N = 1684 Definition: Primary osteoarthritis meeting the	Pain at ≤3 months Physical function at ≤3 months Serious adverse events 2: cardiovascular adverse events at ≤3 months	Study design classification: 2) Excluding non-responders

Study	Intervention and comparison	Population	Outcomes	Comments
	A third group (n=840) was not included in the analysis due to the medication not being licensed for use in the UK (lumiracoxib). **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).	American College of Rheumatology criteria Severity: Not stated Duration of symptoms (mean [SD]): 4.2 (5.8) years Presence of multimorbidities: Not stated/unclear	Serious adverse events 4: central nervous system adverse events at ≤3 months	

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

Study	Intervention and comparison	Population	Outcomes	Comments
Lohmander 2005[128]	**Non-steroidal anti-inflammatory drugs** (n=417) Naproxen 500mg twice daily for 6 weeks **Placebo** (n=116) A third group (n=437) was not included in the analysis due to the medication not being licensed for use in the UK (AZD3582). **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	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 59.3 (8.5) years N = 970 Definition: Symptomatic osteoarthritis with radiographic evidence Severity: Not stated Duration of symptoms: At least 3 months Presence of multimorbidities: Not stated/unclear	Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months Serious adverse events 2: cardiovascular adverse events at ≤3 months	Study design classification: 3) Selection of specific population
Lopez sanchez 1983[130]	**Non-steroidal anti-inflammatory drugs** (n=10) Naproxen 500mg/day for 6 weeks **Placebo** (n=10) A third group (n=10) and a fourth group (n=10) was not included in the analysis due to the medication not being	**Mixed osteoarthritis (knee and/or hip)** Median age (range): 52.3 (39-71) years N = 40 Definition: Radigraphically verified degenerative joint disease with pain Severity: Not stated	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
	licensed for use in the UK (meclofenamate sodium and phenylbutazone respectively). **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.	Duration of symptoms (median [range]): 2.25 (1-12) years Presence of multimorbidities: Not stated/unclear		
Lund 1998[131]	**Non-steroidal anti-inflammatory drugs** (n=274) Meloxicam 7.5mg or 15mg once daily for 3 weeks **Placebo** (n=137) 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. **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	**Knee osteoarthritis** Mean age (SD): 68.5 (11.8) years N = 513 Definition: Clinically and radiographically confirmed osteoarthritis Severity: Not stated Duration of symptoms (mean [SD]): 8.4 (8.4) years 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 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

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

Study	Intervention and comparison	Population	Outcomes	Comments
	before the baseline arthritis assessment.			
Mckenna 2001[138]	**Non-steroidal anti-inflammatory drugs** (n=63) Celecoxib 200mg once a day for 6 weeks **Placebo** (n=60) A third group (n=59) was not included in the analysis due to the medication not being licensed for use in the UK (rofecoxib). **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	**Knee osteoarthritis** Mean age (SD): 62.2 (10.3) years N = 182 Definition: Knee osteoarthritis as defined by the American College of Rheumatology criteria (unclear if imaging was involved) Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 10.9 (9.5) years 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 4: central nervous system adverse events at ≤3 months	Study design classification: 1) Including only responders In Forest plots this study is referred to as Mckenna 2001A

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

Study	Intervention and comparison	Population	Outcomes	Comments
	Aceclofenac 100mg or nabumetone 750mg twice daily for 4 weeks **Placebo** (n=141) **Concomitant therapy:** No additional information	Mean age (range): 53.5 (40-64) years N = 423 Definition: Osteoarthritis fulfilling radiographic criteria Severity: Kellgren Lawrence grade 2-3. Functional class 1-3. Duration of symptoms: At least 6 months Presence of multimorbidities: Not stated/unclear	Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months	
Pincus 2004[156] PACES trial	**Paracetamol** (n=631) Paracetamol 1000mg four times a day for 6 weeks **Non-steroidal anti-inflammatory drugs** (n=723) Celecoxib 200mg/day for 6 weeks **Placebo** (n=562) **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	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 63.45 (10.03) years N = 1916 Definition: Radiographic and clinical osteoarthritis Severity: Kellgren Lawrence mean grade 2-3 Duration of symptoms (mean [SD]): 9.36 (8.99) years 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 4: central nervous system adverse events at ≤3 months	Study design classification: 4) Unclear Pooled analysis of two trials Crossover trial

Study	Intervention and comparison	Population	Outcomes	Comments
Puopolo 2007[161]	**Non-steroidal anti-inflammatory drugs** (n=437) Ibuprofen 800mg three times a day for 12 weeks **Placebo** (n=111) **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	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 62.6 (9.5) years N = 548 Definition: Clinical and radiographic diagnosis of osteoarthritis Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 6.6 (7.5) years Presence of multimorbidities: Not stated/unclear	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
Rother 2007[168]	**Oral non-steroidal anti-inflammatory drugs** (n=132) Celecoxib 100mg twice a day for 6 weeks **Topical non-steroidal anti-inflammatory drugs** (n=138) 110mg epicutaneous ketoprofen in 4.8 grams Transfersome twice a day for 6 weeks	**Knee osteoarthritis** Mean age (SD): 62.8 (9.8) years N = 397 Definition: Fulfilling clinical criteria for osteoarthritis Severity: Not stated Duration of symptoms: At least 6 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	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo (n=127) **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	Presence of multimorbidities: Not stated/unclear		
Sanda 1983[172]	**Non-steroidal anti-inflammatory drugs** (n=42) Aspirin 2400-4800mg/day or etodolac 100-400mg/day for 12 weeks **Placebo** (n=16) **Concomitant therapy:** Non-narcotic, analgesic paracetamol (650mg four times daily PRN) was permitted only during the washout period	**Hip osteoarthritis** Mean age (range): 59 (33-70) years N = 58 Definition: Osteoarthritis confirmed with clinical and radiographic evidence Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Serious adverse events 4: central nervous system adverse events at ≤3 months	Study design classification: 1) Including only responders
Sandelin 1997[173]	**Oral non-steroidal anti-inflammatory drugs** (n=82) Diclofenac 50mg twice daily for 4 weeks **Topical non-steroidal anti-inflammatory drugs** (n=126) Elternac gel 1%, 3g (300mg Elternac) applied 3 times daily for 4 weeks	**Knee osteoarthritis** Mean age (SD): 61 (8.1) years N = 290 Definition: Radiographically confirmed osteoarthritis with pain most days Severity: Not stated	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	Study design classification: 4) Unclear

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo (n=82) **Concomitant therapy:** No additional treatment	Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear		
Schiff 1996[176]	**Non-steroidal anti-inflammatory drugs** (n=231) Naproxen (Naprelan) 1000mg once a day or naproxen (Naprosyn) 500mg twice a day for 12 weeks **Placebo** (n=116) **Concomitant therapy:** They were allowed to use commercially available paracetamol 325mg for rescue analgesia	**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 Definition: Osteoarthritis of the knee diagnosed clinically Severity: Not stated Duration of symptoms: At least 6 months 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	Study design classification: 1) Including only responders
Schmitt 1999[177]	**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 **Placebo** (n=56) **Concomitant therapy:** Paracetamol was allowed until one day before the baseline visit	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 61 (9) years N = 393 Definition: Activated osteoarthritis with clinical and radiological features Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain 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	Study design classification: 2) Excluding non-responders

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

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]	**Non-steroidal anti-inflammatory drugs** (n=419) Celecoxib 200mg once a day for 13 weeks **Placebo** (n=416) A third group (n=427) was not included in the analysis due to the medication not being licensed for use in the UK (valdecoxib). **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.	**Hip osteoarthritis** Mean age (SD): 61.6 (10.0) years N = 1262 Definition: Symptomatic primary osteoarthritis with radiographic confirmation Severity: Not stated Duration of symptoms (mean [SD]): 3.9 (5.2) years Presence of multimorbidities: Not stated/unclear	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	Study design classification: 1) Including only responders In Forest plots this study is referred to as Schnitzer 2011A
Schnitzer 2011[181]	**Non-steroidal anti-inflammatory drugs** (n=256) Naproxen 500mg twice daily for 13 weeks	**Knee osteoarthritis** Mean age (SD): 59.8 (9.78) years N = 1002	Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1A: gastrointestinal (bleeding and	Study design classification: 1) Including only responders In Forest plots this study is referred to as Schnitzer 2011B

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo (n=257) A third group (n=489) was not included in the analysis due to the medication not being licensed for use in the UK (naproxcinod). **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	Definition: Clinical and radiographic diagnosis of osteoarthritis Severity: Kellgren Lawrence grade 1-3, functional class 1-3 Duration of symptoms: Not stated Presence of multimorbidities: Low comorbidity score	perforation) adverse events 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	
Schubiger 1980[185]	**Non-steroidal anti-inflammatory drugs** (n=114) Diclofenac 100mg sustained release once a day or diclofenac 50mg twice a day **Placebo** (n=34) **Concomitant therapy:** No additional information	**Mixed osteoarthritis (hip and/or knee)** Median age: 58 years N = 148 Definition: Clinically diagnosed osteoarthritis Severity: Not stated Duration of symptoms: Not stated	Pain 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 4: central nervous system adverse events at ≤3 months	Study design classification: 4) Unclear

Study	Intervention and comparison	Population	Outcomes	Comments
		Presence of multimorbidities: Not stated/unclear		
Scott 2000[186]	**Non-steroidal anti-inflammatory drugs** (n=202) Indomethacin 25mg three times a day for up to 5 years **Placebo** (n=303) 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). **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	**Knee osteoarthritis** Mean age (range): 61 (27-87) years N = 812 Definition: Symptomatic and radiological evidence of osteoarthritis Severity: Not stated Duration of symptoms (median [SD]): 61 (27-87) years Presence of multimorbidities: Not stated/unclear	Pain 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 2: cardiovascular adverse events at >3 months Serious adverse events 4: central nervous system adverse events at >3 months	Study design classification: 4) Unclear
Sheldon 2005[188]	**Non-steroidal anti-inflammatory drugs** (n=393) Celecoxib 200mg once a day for 13 weeks **Placebo** (n=382) A third group (n=776) was not included in the analysis due to the medication not being licensed for use in the UK (lumiracoxib).	**Knee osteoarthritis** Mean age (SD): 60.5 (10.8) years N = 1551 Definition: Primary osteoarthritis based on American College of Rheumatology criteria Severity: Not stated	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	Study design classification: 2) Excluding non-responders

Study	Intervention and comparison	Population	Outcomes	Comments
	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, ophthalamic, 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	Duration of symptoms (mean [SD]): 7.0 (7.8) years Presence of multimorbidities: Not stated/unclear	Serious adverse events 4: central nervous system adverse events at ≤3 months	
Sikes 2002[189]	**Non-steroidal anti-inflammatory drugs** (n=419) Ibuprofen 800mg three times a day or diclofenac 75mg twice a day **Placebo** (n=210) A third group (n=423) was not included in the analysis due to the medication not being	**Osteoarthritis (unclear site)** Mean age: 59.9 years N = 1052 Definition: Documented clinical diagnosis of osteoarthritis Severity: Not stated Duration of symptoms (mean): 10.4 years	Serious adverse events 1A: gastrointestinal (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: 4) Unclear

