WEB-APPENDIX

Comparative effectiveness of non-steroidal anti-inflammatory drugs and opioid therapy for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis

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Web-appendix 1. Protocol

Protocol for a systematic review and network meta-analysis: Comparative effectiveness of non-steroidal anti-inflammatory drugs and opioid therapy for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis

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Note: This protocol is based on our previous network meta-analysis and its protocol (da Costa et al., 2017).

Date: August 5th, 2021 (replaces the initial versions of October 9th and November 15th 2020)

Introduction

Osteoarthritis (OA) is a clinical syndrome that most commonly affects the knee, hip, and hand joints in the elderly population [1]. It is accompanied by increased pain symptoms, which result in reduced physical function and quality of life, thereby increasing the risk of all-cause mortality [2-3]. Based on the hierarchical treatment modalities for managing osteoarthritis, non-steroidal anti-inflammatory drugs (NSAIDs) followed by opioids are the first line of pharmacotherapy, after nonpharmacologic therapy, such as exercise and weight loss [4]. While considerable uncertainty remains regarding the benefits and risks of opioid therapy to treat pain and function in the knee or hip OA patients [5], prescribed opioid use for musculoskeletal pain has increased by 70% between 2001 and 2010 in the US [6]. Therefore, we will conduct a network meta-analysis to assess the efficacy and safety of different drugs and doses of NSAIDs and opioids, establish a more comprehensive panorama about the benefits and risks of those therapies to treat pain and function in patients with knee or hip OA.

Objectives

- To describe the effectiveness and safety of NSAIDs, opioids, and acetaminophen (paracetamol) for pain and function management of patients with knee or hip OA using large randomized trials.

- To provide a risk-benefit perspective of the different preparations and doses of NSAIDs, opioids, and acetaminophen (paracetamol) considering their effects on pain and function and their safety profiles as measured by the rate of adverse events and dropouts.

Criteria for considering trials for this review

Types of trials

We will include only randomized trials with, on average, at least 100 patients per arm. Any non-randomized study will not be eligible.

Types of participants (population)

Patients with knee or hip osteoarthritis will be the study population. More specifically, we will consider large randomized co), or placebo. Trials that included patients with other types of arthritis or joints other than knee or hip will be only included if at least 75% of the included patients were confirmed to have knee or hip osteoarthritis and data pertaining to that cohort are retrievable. In addition, trials must have at least one follow-up measurement of pain or another algo-functional outcome. To reduce small-study bias, trials must have randomly assigned, on average, at least 100 patients per group. We will include trials and/or reports published in English only. However, no restriction will be applied to publication status or year of publication as long as data are retrievable.

Type of interventions

We will include trials examining the effects of any non-steroidal anti-inflammatory drugs (NSAIDs), any opioids, and any preparation of acetaminophen (paracetamol) on knee/hip OA.

Control

We will use as comparator acetaminophen (paracetamol) or placebo.

Type of outcomes

Primary outcome

Our prespecified primary outcome will be pain. If a trial presented pain outcome on more than one scale, the following hierarchical list will be used to extract data from the scale higher on the list (1) global pain score; (2) pain on walking; (3) WOMAC osteoarthritis index pain subscore; (4) composite pain scores other than WOMAC; (5) pain on activities other than walking (such as stair climbing); (6) WOMAC global score; (7) Lequesne osteoarthritis index global score; (8) other algo-functional composite scores; (9) patient's global assessment; (10) physician's global assessment. Data will be extracted for the following time points whenever available: 1 week (± 2 days), 2 weeks (± 2 days), 4 weeks (± 3 to 4.5 weeks), 6 weeks (± 1 week), 12 weeks (± 4 weeks), 24 weeks (± 4 weeks), 48 weeks (± 4 weeks), or at the end of treatment if not covered by the prespecified time points.