Study	Intervention and comparison	Population	Outcomes	Comments
	licensed for use in the UK (valdecoxib). **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.	Presence of multimorbidities: Not stated/unclear		
Simon 2009[190] Subsidiary paper: Roth 2011[165]	**Oral non-steroidal anti-inflammatory drugs** (n=151) Diclofenac slow release 100mg once a day for 12 weeks **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 **Placebo** (n=318) 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). **Concomitant therapy:**	**Knee osteoarthritis** Mean age (SD): 61.6 (9.9) years N = 775 Definition: Primary osteoarthritis based on standard radiological criteria and pain Severity (mean radiographic score [SD]): 16.5 (3.1) Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months	Study design classification: 1) Including only responders

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 (≤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.			
Smugar 2006[192]	**Non-steroidal anti-inflammatory drugs** (n=916) Celecoxib 200mg once a day for 6 weeks **Placebo** (n=301) A third group (n=1389) was not included in the analysis due to the medication not being licensed for use in the UK (rofecoxib). **Concomitant therapy:** Paracetamol was permitted as rescue medication	**Mixed osteoarthritis (knee or hip)** Mean age (range): 61.7 (39-92) years N = 2606 Definition: Clinical diagnosis of osteoarthritis Severity: Functional class 1-3 Duration of symptoms (mean): 1-10 years Presence of multimorbidities: Not stated/unclear	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 Pooled analysis of 2 trials
Strand 2017[194]	**Non-steroidal anti-inflammatory drugs** (n=202)	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 61.6 (8.90) years	Quality of life at ≤3 months Pain at ≤3 months	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	SoluMatrix diclofenac 35mg three times daily or twice daily for 12 weeks **Placebo** (n=103) **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	N = 305 Definition: Radiographic evidence of osteoarthritis Severity: Kellgren Lawrence grade 2-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Physical function at ≤3 months	NCT01461369
Tannenbaum 2004[195]	**Non-steroidal anti-inflammatory drugs** (n=481) Celecoxib 200mg once a day for 13 weeks **Placebo** (n=243) A third group (n=978) was not included in the analysis due to the medication not being licensed for use in the UK (lumiracoxib). **Concomitant therapy:** People were permitted to take paracetamol (≤2 grams/day). However, they were asked to refrain from using the rescue	**Knee osteoarthritis** Mean age (SD): 64.2 (10.4) years N = 1702 Definition: Primary osteoarthritis according to the American College of Rheumatology criteria Severity: Not stated Duration of symptoms (median): 4.75 years Presence of multimorbidities: not stated/unclear	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	Study design classification: 2) Excluding non-responders

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 (≤325mg/day) for a cardiovascular indication.			
Trudeau 2015[203]	**Non-steroidal anti-inflammatory drugs** (n=63) Celecoxib 100mg twice a day for 1 week **Placebo** (n=63) **Concomitant therapy:** Paracetamol was allowed as rescue medication as needed (500mg maximum four times a day).	**Knee osteoarthritis** Age: Older than 21, otherwise not reported N = 63 Definition: Primary osteoarthritis Severity: Functional class 1-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Physical function at ≤3 months	Study design classification: 1) Including only responders Crossover trial
Truitt 2001[204]	**Non-steroidal anti-inflammatory drugs** (n=115) Nabumetone 1500mg once daily for 6 weeks **Placebo** (n=52) A third group (n=174) was not included in the analysis due to the medication not being licensed for use in the UK (rofecoxib). **Concomitant therapy:**	**Mixed osteoarthritis (knee or hip)** Mean age (range): 83.0 (80-95) years N = 341 Definition: Clinical and radiographic diagnosis of osteoarthritis Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 15.0 (12.3) years	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 4: central nervous system adverse events at ≤3 months	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]	**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) **Placebo** (n=18) **Concomitant therapy:** No additional information	**Hip osteoarthritis** Mean age (range): 65 (50-78) years N = 18 Definition: Osteoarthritis with clinical and radiological features Severity: Radiographic severity 1-4 Duration of symptoms (mean [range]): 6 (1-14) years Presence of multimorbidities: Not stated/unclear	Serious adverse events 2: cardiovascular adverse events at ≤3 months	Study design classification: 4) Unclear Crossover trial
Wasserman 1984[215]	**Non-steroidal anti-inflammatory drugs** (n=14) Indomethacin 25mg once a day for 2 weeks **Placebo** (n=14)	**Mixed osteoarthritis (knee and/or hip)** Age (range): 45-78 years N = 14 Definition: Symptomatic osteoarthritis with clinical and	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	Study design classification: 4) Unclear Crossover trial

Study	Intervention and comparison	Population	Outcomes	Comments
	A third group (n=14) was not included in the analysis due to the medication not being licensed for use in the UK (carprofen). **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.	radiological evidence of disease Severity: Not stated Duration of symptoms: At least 6 months Presence of multimorbidities: Not stated/unclear		
Wiesenhutter 2005[216]	**Non-steroidal anti-inflammatory drugs** (n=424) Ibuprofen 800mg three times a day or etoricoxib 30mg once daily for 12 weeks **Placebo** (n=104) **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	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 62.0 (9.9) years N = 528 Definition: Clinical and radiographic diagnosis Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 7.8 (7.9) years 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	Study design classification: 1) Including only responders

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]	**Non-steroidal anti-inflammatory drugs** (n=454) Celecoxib 100mg twice a day or celecoxib 200mg once a day for 6 weeks **Placebo** (n=232) **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.	**Knee osteoarthritis** Mean age (SD): 62.8 (10.9) years N = 686 Definition: Clinical diagnosis of osteoarthritis Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 8.89 (8.33) years Presence of multimorbidities: Not stated/unclear	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: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
Williams 2001[218]	**Non-steroidal anti-inflammatory drugs** (n=474) Celecoxib 100mg twice a day or 200mg once a day for 6 weeks **Placebo** (n=233) **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).	**Knee osteoarthritis** Mean age (SD): 61.5 (11.9) years N = 718 Definition: Clinical and radiographic diagnosis of osteoarthritis Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 9.5 (8.5) years 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 4: central nervous system adverse events at ≤3 months	Study design classification: 1) Including only responders
Wittenberg 2006[220]	**Non-steroidal anti-inflammatory drugs** (n=145) Celecoxib 200mg twice daily for 1 week **Placebo** (n=75) A third group (n=144) was not included in the analysis due to the medication not being licensed for use in the UK (lumiracoxib).	**Knee osteoarthritis** Mean age (SD): 65.0 (8.3) years N = 364 Definition: Clinical osteoarthritis Severity: Moderate to severe Duration of symptoms (mean [SD]): 7.4 (7.1) years	Pain at ≤3 months Physical function at ≤3 months	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	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	Presence of multimorbidities: Not stated/unclear		
Yocum 2000[222]	**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 **Placebo** (n=157) **Concomitant therapy:** No additional information	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 62.9 (10.3) years N = 774 Definition: Radiographically confirmed osteoarthritis Severity: Not stated Duration of symptoms (mean [SD]): 8.2 (8.3) years 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 4: central nervous system adverse events at ≤3 months	Study design classification: 1) Including only responders
Zhao 1999[226]	**Non-steroidal anti-inflammatory drugs** (n=873) Naproxen 500mg twice a day or Celecoxib 50mg, 100mg or 200mg twice a day for 12 weeks **Placebo** (n=219) **Concomitant therapy:**	**Knee osteoarthritis** Mean age (range): 62 (21-89) years N = 1092 Definition: Symptomatic osteoarthritis fulfilling the American College of Rheumatology clinical criteria	Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	Low dose aspirin (≤325mg/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		

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

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

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

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

Study	Intervention and comparison	Population	Outcomes	Comments
Bocanegra 1998[27]	**Non-steroidal anti-inflammatory drugs** (n=154) Diclofenac 75mg twice a day for 6 weeks **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 **Placebo** (n=91) **Concomitant therapy:** No additional information - all antiinflammatory drugs were not permitted (with the exception of aspirin ≤325mg/day).	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 62.5 (10.4) years N = 572 Definition: Symptomatic osteoarthritis with a functional classification of 1-3 Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 11.2 (8.7) years Presence of multimorbidities: Not stated/unclear	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	Study design classification: 1) Including only responders
Bolten 1992[29]	**Non-steroidal anti-inflammatory drugs and gastroprotection** (n=178) Diclofenac 50mg with misoprostol 200 micrograms twice or three times a day for 4 weeks	**Mixed osteoarthritis (knee and/or hip)** Mean age (SD): 60.3 (12.0) years N = 361	Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months	Study design classification: 4) Unclear

Study	Intervention and comparison	Population	Outcomes	Comments
	Non-steroidal anti-inflammatory drugs (n=183) Diclofenac 50mg two to three times a day for 4 weeks **Concomitant therapy:** The use of any other NSAIDs, analgesics or antiulcer drugs during the study was prohibited	Definition: A confirmed diagnosis of osteoarthritis (at least clinical assessment) 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		
Chan 2010[44] Subsidiary paper: Kellner 2012[107]	**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 **Non-steroidal anti-inflammatory drugs** (n=2238) Celecoxib 200mg twice a day for 26 weeks **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	**Osteoarthritis (unclear site)** 17% of people had rheumatoid arthritis Mean age (SD): 65 (7.7) years N = 4484 Definition: Clinical diagnosis of osteoarthritis or rheumatoid arthritis Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at >3 months	Study design classification: 6) No response criteria NCT00141102

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]	**Non-steroidal anti-inflammatory drugs** (n=494) Celecoxib 200mg once daily for 12 weeks **Non-steroidal anti-inflammatory drugs with gastroprotection** (n=492) Naproxen 500mg and esomeprazole 20mg twice daily for 12 weeks **Placebo** (n=248) **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.	**Knee osteoarthritis** Mean age (range): 61.9 (49-90) years N = 1234 Definition: Symptomatic, clinically diagnosed osteoarthritis Severity: Functional class I-III Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	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 Pooled analysis of 2 trials
Goldstein 2007[91]	**Non-steroidal anti-inflammatory drugs and gastroprotection** (n=529) Naproxen 500mg twice daily plus lansoprazole 30mg once daily	**Osteoarthritis (no statement about the joint site)** Mean age (SD): 56.7 (11.2)years N = 1045	Serious adverse event 1: gastrointestinal adverse events at ≤3 months Serious adverse event 2: cardiovascular adverse events at ≤3 months	Study design classification: 3) Selection of specific population

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

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

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
	Diclofenac 75mg twice a day for 6 weeks **Non-steroidal anti-inflammatory drugs and gastroprotection** (n=327) Diclofenac 50mg with misoprostol 200 microgram three times a day or diclofenac 75mg wth misoprostol 200 microgram two times a day for 6 weeks **Placebo** (n=91) **Concomitant therapy:** No additional information - all antiinflammatory drugs were not permitted (with the exception of aspirin ≤325mg/day).	Mean age (SD): 62.5 (10.4) years N = 572 Definition: Symptomatic osteoarthritis with a functional classification of 1-3 Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 11.2 (8.7) years Presence of multimorbidities: Not stated/unclear	Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months Serious adverse events 3: hepatorenal adverse events at ≤3 months	
Cryer 2011[55]	**Non-steroidal anti-inflammatory drugs** (n=494) Celecoxib 200mg once daily for 12 weeks **Non-steroidal anti-inflammatory drugs with gastroprotection** (n=492) Naproxen 500mg and esomeprazole 20mg twice daily for 12 weeks **Placebo** (n=248)	**Knee osteoarthritis** Mean age (range): 61.9 (49-90) years N = 1234 Definition: Symptomatic, clinically diagnosed osteoarthritis Severity: Functional class I-III Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	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 Pooled analysis of 2 trials

Study	Intervention and comparison	Population	Outcomes	Comments
	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.			

1.1.5.1.7 Weak opioids compared to placebo

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]	**Weak opioids** (n=51) Controlled release codeine 100mg twice a day escalated to a maximum of 400mg per day for 4 weeks **Placebo** (n=52) **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.	**Mixed osteoarthritis (knee and/or hip)** Mean age (SD): 62.2 (10.5) years N = 103 Definition: Symptomatic, radiographically confirmed osteoarthritis Severity: At least radiographic grade 2 Duration of symptoms (mean [SD]): 10.3 (7.5) years Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months	Study design classification:1) Including only responders

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

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

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

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		

1.1.5.1.9 Strong opioids compared to placebo

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]	**Strong opioids** (n=691) Tapentadol extended release 100-250mg twice daily or oxycodone controlled release 20-50mg twice daily for 12 weeks **Placebo** (n=339) **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)	**Knee osteoarthritis** Mean age (SD): 58.3 (9.9) years N = 1030 Definition: Osteoarthritis according to the American College of Rheumatology criteria Severity: Majority severe pain at baseline Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	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	Study design classification: 3) Selection of specific population
Babul 2004[10]	**Strong opioids** (n=124) Tramadol extended release 100mg daily increased to a maximum of 400mg daily for 12 weeks **Placebo** (n=122)	**Knee osteoarthritis** Mean age (SD): 61.4 (10.1) years N = 246 Definition: Primary osteoarthritis meeting the	Pain at ≤3 months Physical function at ≤3 months	Study design classification: 2) Excluding non-responders

Study	Intervention and comparison	Population	Outcomes	Comments
	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.	American College of Rheumatology diagnostic criteria with radiographic evidence Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 12.9 (10.5) years Presence of multimorbidities: Not stated/unclear		
Burch 2007[37]	**Strong opioids** (n=432) Tramadol contramid once daily starting at 100mg increasing a maximum of 300mg for 12 weeks **Placebo** (n=214) **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.	**Knee osteoarthritis** Mean age (SD): 62 (9) years N = 646 Definition: Symptomatic osteoarthritis Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months	Study design classification: 1) Including only responders
Caldwell 2002[39]	**Strong opioids** (n=222) Morphine Avinsa 30mg once a day or morphine sulphate contin	**Mixed osteoarthritis (knee and/or hip)**	Pain at ≤3 months Physical function at ≤3 months	Study design classification: 3) Selection of specific population

Study	Intervention and comparison	Population	Outcomes	Comments
	15mg twice a day for 4 weeks. The dose could be increased if insufficient pain relief. **Placebo** (n=73) **Concomitant therapy:** The use of analgesic preparations other than the cardiovascular prophlyactic 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.	Mean age (SD): 62.4 (10.5) years N = 295 Definition: Clinical diagnosis of osteoarthritis with radiographic evidence Severity: Radiographic grade 2-4 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear		
Chindalore 2005[48]	**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 **Placebo** (n=52) A third group (n=207) was reported which was not included in the analysis as it was excluded in the protocol (oxycodone and naltrexone).	**Mixed osteoarthritis (knee or hip)** Mean age (range): 54.3 (21-70) years N = 362 Definition: Moderate to severe pain caused by osteoarthritis Severity: Moderate to severe Duration of symptoms: At least 3 months	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	Study design classification: 2) Excluding non-responders

Study	Intervention and comparison	Population	Outcomes	Comments
	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.	Presence of multimorbidities: Not stated/unclear		
Delemos 2011[60]	**Non-steroidal anti-inflammatory drugs** (n=203) Celecoxib 200mg once a day for 12 weeks **Strong opioids** (n=606) Tramadol 100mg once to three times a day for 12 weeks **Placebo** (n=202) **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.	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 59.92 (10.96) years N = 1011 Definition: Radiologically confirmed osteoarthritis Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 8.1 (7.9) years Presence of multimorbidities: Not stated/unclear	Quality of life at ≤3 months Pain at ≤3 months Physical function at ≤3 months Psychological distress at ≤3 months	Study design classification: 1) Including only responders
Fishman 2007[73] Subsidiary paper: Kean 2009[106]	**Strong opioids** (n=325) Tramadol Contramid OAD 100mg, 200mg or 300mg once daily for 12 weeks **Placebo** (n=227) **Concomitant therapy:**	**Knee osteoarthritis** Mean age (SD): 61.2 (9.3) years N = 552 Definition: Osteoarthritis according to the American	Pain at ≤3 months	Study design classification: 2) Excluding non-responders

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
	Oxycodone extended release 5mg twice daily increased up to 20mg twice daily for 12 weeks **Placebo** (n=207) **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.	Mean age (SD): 58.3 (8.2) years N = 412 Definition: Osteoarthritis with clinical and radiographic evidence Severity: Moderate to severe Duration of symptoms: At least 3 months Presence of multimorbidities: Not stated/unclear		
Gana 2006[83] Subsidiary papers: Florete 2008[77], Kosinski 2007[113]	**Strong opioids** (n=806) Tramadol extended release 100, 200, 300 or 400mg once daily for 12 weeks **Placebo** (n=205) **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	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 58.2 (10.0) years N = 1011 Definition: Radiographically confirmed osteoarthritis Severity: Functional class 1-3 Duration of symptoms (mean [SD]): 7.8 (7.3) years Presence of multimorbidities: Not stated/unclear	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	Study design classification: 2) Excluding non-responders

Study	Intervention and comparison	Population	Outcomes	Comments
	before each study visit after the screening visit.			
Malonne 2004[134]	**Strong opioids** (n=111) Tramadol LP 200mg once daily for 14 days **Placebo** (n=119) **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.	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 66.7 (8.3) years N = 230 Definition: Symptomatic osteoarthritis Severity: Not stated Duration of symptoms (mean [SD]): 5.7 (5.1) years Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months	Study design classification: 3) Selection of specific population
Matsumoto 2005[136]	**Strong opioids** (n=125) Oxymorphone extended release 20 or 40mg or oxycodone controlled release 20mg given every 12 hours for 4 weeks **Placebo** (n=124) 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. **Concomitant therapy:** No additional information	**Mixed osteoarthritis (knee or hip)** Mean age (SE): 62.3 (0.98) years N = 491 Definition: Symptomatic and radiographic evidence of osteoarthritis 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	Quality of life at ≤3 months Pain at ≤3 months	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
Serrie 2017[187] Subsidiary papers: Biondi 2015[24], Etropolski 2015[28], Lange 2010[117], Lange 2018[118], Lange 2017[119]	**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 **Placebo** (n=337) **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.	**Knee osteoarthritis** Mean age (SD): 62.1 (9.3) years N = 987 Definition: Diagnosis of osteoarthritis based on the American College of Rheumatology criteria Severity: Majority pain severity severe, functional class 1-3 Duration of symptoms: At least 3 months Presence of multimorbidities: Not stated/unclear	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	Study design classification: 3) Selection of specific population
Thorne 2008[197]	**Strong opioids** (n=100) Tramadol 150mg once daily increased to the maximal tolerated dose for 4 weeks	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 61.0 (10.3) years N = 100	Quality of life at ≤3 months Pain at ≤3 months Physical function at ≤3 months	Study design classification: 3) Selection of specific population Crossover trial

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

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

1.1.5.1.10 Anti-epileptic drugs compared to antidepressant drugs

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]	**Antidepressant drugs**(n=50) Duloxetine 30mg daily increased to a maximum of 60mg daily after two weeks **Anti-epileptic drugs** (n=50) Gabapentin 300mg daily increased to a maximum of 600mg daily after two weeks **Paracetamol** (n=50) Paracetamol 1000mg daily increased to a maximum of 2000mg daily after two weeks **Concomitant therapy:** Opioid usage was not allowed during the intervention period. People were asked to continue their previous medications for	**Knee osteoarthritis** Mean age (SD): 54.44 (7.17) years N = 150 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. Severity: Kellgren Lawrence grade II-III Duration of symptoms (mean [SD]): 8.44 (4.07) years	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
	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]	**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 **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 **Placebo** (n=22) **Concomitant therapy:** No additional information	**Hand osteoarthritis** Mean age (SD): 62.9 (7.2) years N = 65 Definition: Osteoarthritis diagnosed by the American College of Rheumatology criteria Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	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	Study design classification: 6) No response criteria

1.1.5.1.11 Anti-epileptic drugs compared to placebo

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]	**Anti-epileptic drugs** (n=22) Pregabalin 150mg once a day for 1 week, 300mg once a day	**Hand osteoarthritis** Mean age (SD): 62.9 (7.2) years N = 65	Pain at ≤3 months Physical function at ≤3 months	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
	for 10 weeks, and 150mg once a day for 2 more weeks **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 **Placebo** (n=22) **Concomitant therapy:** No additional information	Definition: Osteoarthritis diagnosed by the American College of Rheumatology criteria Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	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	

1.1.5.1.12 Anti-epileptic drugs compared to paracetamol

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]	**Antidepressant drugs** (n=50) Duloxetine 30mg daily increased to a maximum of 60mg daily after two weeks **Anti-epileptic drugs** (n=50) Gabapentin 300mg daily increased to a maximum of 600mg daily after two weeks **Paracetamol** (n=50) Paracetamol 1000mg daily increased to a maximum of 2000mg daily after two weeks	**Knee osteoarthritis** Mean age (SD): 54.44 (7.17) years N = 150 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.	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
	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.	Severity: Kellgren Lawrence grade II-III Duration of symptoms (mean [SD]): 8.44 (4.07) years Presence of multimorbidities: Not stated/unclear		

1.1.5.1.12 Antidepressant drugs compared to placebo

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]	**Antidepressant drugs** (n=144) Duloxetine 60mg/day for 16 weeks **Placebo** (n=144) **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	**Knee osteoarthritis** Mean age (SD): 68.7 (6.0) years N = 288 Definition: American College of Rheumatology clinical and radiographic criteria of primary knee osteoarthritis Severity: Kellgren Lawrence grade II-III (majority grade II)	Pain at ≤3 months Physical function at ≤3 months Psychological distress at ≤3 months	Study design classification: 6) No response criteria NCT01425827

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]	**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. **Placebo** (n=120) **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	**Knee osteoarthritis** Mean age (SD): 62.3 (9.5) years N = 231 Definition: Clinical and radiographic evidence of osteoarthritis Severity: Not stated Duration of symptoms (mean [SD]): 7.0 (7.8) years Presence of multimorbidities: Not stated/unclear	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
	surgery or for rescue from an osteoarthritis knee pain flare.			
Chappell 2011[45]	**Antidepressant drugs** (n=128) Duloxetine 60-120mg once daily for 13 weeks **Placebo** (n=128) **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.	**Knee osteoarthritis** Mean age (SD): 62.6 (9.0) years N = 256 Definition: Clinical and radiographic evidence of osteoarthritis Severity: Not stated Duration of symptoms (mean [SD]): 5.9 (6.1) years Presence of multimorbidities: Not stated/unclear	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	Study design classification: 6) No response criteria NCT00433290
Frakes 2011[78]	**Antidepressant drugs** (n=264) Duloxetine starting at 30mg/day increased up to 120mg/day for 10 weeks **Placebo** (n=260) **Concomitant therapy:** Before the study started, each person had their NSAID therapy optimised. During the study they stayed on the same dose	**Knee osteoarthritis** Mean age (SD): 61.0 (9.2) years N = 524 Definition: Clinical and radiographic evidence of osteoarthritis Severity: Not stated Duration of symptoms (mean [SD]): 9.5 (8.9) years	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	Study design classification: 6) No response criteria NCT01018680

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]	**Antidepressant drugs** (n=102) Nortryptyline 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. **Placebo** (n=103) **Concomitant therapy:**	**Knee osteoarthritis** Mean age (SD): 64.5 (9.2) years N = 205 Definition: Knee osteoarthritis assessed by an orthopaedic surgeon through referral letters and accompanying pre-referral X-rays) Severity: Not stated/unclear Duration of symptoms (mean [SD]): 7.6 (7.6) years	Quality of life at ≤3 months Pain at ≤3 months Physical function at ≤3 months Serious adverse event 2: cardiovascular adverse events at ≤3 months Serious adverse event 2: renal and hepatic adverse events 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
	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]	**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 **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 **Placebo** (n=22) **Concomitant therapy:** No additional information	**Hand osteoarthritis** Mean age (SD): 62.9 (7.2) years N = 65 Definition: Osteoarthritis diagnosed by the American College of Rheumatology criteria Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	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	Study design classification: 6) No response criteria
Uchio 2018[206] Subsidiary paper: Uchio 2018[207]	**Antidepressant drugs** (n=178) Duloxetine 20mg increased up to 60mg for 14 weeks **Placebo** (n=176) **Concomitant therapy:** Drugs with analgesic effect (e.g. NSAIDs) were permitted as rescue medication for up to 3	**Knee osteoarthritis** Mean age (SD): 66.0 (8.2) years N = 354 Definition: Clinical and radiographic evidence of osteoarthritis Severity: Kellgren Lawrence grade 1-4	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	Study design classification: 6) No response criteria NCT02248480

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

1.1.5.1.12 Antidepressant drugs compared to paracetamol

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]	**Antidepressant drugs** (n=50) Duloxetine 30mg daily increased to a maximum of 60mg daily after two weeks **Anti-epileptic drugs** (n=50) Gabapentin 300mg daily increased to a maximum of 600mg daily after two weeks	**Knee osteoarthritis** Mean age (SD): 54.44 (7.17) years N = 150 Definition: Moderate to severe idiopathic knee osteoarthritis able to walk with knee pain more than five by visual	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
	Paracetamol(n=50) Paracetamol 1000mg daily increased to a maximum of 2000mg daily after two weeks **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.	analogue scale or more than 48 score in the WOMAC score with radiographic evidence of osteoarthritis with Kellgren Lawrence score of III-IV. Severity: Kellgren Lawrence grade II-III Duration of symptoms (mean [SD]): 8.44 (4.07) years Presence of multimorbidities: Not stated/unclear		

1.1.5.1.13 Glucosamine compared to paracetamol

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]	**Paracetamol** (n=108) Paracetamol 1 gram three times a day and matching placebo for 26 weeks **Glucosamine** (n=106)	**Knee osteoarthritis** Mean age (SD): 63.9 (7.0) years N = 318 Definition: Primary symptomatic knee	Pain at >3 months Physical function at >3 months Serious adverse events 2: cardiovascular adverse events at >3 months	Study design classification: 6) No response criteria

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

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

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

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: Paracetamol (500mg tablet) was provided for emergency analgesic use. Ongoing concomitant medication for concurrent chronic illness was permitted.			
Clegg 2006[51] GAIT trial Subsidiary papers: Hochberg 2008[97] Sawitzke 2008[174] Sawitzke 2010[175]	**Non-steroidal anti-inflammatory drugs** (n=318) Celecoxib 200mg daily for 24 weeks **Glucosamine** (n=317) Glucosamine hydrochloride 500mg three times daily for 24 weeks **Placebo** (n=313) 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). Glucosamine purity: Statement regarding purity **Concomitant therapy:** People were allowed to take paracetamol up to 4000mg per	**Knee osteoarthritis** Mean age (SD): 58.6 (10.4) years N = 1583 Definition: Clinical and radiographic evidence of osteoarthritis Severity: Kellgren Lawrence grade 2-3. Functional class 1-3. Duration of symptoms (mean [SD]): 10.0 (9.8) years Presence of multimorbidities: Not stated/unclear	Pain at >3 months Physical function at >3 months Serious adverse events 2: cardiovascular adverse events at >3 months	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
	day, except during the 24 hours before a clinical evaluation for joint pain.			
Lopes vaz 1982[129]	**Glucosamine** (n=20) Glucosamine 500mg three times a day for 8 weeks **Non-steroidal anti-inflammatory drugs** (n=20) Ibuprofen 300mg three times a day for 8 weeks Glucosamine purity: Purity not stated **Concomitant therapy:** No additional information	**Knee osteoarthritis** Mean age (SD): 57.8 (5.5) years N = 40 Definition: Unilateral osteoarthritis Severity: Not stated Duration of symptoms (mean [SD]): 3.2 (2.0) years Presence of multimorbidities: Not stated/unclear	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	Study design classification: 4) Unclear
Muller-fassbender 1994[142]	**Glucosamine** (n=100) Glucosamine sulfate 500mg three times a day for 4 weeks **Non-steroidal anti-inflammatory drugs** (n=100) Ibuprofen 400mg three times a day for 4 weeks Glucosamine purity: Purity not stated **Concomitant therapy:** The person's program for physical therapy (including exercise, cold or heat	**Knee osteoarthritis** Mean age (SD): 54 (8.5) years N = 200 Definition: Painful, active osteoarthritis based on Lequesne's clinical and radiographic criteria Severity: Not stated Duration of symptoms (mean [SD]): 4.8 (3.4) years Presence of multimorbidities: Not stated/unclear	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	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]	**Glucosamine** (n=20) Glucosamine sulfate 500mg three times a day for 12 weeks **Non-steroidal anti-inflammatory drugs** (n=20) Ibuprofen 400mg three times daily for 12 weeks Glucosamine purity: Purity not stated **Concomitant therapy:** Paracetamol 500mg to be used as necessary as an adjuvant medicine for relief of arthritis pain	**Osteoarthritis (unclear site)** Mean age (SD): 65.2 (9.0) years N = 40 Definition: Diagnosis with either radiographic or clinical evidence of osteoarthritis Severity: Not stated Duration of symptoms (mean [SD]): 65.2 (9.0) years Presence of multimorbidities: Not stated/unclear	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: 4) Unclear
Qiu 1998[162]	**Glucosamine** (n=88) Glucosamine 500mg three times a day for 4 weeks **Non-steroidal anti-inflammatory drugs** (n=90) Ibuprofen 400mg three times a day for 4 weeks Glucosamine purity: Purity not stated	**Knee osteoarthritis** Mean age (SD): 56 (10) years N = 178 Definition: People with osteoarthritis of the knee Severity: Not stated Duration of symptoms: Not stated	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	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	

1.1.5.1.15 Glucosamine compared to placebo

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]	**Glucosamine** (n=40) Glucosamine was administered as a sachet of powder in a 1500 mg oral solution, once daily without food for 2 months. **Placebo** (n=50) Glucosamine purity: Purity not stated **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.	**Knee osteoarthritis** Mean age (SD): 55 (10) years N = 90 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 Severity: Kellgren-Lawrence grade 2 Duration of symptoms (mean [SD]): 13 (11) years Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months and >3 months Serious adverse event 1: gastrointestinal adverse events 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
Cahlin 2011[38]	**Glucosamine** (n=30) Glucosamine 400mg three times a day for 6 weeks **Placebo** (n=29) Glucosamine purity: Purity not stated **Concomitant therapy:** Paracetamol 1000mg could be used for rescue medication	**Temporomandibular joint osteoarthritis** Mean age (SD): 59 (12) years N = 59 Definition: Radiographically confirmed osteoarthritis Severity: Not stated Duration of symptoms: 2 to >24 months (median 13-24 months) Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months	Study design classification: 6) No response criteria
Cibere 2004[50]	**Glucosamine** (n=71) Glucosamine 1500mg per day as a potassium salt for 26 weeks **Placebo** (n=66) Glucosamine purity: Purity not stated **Concomitant therapy:** Rescue analgesic medications including paracetamol and NSAIDs were allowed and recorded by the patient in a daily diary	**Knee osteoarthritis** Mean age (range): 65 (40-88) years N = 137 Definition: Clinical and radiographic evidence of osteoarthritis Severity: Kellgren Lawrence grade 2-4 Duration of symptoms (median [range]): 3 (0-29) years Presence of multimorbidities: Not stated/unclear	Quality of life at >3 months Pain at >3 months Physical function at >3 months Osteoarthritis flares at >3 months	Study design classification: 3) Selection of specific population
Clegg 2006[51] GAIT trial Subsidiary papers:	**Non-steroidal anti-inflammatory drugs** (n=318)	**Knee osteoarthritis** Mean age (SD): 58.6 (10.4) years	Pain at >3 months Physical function at >3 months	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
Hochberg 2008[97] Sawitzke 2008[174] Sawitzke 2010[175]	Celecoxib 200mg daily for 24 weeks **Glucosamine** (n=317) Glucosamine hydrochloride 500mg three times daily for 24 weeks **Placebo** (n=313) 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). Glucosamine purity: Statement regarding purity **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.	N = 1583 Definition: Clinical and radiographic evidence of osteoarthritis Severity: Kellgren Lawrence grade 2-3. Functional class 1-3. Duration of symptoms (mean [SD]): 10.0 (9.8) years Presence of multimorbidities: Not stated/unclear	Serious adverse events 2: cardiovascular adverse events at >3 months	
Fransen 2015[79] (LEGS trial)	**Glucosamine** (n=152) Glucosamine sulfate potassium chloride 1506mg once a day for 2 years **Placebo** (n=151)	**Knee osteoarthritis** Mean age (SD): 60.5 (8.1) years N = 605	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	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
	A third and forth 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). Glucosamine purity: Statement on purity **Concomitant therapy:** No additional information	Definition: Symptomatic and radiographic evidence of osteoarthritis Severity: 48-61% had less than Kellgren-Lawrence grade 2 osteoarthritis Duration of symptoms: Not stated Presence of multimorbidities: Not stated		
Frestedt 2008[80] Subsidiary paper: Frestedt 2009[81]	**Glucosamine** (n=19) Glucosamine sulfate 1500mg per day for 12 weeks **Placebo** (n=16) 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). Glucosamine purity: Purity not stated **Concomitant therapy:** The rescue medication was paracetamol, 325mg, 1-2 tablets every 4-6 hours as needed for intractable pain.	**Knee osteoarthritis** Mean age (SD): 59.2 (9.7) years N = 70 Definition: Clinical diagnosis of osteoarthritis Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	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 4: central nervous system adverse events at ≤3 months	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
Giordano 2009[89]	**Glucosamine** (n=30) Glucosamine 15000mg once a day for 12 weeks **Placebo** (n=30) Glucosamine purity: Purity not stated **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.	**Knee osteoarthritis** Mean age (SD): 57.7 (7.8) years N = 60 Definition: Osteoarthritis diagnosed according to the American Rheumatism Association criteria Severity: Kellgren Lawrence grade 1-3 Duration of symptoms (mean [SD]): 6.3 (4.8) years Presence of multimorbidities: Not stated/unclear	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	Study design classification: 6) No response criteria
Herrero-beaumont 2007[96]	**Paracetamol** (n=108) Paracetamol 1 gram three times a day and matching placebo for 26 weeks **Glucosamine** (n=106) Glucosamine 1500mg oral powder for solution per day and matching placebo for 26 weeks Glucosamine purity: Purity not stated **Placebo** (n=104)	**Knee osteoarthritis** Mean age (SD): 63.9 (7.0) years N = 318 Definition: Primary symptomatic knee osteoarthritis according to the clinical and radiographic American College of Rheumatology criteria Severity: Kellgren Lawrence grade 2-3 Duration of symptoms (mean [SD]): 7.0 (5.7) years	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	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
	Concomitant therapy: Ibuprofen 400mg was permitted for rescue medication	Presence of multimorbidities: Not stated/unclear		
Houpt 1999[98]	**Glucosamine** (n=58) Glucosamine hydrochloride 500mg three times a day for 8 weeks **Placebo** (n=60) Glucosamine purity: Purity not stated **Concomitant therapy:** People were permitted to use paracetamol 500mg up to a maximum of eight capsules per day	**Knee osteoarthritis** Mean age (SD): 64.5 (9.8) years N = 118 Definition: Clinical and radiological evidence of osteoarthritis 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	Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months	Study design classification: 6) No response criteria
Hughes 2002[101]	**Glucosamine** (n=40) Glucosamine sulphate 1500mg a day for 24 weeks **Placebo** (n=40) Glucosamine purity: Purity not stated **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	**Knee osteoarthritis** Mean age (SD): 62.28 (9.12) years N = 80 Definition: Radiologicall defined, symptomatic osteoarthritis 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	Pain at >3 months Physical function at >3 months	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]	**Glucosamine** (n=98) Glucosamine 1500mg once a day for 24 weeks **Placebo** (n=103) Glucosamine purity: Purity not stated **Concomitant therapy:** Paracetamol was the only analgesic allowed during the study	**Knee osteoarthritis** Mean age (SD): 52.23 (6.40) years N = 201 Definition: Symptomatic osteoarthritis Severity: Kellgren Lawrence grade Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months and >3 months Physical function at ≤3 months and >3 months	Study design classification: 6) No response criteria
Noack 1994[147]	**Glucosamine** (n=126) Glucosamine 500mg three times a day for 4 weeks **Placebo** (n=126) Glucosamine purity: Purity not stated **Concomitant therapy:**	**Knee osteoarthritis** Mean age (SD): 55 (14.5) years N = 252 Definition: Osteoarthritis defined according to the clinical and radiological criteria of Lequesne	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: 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]	**Glucosamine** (n=101) Glucosamine sulfate 1500mg per day for 3 years **Placebo** (n=101) Glucosamine purity: Purity not stated **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.	**Knee osteoarthritis** Mean age (SD): 62.4 (7.2) years N = 202 Definition: Clinical and radiologically defined osteoarthritis Severity: Kellgren and Lawrence grade 2-3 Duration of symptoms (mean [SD]): 10.6 (7.5) years Presence of multimorbidities: Not stated/unclear	Pain at >3 months Physical function at >3 months Serious adverse events 2: cardiovascular adverse events at >3 months	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
Pujalte 1980[159]	**Glucosamine** (n=12) Glucosamine 500mg three times daily for 6-8 weeks **Placebo** (n=12) Glucosamine purity: Purity not stated **Concomitant therapy:** No other analgesic, antirheumatic or anti-inflammatory drug was allowed during the observation period	**Knee osteoarthritis** Mean age (range): 61.7 (45-73) years N = 24 Definition: Clinical and radiological osteoarthritis Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Serious adverse events 4: central nervous system adverse events at ≤3 months	Study design classification: 4) Unclear
Rindone 2000[164]	**Glucosamine** (n=54) Glucosamine 500mg three times day for 8 weeks **Placebo** (n=54) Glucosamine purity: Purity not stated **Concomitant therapy:** People who were taking other analgesics were instructed to continue them for the duration of the study.	**Knee osteoarthritis** Mean age (SD): 64.5 (11.5) years N = 108 Definition: Clinical and radiographic osteoarthritis of the knee Severity: Radiographic stage 1-4 Duration of symptoms (mean [SD]): 13 (12) years Presence of multimorbidities: Not stated	Pain at ≤3 months	Study design classification: 6) No response criteria
Rozendaal 2008[170] Subsidiary paper: Rozendaal 2009[171]	**Glucosamine** (n=111) Glucosamine sulfate 1500mg/day for 2 years	**Hip osteoarthritis** Mean age (SD): 63.4 (9.0) years N = 222	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
	Placebo (n=111) Glucosamine purity: Purity not stated **Concomitant therapy:** No additional information	Definition: Clinical osteoarthritis Severity: Kellgren Lawrence grade 1-4 Duration of symptoms: Majority >3 years Presence of multimorbidities: Not stated/unclear		
Zenk 2002[225]	**Glucosamine** (n=14) Glucosamine 500mg three times a day for 6 weeks **Placebo** (n=14) A third group (n=14) was reported which was not included in the analysis as it was excluded in the protocol (milk protein concentrate). Glucosamine purity: Purity not stated **Concomitant therapy:** The use of approved rescue medications were permitted, including naproxen 220mg, ibuprofen 200mg, paracetamol 325mg, and acetylsalicylic acid 325mg	**Osteoarthritis (site unclear)** Mean age (SD): 58 (12) years N = 42 Definition: Physician diagnosed osteoarthritis with symptoms Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months	Study design classification: 6) No response criteria

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

1.1.5.2.1 Capsaicin compared to placebo for knee osteoarthritis

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]	**Capsaicin** (n=99) Capiscum tincture 45.50 grams (equivalent to capsaicin 0.0125%) per 100g of Capsika gel. 2 inches applied three times a day for 4 weeks. **Placebo** (n=99) **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	**Knee osteoarthritis** Mean age (range): 61 (44-82) years N = 198 Definition: Idiopathic osteoarthritis with radiographic evidence Severity: Kellgren Lawrence grade 2-3 Duration of symptoms: At least 6 months Presence of multimorbidities: Not stated/unclear	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	Study design classification: 6) No response criteria

1.1.5.2.2 Capsaicin compared to placebo for knee osteoarthritis

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]	**Capsaicin** (n=29) 0.025% capsaicin cream. Applied four times a day for 3 weeks, then twice a day for 6 weeks **Placebo** (n=30)	**Hand osteoarthritis** Mean age (SD): 68.0 (8.8) years N = 59	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		

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

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

Study	Intervention and comparison	Population	Outcomes	Comments
Conaghan 2013[53]	**Oral non-steroidal anti-inflammatory drug**s (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
	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.			
Dickson 1991[62]	**Topical non-steroidal anti-inflammatory drugs** (n=117) Piroxicam gel, 1 gram applied to the affected knee three times daily for 4 weeks **Oral non-steroidal anti-inflammatory drugs** (n=118) Ibuprofen 400mg three times day for 4 weeks **Concomitant therapy:** During the washout period and throughout the trial, paracetamol up to 4 grams per day was allowed as rescue analgesia	**Knee osteoarthritis** Mean age (SD): 62.5 (11.5) years N = 235 Definition: Well document osteoarthritis Severity: Mild Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	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: 6) No response criteria
Rother 2007[168]	**Oral non-steroidal anti-inflammatory drugs** (n=132) Celecoxib 100mg twice a day for 6 weeks	**Knee osteoarthritis** Mean age (SD): 62.8 (9.8) years N = 397	Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	Topical non-steroidal anti-inflammatory drugs (n=138) 110mg epicutaneous ketoprofen in 4.8 grams Transfersome twice a day for 6 weeks **Placebo** (n=127) **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	Definition: Fulfilling clinical criteria for osteoarthritis Severity: Not stated Duration of symptoms: At least 6 months Presence of multimorbidities: Not stated/unclear	and perforation) adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months	
Simon 2009[190] Subsidiary paper: Roth 2011[165]	**Oral non-steroidal anti-inflammatory drugs** (n=151) Diclofenac slow release 100mg once a day for 12 weeks **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 **Placebo** (n=318) A fourth group (n=152) was reported which was not included in the analysis as it was excluded in the protocol	**Knee osteoarthritis** Mean age (SD): 61.6 (9.9) years N = 775 Definition: Primary osteoarthritis based on standard radiological criteria and pain Severity (mean radiographic score [SD]): 16.5 (3.1) Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	(combination topical and oral NSAID). **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.			
Tiso 2010[198]	**Topical non-steroidal anti-inflammatory drugs** (n=10) Ibuprofen gel 4%, 2mL applied to the target area four times daily for 2 weeks **Oral non-steroidal anti-inflammatory drugs** (n=10) Ibuprofen 800mg three times daily for 2 weeks **Concomitant therapy:** No additional information	**Knee osteoarthritis** Mean age (SD): 57.9 (9.2) years N = 20 Definition: Pain for at least 3 months Severity: Chronic pain grade 1-4, median grade 3 Duration of symptoms: Median >12 months Presence of multimorbidities: Not stated/unclear	Quality of life at ≤3 months Pain at ≤3 months Physical function at ≤3 months	Study design classification: 6) No response criteria

Study	Intervention and comparison	Population	Outcomes	Comments
Tugwell 2004[205]	**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 capules three times a day. **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. **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.	**Knee osteoarthritis** Mean age (SD): 63.5 (10.0) years N = 622 Definition: clinical and radiographic osteoarthritis Severity: Total x-ray score (0-27) mean (SD): 6.3 (3.7) Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months	Study design classification: 2) Excluding non-responders
Underwood 2008[209] Subsidiary paper: Underwood 2008[208]	**Topical non-steroidal anti-inflammatory drugs** (n=138) Ibuprofen gel applied for 24 months **Oral non-steroidal anti-inflammatory drugs** (n=144)	**Knee osteoarthritis** Median age (IQR): 60 (56-69) years N = 282	Quality of life at ≤3 months and >3 months Pain at ≤3 months and >3 months Physical function at ≤3 months and >3 months	Study design classification: 4) Unclear

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

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

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

Study	Intervention and comparison	Population	Outcomes	Comments
Baer 2005[11]	**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 **Placebo** (n=109) **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	**Knee osteoarthritis** Mean age (SD): 64.8 (11.0) years N = 216 Definition: Radiographic evidence of osteoarthritis Severity: Total X-ray score (0-27) mean (SD): 7.3 (5.2) Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months	Study design classification: 1) Including only responders ISRCTN53366886

Study	Intervention and comparison	Population	Outcomes	Comments
	week 6. Acetylsalicylic acid (no more than 325mg/day) was permitted for cardiovascular prophylaxis			
Baraf 2010[15]	**Topical non-steroidal anti-inflammatory drugs** (n=208) Diclofenac sodium gel 4g per knee 4 times daily for 12 weeks **Placebo** (n=212) **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 ≤162mg/day started ≥30 days before randomisation), topical analgesics applied to the knee, and intra- or periarticular knee injections	**Knee osteoarthritis** Mean age (SD): 61.4 (10.9) years N = 420 Definition: Clinical and radiographic osteoarthritis Severity: Kellgren Lawrence grade 1-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	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 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: 1) Including only responders
Barthel 2009[16]	**Topical non-steroidal anti-inflammatory drugs** (n=254) Diclofenac gel 1% 4 grams applied 4 times daily for 12 weeks **Placebo** (n=238)	**Knee osteoarthritis** Mean age (SD): 59.5 (10.6) years N = 492 Definition: Radiographic and clinical osteoarthritis	Pain at ≤3 months Physical function at ≤3 months 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
	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	Severity: Kellgren Lawrence grade 1-3 Duration of symptoms: At least 3 months 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	
Bhatia 2020[22]	**Topical non-steroidal anti-inflammatory drugs** (n=24) The gel was applied to the knee twice a day for 6 weeks. **Placebo** (n=12) Placebo gel **Concomitant therapy:** No further details	**Knee osteoarthritis** Age range: 23 to 75 years N = 37 Definition: People with signs and symptoms of osteoarthritis of the knee Severity: Not stated/unclear Duration of symptoms: Not stated/unclear Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months Serious adverse event 1: gastrointestinal adverse events at ≤3 months	Study design classification: 6) No response criteria
Bookman 2004[30]	**Topical non-steroidal anti-inflammatory drugs** (n=84) Diclofenac gel 1.5% (wt/wt) In a carrier containing dimethylsulfoxide (45.5% wt/wt),	**Knee osteoarthritis** Mean age (SD): 61.8 (11.5) years N = 248	Pain at ≤3 months Physical function at ≤3 months Serious adverse events 3: hepatorenal adverse events at ≤3 months	Study design classification: 2) Excluding non-responders

Study	Intervention and comparison	Population	Outcomes	Comments
	propylene glycol, glycerine, ethanol and water for 4 weeks **Placebo** (n=164) **Concomitant therapy:** The use of acetylsalicylic acid (no more than 325mg/day) was permitted for cardiovascular prophylaxis.	Definition: Primary osteoarthritis verified radiologically Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear		
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 **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	**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
	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]	**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. **Placebo** (n=48) A third arm (n=48) was included in the study but not extracted in this review as it did not fulfil the inclusion criteria. **Concomitant therapy:** All people were given celecoxib 200mg capsules daily in addition to the topical gels	**Knee osteoarthritis** Age range: 45 to 75 years N = 145 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. Severity: Not stated/unclear Duration of symptoms: Not stated/unclear Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months	Study design classification: 6) No response criteria
Grace 1999[94]	**Topical non-steroidal anti-inflammatory drugs** (n=38) Diclofenac gel 2.5 grams for 2 weeks **Placebo** (n=36) **Concomitant therapy:**	**Knee osteoarthritis** Mean age (SD): 62.0 (13.0) years N = 74 Definition: Symptomatic and radiologic osteoarthritis	Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1B: gastrointestinal (non-bleeding and perforation) adverse events at ≤3 months	Study design classification: 1) Including only responders

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]	**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 **Placebo** (n=199) **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	**Knee osteoarthritis** Mean age (SD): 61.7 (9.3) years N = 866 Definition: Clinical and radiographic osteoarthritis Severity: Kellgren Lawrence grade 2-3 Duration of symptoms: At least 6 months Presence of multimorbidities: Not stated/unclear	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	Study design classification: 1) Including only responders
Niethard 2005[146]	**Topical non-steroidal anti-inflammatory drugs** (n=117) Diclofenac diethylamine gel 1.16% 4 grams applied four times a day for 3 weeks **Placebo** (n=121) **Concomitant therapy:** People were permitted to use up to 4 tablets of rescue medication	**Knee osteoarthritis** Mean age (SD): 66 (9) years N = 238 Definition: Clinically diagnosed osteoarthritis with radiographic evidence Severity: Not stated Duration of symptoms: At least 6 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	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]	**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 **Placebo** (n=162) **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	**Knee osteoarthritis** Mean age (SD): 64.2 (10.6) years N = 326 Definition: Symptomatic and radiological evidence of osteoarthritis Severity: Total radiographic score (0-27) (mean [SD]): 6.8 (3.7) Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	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	Study design classification: 1) Including only responders
Rother 2007[168]	**Oral non-steroidal anti-inflammatory drugs** (n=132) Celecoxib 100mg twice a day for 6 weeks **Topical non-steroidal anti-inflammatory drugs** (n=138) 110mg epicutaneous ketoprofen in 4.8 grams Transfersome twice a day for 6 weeks	**Knee osteoarthritis** Mean age (SD): 62.8 (9.8) years N = 397 Definition: Fulfilling clinical criteria for osteoarthritis Severity: Not stated	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	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo (n=127) **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	Duration of symptoms: At least 6 months Presence of multimorbidities: Not stated/unclear		
Rother 2013[167]	**Topical non-steroidal anti-inflammatory drugs** (n=274) Ketoprofen gel, 100mg in 4.4g transfersome gel (IDEA-033) applied twice daily for 12 weeks **Placebo** (n=281) **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	**Knee osteoarthritis** Mean age (SD): 62.2 (10.4) years N = 555 Definition: Clinical osteoarthritis Severity: Functional class 1-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	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
Rovensky 2001[169]	**Topical non-steroidal anti-inflammatory drugs** (n=50)	**Knee osteoarthritis** Mean age (SD): 63.4 (8.3) years	Pain at ≤3 months	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	5% ibuprofen cream applied 3 times daily for 1 week **Placebo** (n=50) **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	N = 100 Definition: Primary osteoarthritis defined clinically and radiographically Severity: Kellgren Lawrence grade 2-3 Duration of symptoms: At least 1 month Presence of multimorbidities: Not stated/unclear	Serious adverse events 3: hepatorenal adverse events at ≤3 months	
Simon 2009[190] Subsidiary paper: Roth 2011[165]	**Oral non-steroidal anti-inflammatory drugs** (n=151) Diclofenac slow release 100mg once a day for 12 weeks **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 **Placebo** (n=318) A fourth group (n=152) was reported which was not included in the analysis as it was excluded in the protocol	**Knee osteoarthritis** Mean age (SD): 61.6 (9.9) years N = 775 Definition: Primary osteoarthritis based on standard radiological criteria and pain Severity (mean radiographic score [SD]): 16.5 (3.1) Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months Serious adverse events 1A: gastrointestinal (bleeding and perforation) adverse events at ≤3 months	Study design classification: 1) Including only responders

Study	Intervention and comparison	Population	Outcomes	Comments
	(combination topical and oral NSAID). **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.			
Trnavsky 2004[202]	**Topical non-steroidal anti-inflammatory drugs** (n=25) Ibuprofen cream 5%, 1cm cream three times daily for 8 days **Placebo** (n=25) **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	**Knee osteoarthritis** Mean age (SD): 67.0 (7.1) years N = 50 Definition: Radiographical and clinical osteoarthritis Severity: Not stated Duration of symptoms: 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 3: hepatorenal adverse events at ≤3 months Serious adverse events 4: central nervous system adverse events at ≤3 months	Study design classification: 4) Unclear

Study	Intervention and comparison	Population	Outcomes	Comments
	rescue medication up to 2 days before the start of the study treatment			
Wadsworth 2016[212]	**Topical non-steroidal anti-inflammatory drugs** (n=130) Diclofenac 1.5% gel, 2mL applied twice a day for 4 weeks **Placebo** (n=129) **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	**Knee osteoarthritis** Mean age (SD): 61.1 (9.2) years N = 259 Definition: Radiographically confirmed primary osteoarthritis Severity: Kellgren Lawrence grade 2-3 Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Physical function at ≤3 months	Study design classification: 1) Including only responders NCT01119898

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

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

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

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	

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

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]	**Topical non-steroidal anti-inflammatory drugs** (n= 22) 5% w/w ibuprofen gel. Applied four times daily to the painful knee(s). **Capsaicin**(n=22) 0.025% w/w capsaicin cream applied four times daily to the painful knee(s). **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	**Knee osteoarthritis** Mean age (SD): 67.0 (9.3) years N = 22 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. Severity: Total NLDA score (median [IQR]) = 13 (9 to 18) Duration of symptoms (mean [SD]): 7.6 (7.6) years	Pain at ≤3 months	Study design classification: 5) All treatment naïve Crossover study (washout: 4 weeks)

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		

1.1.5.3 Topical (systemic) (including comparisons to oral formulations)

1.1.5.3.1 Transdermal opioids compared to oral strong opioids

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]	**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 **Oral strong opioids** (n=66) Tramadol twice daily, the possible doses were 150, 200, 300 and 400mg/day for 12 weeks **Concomitant therapy:** Paracetamol could be used for rescue medication	**Mixed osteoarthritis (knee and/or hip)** Mean age (SD): 64.3 (10.3) years N = 135 Definition: Clinical diagnosis based on the American College of Rheumatology and radiographic criteria Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	Pain at ≤3 months Serious adverse events 2: cardiovascular adverse events at ≤3 months	Study design classification: 3) Selection of specific population

1.1.5.3.2 Transdermal opioids compared to placebo

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]	**Transdermal opioids** (n=100) Buprenorphine patch, initial dose 5 microgram/hour **Placebo** (n=99) **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	**Mixed osteoarthritis (knee and/or hip)** Mean age (SD): 62.9 (9.5) years N = 199 Definition: Clinical and radiographic osteoarthritis Severity: Kellgren Lawrence grade 2-4 Duration of symptoms: At least 1 year Presence of multimorbidities: Not stated/unclear	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	Study design classification: 3) Selection of specific population
Langford 2006[120]	**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 **Placebo** (n=200) **Concomitant therapy:** People were asked to continue to receive stable doses of antiinflammatory agents (steroids or NSAIDs, including	**Mixed osteoarthritis (knee or hip)** Mean age (range): 66 (40-90) years N = 416 Definition: Clinical and radiographic osteoarthritis Severity: Not stated Duration of symptoms: At least 3 months Presence of multimorbidities: Not stated/unclear	Quality of life at ≤3 months Pain at ≤3 months Physical function at ≤3 months	Study design classification: 2) Excluding non-responders

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]	**Transdermal opioids** (n=152) Buprenorphine transdermal system 5 microgram/hour uptitrated to 10-20 microgram/hour as needed for 4 weeks **Placebo** (n=163) **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	**Mixed osteoarthritis (knee or hip)** Mean age (SD): 61.0 (12.7) years N = 315 Definition: Radiological evidence of osteoarthritis Severity: Not stated Duration of symptoms: Not stated Presence of multimorbidities: Not stated/unclear	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			

See evidence review I2 for full evidence tables.

1.1.5.4 Summary matrices

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

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

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

Table 29: Summary matrix for pharmacological agents compared to other pharmacological agents for quality of life, pain, physical function, psychological distress and osteoarthritis flares

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

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-eplieptic 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

1.1.6 Summary of the effectiveness evidence

1.1.6.1 Oral

1.1.6.1.1 Paracetamol compared to placebo

Table 31: Clinical evidence summary: paracetamol 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 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	№ 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.
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	№ 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)

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

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

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	№ 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	№ 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	№ 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

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

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	№ 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						

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	№ 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	№ 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

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

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

1.1.6.1.7 Weak opioids compared to placebo

Table 37: Clinical evidence summary: weak 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 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

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

Table 38: Clinical evidence summary: strong opioids 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 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	№ 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

1.1.6.1.9 Strong opioids compared to placebo

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	№ 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	№ 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

1.1.6.1.10 Anti-epileptic 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 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	№ 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

1.1.6.1.10 Anti-epileptic drugs compared to antidepressant drugs

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

Outcomes	№ 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	№ 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	№ 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	

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

1.1.6.1.11 Anti-epileptic drugs compared to placebo

Table 41: Clinical evidence summary: anti-epileptic 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 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	№ 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

1.1.6.1.12 Antidepressant 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 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	№ 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					

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

1.1.6.1.12 Antidepressant drugs compared to placebo

Table 42: Clinical evidence summary: antidepressants 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 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	№ 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	№ 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	№ 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

1.1.6.1.13 Glucosamine compared to paracetamol

Table 43: Clinical evidence summary: glucosamine 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 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

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

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	№ 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)

1.1.6.1.15 Glucosamine compared to placebo

Table 45: Clinical evidence summary: glucosamine 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 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	№ 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.
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	№ 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

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

1.1.6.2.1 Capsaicin compared to placebo for people with knee osteoarthritis

Table 46: Clinical evidence summary: capsaicin compared to placebo in knee 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 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	№ 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.

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 to 2 increments for imprecision due to zero events and small sample size
d. Absolute effect calculated by risk difference due to zero events in at least one arm of one study

1.1.6.2.2 Capsaicin compared to placebo for people with hand osteoarthritis

Table 47: Clinical evidence summary: capsaicin 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 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)

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

1.1.6.2.3 Topical non-steroidal anti-inflammatory drugs compared to oral non-steroidal anti-inflammatory drugs for people with knee osteoarthirtis

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

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 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	№ 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	№ 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)						

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

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

Outcomes	№ 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						

1.1.6.2.4 Topical non-steroidal anti-inflammatory drugs compared to placebo for people with knee osteoarthirtis

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

1.1.6.2.5 Topical non-steroidal anti-inflammatory drugs compared to placebo for people with hand osteoarthirtis

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

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

1.1.6.3.1 Transdermal strong opioids compared to oral strong opioids

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

Outcomes	№ 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

1.1.6.3.2 Transdermal strong opioids compared to placebo

Table 53: Clinical evidence summary: transdermal 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 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	№ 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	№ 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.

[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

See evidence review I2 for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

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

- 1 comparing NSAIDs to NSAIDs with gastroprotection [47];
- 1 comparing paracetamol, NSAIDs, NSAIDs with gastroprotection and no treatment[121];
- 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 NSAIDs[42];
- 2 comparing glucosamine with no treatment[26, 36] and
- 1 comparing glucosamine with no treatment and paracetamol[184].

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

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

1.1.7.2 Excluded studies

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

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

1.1.8 Summary of included economic evidence

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]	Probabilistic model based on meta-analysis of RCTs Cost-utility analysis (QALYs) Population: People with arthritis (majority osteoarthritis) Comparators: NSAIDs (ibuprofen, diclofenac, low and high dose celecoxib, branded and generic etodolac, etoricoxib, lumiracoxib, low and high dose meloxicam, rofecoxib, valdecoxib) NSAIDs with gastroprotection (ibuprofen + PPI, diclofenac + PPI) Time horizon: 5 years	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)	Multiple deterministic sensitivity analyses were undertaken in which low dose meloxicam remains the most cost-effective option. 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.
Latimer 2009[121] UK	Directly applicable [c]	Potentially serious limitations[d]	Probabilistic model based on meta-analysis of RCTs Cost-utility analysis (QALYs) Population: People with symptomatic osteoarthritis Comparators: No treatment Paracetamol	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).	Celecoxib plus gastroprotection remains most cost effective option for a number of sensitivity analyses. Etoricoxib plus gastroprotection becomes the most cost effective option when

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			NSAIDs (diclofenac, naproxen, ibuprofen, etoricoxib, celecoxib) NSAIDs with gastroprotection (diclofenac + PPI, naproxen + PPI, ibuprofen + PPI, etoricoxib + PPI, celecoxib + PPI) Time horizon: Lifetime			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]	Probabilistic model based on meta-analysis of RCTs Cost-utility analysis (QALYs) Population: People with osteoarthritis Comparators: No treatment Paracetamol NSAIDs (diclofenac, naproxen, ibuprofen, etoricoxib, celecoxib) NSAIDs with gastroprotection (diclofenac + PPI, naproxen + PPI, ibuprofen + PPI, etoricoxib + PPI, celecoxib + PPI) Fixed-dose NSAID with gastroprotection	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).	Etericoxib + 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. However the results of probabilistic analysis highlighted the overall uncertainty about which drug is the most

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.

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)]	• Within-RCT analysis (Underwood 2008[208]) • 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: 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.

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

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

(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 longer time horizon may be preferable given that glucosamine seems to become less cost effective over time.

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

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)]	• Probabilistic model based on progression to total knee replacement. • Cost-utility analysis (QALYs) • Population: People with knee osteoarthritis • Comparators: 1.Usual care 2.Glucosamine sulphate plus usual care • Lifetime horizon	£2,405[(c)]	0.11	£21,335 per QALY gained	Probability glucosamine sulphate in addition to usual care cost effective (£20/£30K threshold): 43% Results robust to one-way sensitivity analyses on key parameters.
Bruyere 2019[36] Belgium	Partially applicable [(d)]	Potentially serious limitations[(e)]	• Individual patient data simulation • Cost-utility analysis (QALYs) • Population: People with osteoarthritis • Comparators: 1. No treatment (placebo) 2. Prescription crystalline glucosamine sulphate 3. Other forms of glucosamine • Time horizon: 3, 6 & 36 months	3 months: [(f)] 2 – 1: £124 3 – 1: £44 6 months: 2 – 1: £247 3 – 1: £88 36 months: 2 – 1: £1,484	3 months: 2 – 1: 0.026 3 – 1: 0.001 6 months: 2 – 1: 0.058 3 – 1: -0.003 36 months: 2 – 1: 0.145	3 months: 2 – 1: £4,730 per QALY gained 3 – 1: £43,990 per QALY gained 6 months: 2 – 1: £4,252 per QALY gained 3 – 1: Int 1 dominates 3 36 months: 2 – 1: £10,203 per QALY gained	Probability interventions cost effective (£20/£30K threshold): NR 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.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental QALYs	Cost effectiveness	Uncertainty
Scholtissen 2010 [184] Spain	Partially applicable (g)	Potentially serious limitations(h)	• Deterministic decision analytic model • Cost-utility analysis (QALYs) • Population: People with symptomatic osteoarthritis • Comparators: 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%

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

(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 directly from EQ-5D questionnaire in line with NICE reference case, but from mapping from WOMAC to HUI3.

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

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

(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 mapping from WOMAC.

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

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

(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 from EQ-5D in line with NICE reference case.

(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 uncertainty undertaken.

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

1.1.9 Economic model

1.1.9.1 Population and strategies evaluated

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

1. No treatment: patients do not have drug treatment for their osteoarthritis.
2. Paracetamol
3. Oral NSAIDs plus PPIs
4. Oral NSAIDs alone
5. Topical NSAIDs
6. Oral strong opioids
7. Transdermal buprenorphine.

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

1.1.9.2 Methods and data sources (Summary)

Baseline adverse event probabilities

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

Treatment effects - adverse events

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

Mortality

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

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

Treatment effects – utilities

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

1.1.9.3 Resource use and costs

- The cost of the different drug treatments were obtained from the Drug Tariff[71], with doses based on Average Daily Quantities (ADQs) for the relevant indication taken from the online BNF.[63] A weighted average of drug class costs was used based on prescription usages data between 2020/21 released by the NHS.[72]
- It was assumed that all people with osteoarthritis attended annual follow-ups with their GP. Patients receiving NSAIDs or opioids were also assumed to attend an additional appointment with their GP during the year, with patients receiving NSAIDs also having an annual biochemistry test.
- The costs of hospital resources (e.g., endoscopy) were taken from the NHS Reference Costs 2019/20.[73] Staff costs were taken from the PSSRU unit costs 2020.[27]
- Resource use associated with gastrointestinal (GI) bleeds, dyspepsia and symptomatic ulcer were based on a decision tree, following assumptions made in the 2006 HTA paper on gastroprotection (Brown 2006).{Brown, 2006 #4185} Costs of each branch in the decision tree were calculated using HRG codes from the NHS reference costs 2019/20.{NHS England and NHS Improvement, 2020 #4188}
- For the remaining non-bleeding GI adverse events (constipation, nausea, vomiting and vertigo), a single GP consultation along with a prescription for 14 days treatment was assumed.
- For cardiovascular (CV) adverse events, costs for stroke were taken from Xu 2016[60], costs for transient iscahemic attack (TIA), unstable angina (UA) and heart failure (HF) were taken from Danese 2016{Danese, 2016 #4169}, while the cost of treating stable angina (SA) was taken from NHS Reference costs 2019/20.[74] All costs were inflated to 2019/20 costs.
- The cost of treating acute kidney injury was taken from NHS Reference Costs 2019/20.[74] The cost of treating chronic kidney disease were also based on NHs Reference costs and further calculations were based on assumptions made in the NICE acute kidney injury guideline [CG169,NG148]{National Institute for, 2013 #4289}{National Institute for, 2019 #4291}
- The cost of acute liver failure (ALF) and liver transplant were taken from the NHS Reference costs 2019/20.[74]
- For vertigo, a single GP consultation along with a prescription for 14 days treatment was assumed.

1.1.9.4 Computations

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

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

1.1.9.5 Results

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

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

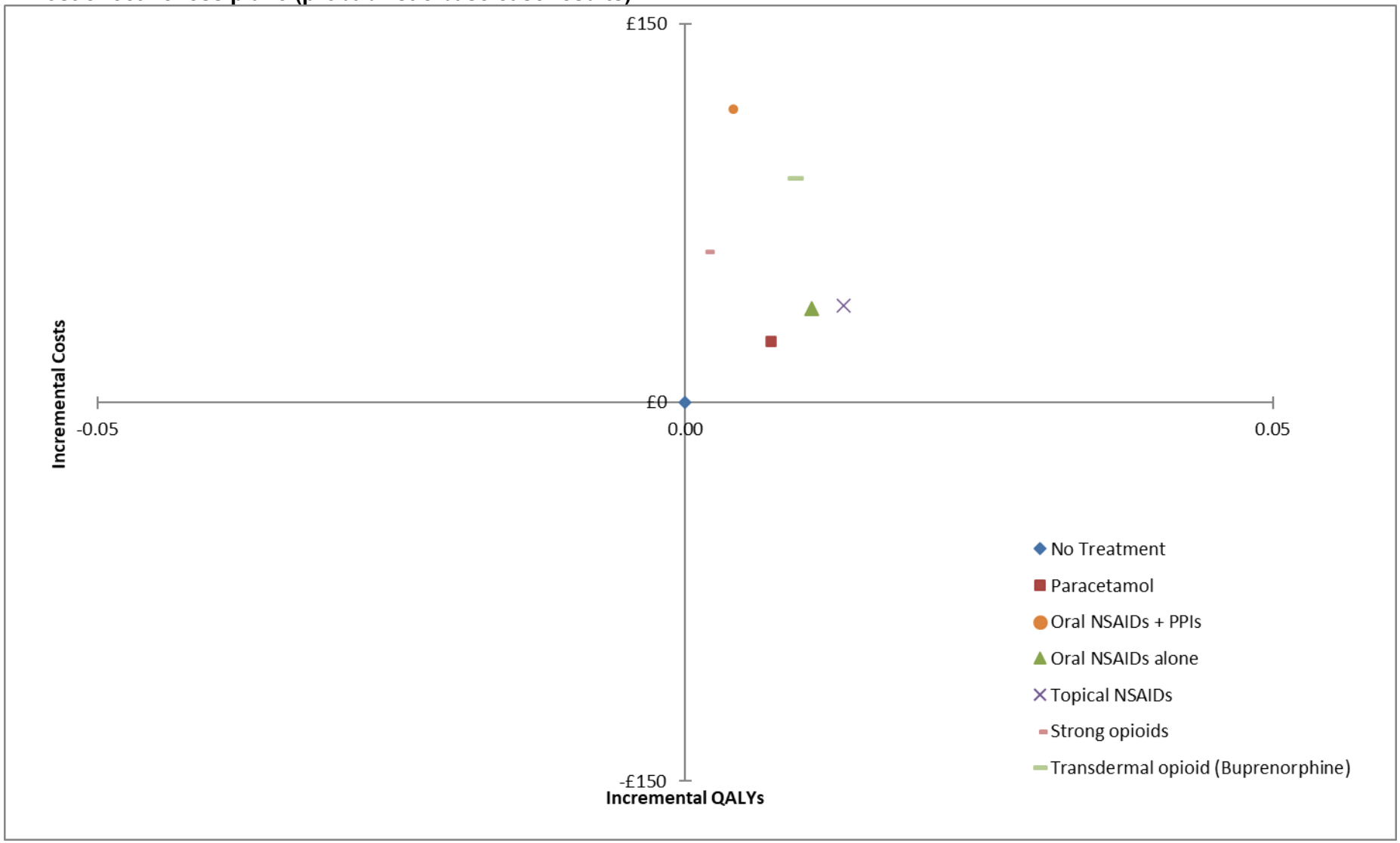

Table 58. Rank of net health benefit (£20,000 per QALY gained) (probabilistic sensitivity analyses)

Analysis	Costs						
	No treatment	Paracetamol	Oral NSAIDs + PPIs	Oral NSAIDs alone	Topical NSAIDs	Oral strong opioids	Buprenorphine
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

1.1.11 Economic evidence statements

In a comparison of paracetamol and no treatment

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

In a comparison of oral NSAIDs alone and no treatment

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

In a comparison of oral NSAIDs plus PPIs and no treatment

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

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

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

- One original cost utility analysis from this guideline review reported that oral NSAIDs plus PPIs were dominated by oral NSAIDs alone. This analysis was assessed as directly applicable with minor limitations.

In a comparison of topical NSAIDs and no treatment

- One original cost utility analysis reported that topical NSAIDs were cost effective compared with no treatment (£2,847). This analysis was assessed as directly applicable with minor limitations.

In a comparison of oral NSAIDs and topical NSAIDs

- One cost utility analysis reported that oral ibuprofen was cost effective compared with topical ibuprofen (£9,114). This analysis was assessed as partially applicable with potentially serious limitations.{Castelnuovo, 2008 #150}
- One original cost utility analysis from this guideline review reported that oral NSAIDs with and without PPIs were dominated by topical NSAIDs. This analysis was assessed as directly applicable with minor limitations.

In a comparison of oral strong opioids and no treatment

- One original cost utility analysis from this guideline review reported that oral strong opioids were not cost effective compared with no treatment (£32,916). This analysis was assessed as directly applicable with minor limitations.

In a comparison of transdermal buprenorphine and no treatment

- One original cost utility analysis from this guideline review reported that the transdermal opioid buprenorphine was cost effective compared with no treatment (£9,454). This analysis was assessed as directly applicable with minor limitations.

In a comparison of glucosamine with no treatment or paracetamol

- One cost utility analysis reported that glucosamine was not cost effective compared with no treatment (£21,335). This analysis was assessed as directly applicable with minor limitations.{Black, 2009 #155}
- One cost utility reported thar prescription crystalline glucosamine sulphate was cost effective compared to no treatment (£10,203), but that other forms of glucosamine were dominated by no treatment. This analysis was assessed as partially applicable with potentially serious limitations.{Bruyere, 2019 #253}
- One cost utility analysis reported that glucosamine was cost effective compared with no treatment (£3,488). It also reported that that glucosamine dominated paracetamol. This analysis was assessed as partially applicable with potentially serious limitations.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

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

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

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

1.1.12.2 The quality of the evidence

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

- Comparisons to placebo
  - Oral medicines
    - Paracetamol
    - Non-steroidal anti-inflammatory drugs
    - Non-steroidal anti-inflammatory drugs with gastroprotection
    - Weak opioids
    - Strong opioids
    - Anti-epileptic drugs
    - Antidepressant drugs
    - Glucosamine
  - Topical (local) medicines
    - Capsaicin for knee osteoarthritis
    - Non-steroidal anti-inflammatory drugs for knee osteoarthritis
    - Non-steroidal anti-inflammatory drugs for hand osteoarthritis
  - Topical (systemic) medicines
    - Transdermal opioids
- Interventions compared to other interventions
  - Oral medicines
    - Non-steroidal anti-inflammatory drugs compared to paracetamol
    - Non-steroidal anti-inflammatory drugs with gastroprotection compared to paracetamol
    - Non-steroidal anti-inflammatory drugs with gastroprotection compared to non-steroidal anti-inflammatory drugs
    - Strong opioids compared to non-steroidal anti-inflammatory drugs
    - Anti-epileptic drugs compared to antidepressant drugs
    - Glucosamine compared to paracetamol
    - Glucosamine compared to non-steroidal anti-inflammatory drugs

- Topical (local) medicines (including comparisons to oral medicines)
  - Topical non-steroidal anti-inflammatory drugs compared to oral non-steroidal anti-inflammatory drugs for knee osteoarthritis
- Topical (systemic) medicines (including comparisons to oral medicines)
  - Transdermal opioids compared to oral strong opioids

There were no relevant clinical studies comparing the following interventions:

- Rubefacients
- Local anaesthetic

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

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

Paracetamol

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

- When compared to placebo, evidence was generally of low quality, but ranged from moderate to very low quality. Where downgrading occurred, this was often for risk of bias (in particular selection and attrition bias) and imprecision.
- When compared to oral non-steroidal anti-inflammatory drugs (without gastroprotection), evidence was generally of very low quality, but ranged from moderate to very low. Where downgrading occurred, this was often for risk of bias (in particular selection and attrition bias) and imprecision.
- When compared to oral non-steroidal anti-inflammatory drugs with gastroprotection, evidence was generally of very low quality, but ranged from low to very low quality. When downgrading occurred, this was often for risk of bias (in particular selection and attrition bias) and imprecision.
- When compared to glucosamine, evidence was generally of low quality, but ranged from low to very low. Where downgrading occurred, this was mainly due to risk of bias (in particular selection and attrition bias).

Oral non-steroidal anti-inflammatory drugs

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

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

- When compared to paracetamol, evidence was generally of very low quality, but ranged from moderate to very low. Where downgrading occurred, this was often for risk of bias (in particular selection and attrition bias) and imprecision.
- When compared to oral non-steroidal anti-inflammatory drugs with gastroprotection, evidence was generally of low quality, but ranged from moderate to very low quality. Where downgrading occurred, this was for risk of bias (in particular selection and attrition bias), imprecision or indirectness (namely population indirectness where 10-20% of the population of one study had rheumatoid arthritis).
- When compared to strong opioids, evidence was generally of very low quality, but ranged from low to very low quality. Where downgrading occurred, this was often for risk of bias (in particular selection and attrition bias) or imprecision.
- When compared to glucosamine, evidence was generally of very low quality, but ranged from low to very low quality. Where downgrading occurred, this was often for risk of bias (in particular selection and attrition bias) or inconsistency (where subgroup analysis did not resolve the heterogeneity).
- When compared to topical non-steroidal anti-inflammatory drugs, evidence was generally of low quality, but ranged from moderate to very low quality. Where downgrading occurred, this was often for risk of bias and imprecision. Some outcomes were downgraded for inconsistency (where subgroup analysis did not resolve the heterogeneity).

Oral non-steroidal anti-inflammatory drugs with gastroprotection

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

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

Opioids: Strong opioids, weak opioids and transdermal opioids

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

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

- When compared to transdermal opioids, evidence was of low to very low quality. Outcomes were downgraded for risk of bias (in particular attrition bias) and imprecision.

Whereas only one study comparing weak opioids to placebo was included. The quality of evidence was very low. Downgrading occurred due to risk of bias and imprecision.

Finally, studies compared transdermal opioids (which included buprenorphine and fentanyl) to placebo and oral strong opioids were included.

- When compared to placebo, evidence was of low to very low quality. Outcomes were downgraded for risk of bias (in particular selection and attrition bias) and imprecision.
- When compared to oral strong opioids, evidence was of low to very low quality. Outcomes were downgraded for risk of bias (in particular attrition bias) and imprecision.

Anti-epileptic drugs

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

Antidepressant drugs

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

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

Glucosamine

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

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

Topical capsaicin

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

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

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

Topical non-steroidal anti-inflammatory drugs

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

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

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

1.1.12.3 Benefits and harms

Key uncertainties

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

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

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

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

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

Paracetamol

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

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

The committee noted the effect size for pain reduction with paracetamol when compared to placebo was particularly small compared to the other interventions (0.05 standard deviations lower, from 0.11 lower to 0.02 higher) and agreed that paracetamol was unlikely to have any noticeable benefit for the majority of people with osteoarthritis. Taking into account the potential hepatic adverse events that can come from longer term paracetamol use, and the lack of clinical efficacy the committee agreed that paracetamol is unlikely to be beneficial lto people with osteoarthritis. However, taking into account that some people cannot use NSAIDS they recommended that paracetamol should not be routinely used for people with osteoarthritis unless it is for short-term pain relief and if all other pharmacological treatments are contraindicated, not tolerated or ineffective. The committee agreed that the amount of evidence was sufficient and therefore a research recommendation was not required.

Oral non-steroidal anti-inflammatory drugs

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

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

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

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

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

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

Oral non-steroidal anti-inflammatory drugs with gastroprotection

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

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

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

helpful to most people. Although recent thinking suggests that gastroprotection may not be required for all people with osteoarthritis the committee were aware that this guideline did not contain a safety review of non-randomised evidence. Therefore, the committee agreed a recommendation agreeing that gastroprotection should be offered to all people taking non-steroidal anti-inflammatory drugs.

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

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

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

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

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

Studies comparing transdermal opioids to placebo and oral strong opioids were included in the analysis. The studies included a population with mixed joint site (knee or hip) osteoarthritis. The committee agreed that the doses used were representative of clinical practice, except for Langford 2006[120], where the dose was significantly larger than what would be used. In this case, the population were not opioid naïve. However, in current practice clinicians would be more likely to stop the opioid medication, as the pain is deemed to be opioid non-respondent, rather than to further titrate the dose up.

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

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

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

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

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

Anti-epileptic drugs

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

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

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

Antidepressant drugs

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

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

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

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

Glucosamine

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

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

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

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

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

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

Topical capsaicin

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

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

Topical non-steroidal anti-inflammatory drugs

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

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

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

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

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

Other topical treatments: Rubefacients and local anaesthetics

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

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

1.1.12.4 Cost effectiveness and resource use

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

- paracetamol,
- oral or topical non-steroidal anti-inflammatory drugs (with and without gastroprotection),
- oral opioids and
- glucosamine.

An original cost-utility analysis was developed to compare:

- paracetamol
- oral or topical non-steroidal anti-inflammatory drugs (with and without gastroprotection),
- oral or topical opioids.

Paracetamol

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

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

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

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

Oral non-steroidal anti-inflammatory drugs

Oral NSAIDs versus no treatment

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

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

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

Oral non-steroidal anti-inflammatory drugs with gastroprotection

Oral NSAIDs with PPI versus no treatment

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

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

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

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

Oral NSAIDs with PPI versus oral NSAIDs alone

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

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

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

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

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

Oral versus topical NSAIDs

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

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

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

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

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

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

Topical non-steroidal anti-inflammatory drugs

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

Glucosamine

Glucosamine versus no treatment

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

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

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

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

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

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

Glucosamine versus paracetamol

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

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

Other drugs

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

Key uncertainties

The main limitations of the new guideline model were:

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

1.1.12.5 Other factors the committee took into account

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

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

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

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

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.4.1 to 1.4.8. Other evidence supporting these recommendations can be found in evidence review I.

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