Secondary outcomes: Efficacy

Our secondary prespecified outcome will be physical function. If a trial presented function outcome on more than one scale, the following hierarchical list will be used to extract data from the scale higher on the list (1) global function score; (2) walking disability; (3) WOMAC osteoarthritis index physical function subscore; (4) composite physical function scores other than WOMAC; (5) physical function on activities other than walking (such as stair climbing); (6) WOMAC global score; (7) Lequesne osteoarthritis index global score; (8) other algo-functional composite scores; (9) patient's global assessment; (10) physician's global assessment. We will extract data on this outcome for the same time points as those mentioned for pain.

Secondary outcomes: Safety

We will also evaluate safety outcomes: lack of efficacy, any dropouts, any adverse events, serious adverse events, dropouts due to adverse events, and all-cause mortality. Adverse events will be captured as a binary outcome.

Search Strategy

We will use a simple search strategy with high sensitivity. The search will be conducted via the Cochrane Central Register of Controlled Trials (CENTRAL) (inception to date of final search update):

Step
1 (osteoarthriti* OR osteoarthro* OR gonarthriti* OR gonarthro* OR coxarthriti* OR coxarthro* OR arthros* OR arthrot*):ti,ab,kw
2 MeSH descriptor **Osteoarthritis** explode all trees
3 (#1 OR #2) in Trials

Searching other resources

We will screen reference lists of all obtained articles, including relevant reviews. Finally, we will search for clinical trial registries through clinicaltrials.gov

Data collection and analysis

Selection of trials

Two review authors will independently evaluate all identified potentially eligible titles and abstracts for eligibility. Disagreements will be resolved by consensus or discussion with a third investigator. If multiple reports describe the same trial, we will consider the most comprehensive information. In case of discrepancies, information submitted to regulatory authorities will precede peer-reviewed information and non-peer-reviewed information. More up-to-date information will take precedence over older information.

We will screen trials for eligibility, data availability, and all steps based on a consensus reached via a standardized and piloted web-based data management platform.

Data extraction and management

We will extract trial characteristics, such as study design, sample size, and follow-up duration; intervention characteristics, such as dose and treatment duration; participant characteristics, such as mean age, sex, mean duration of symptoms, index joint; type of outcome (pain or function); and outcome data for each time point of interest. We will extract data before the crossover timepoint to eliminate any possible carryover effects in crossover trials. Whenever necessary, we will approximate the means and measures of dispersions from graphs in the reports. Results based on the ITT analysis will be preferred whenever possible.

Assessment of risk of bias in included studies

Two review authors will independently assess randomization, blinding, and adequacy of analyses. Disagreements will be resolved by consensus. We will assess two components of randomization: generation of allocation sequences and concealment of allocation. We will consider the generation adequate if it resulted in unpredictable allocation sequences; mechanisms considered adequate include random-number tables, computer-generated random numbers, minimization, coin tossing, shuffling of cards, and drawing of lots. We will consider allocation concealment adequate if the investigators responsible for patient selection were unable to deduce before allocation which treatment was next; methods considered adequate included central randomization and sequentially numbered, sealed, opaque envelopes. We will consider the blinding of the patients adequate if the interventions were explicitly described as indistinguishable. We will consider analyses adequate if all randomized patients were included in the analysis according to the intention-to-treat principle.

Strategy for data synthesis

Measures of treatment effect

The effect measure will be the standardized mean difference (SMD) for continuous outcomes and the odds ratio (RR) for binary outcomes.

Data synthesis

We will use an extension of multivariable Bayesian random-effects models for mixed multiple treatment comparisons [7]. These models fully preserve the direct randomized comparisons within each trial and compare all available interventions across trials, and account for multiple comparisons in trials with more than two treatment groups. The model includes a random effect at the level of trials and uses a random walk to account for the correlation of longitudinal outcome data in trials reporting results for more than one time point, borrowing strength across timepoints for an estimate. The model assumes that, within a trial with longitudinal outcome data, the data recorded at a specified time point are more similar to the outcome data recorded at adjacent time points immediately before and after than at nonadjacent, more remote time points. We will use the following prior distributions for the heterogeneity parameters: a gamma distribution for between-trial heterogeneity ($1/\tau^2$ ~ gamma(0.1,0.1)I(0,2000)) and a uniform distribution for between-timepoint heterogeneity (τ ~ unif(0,5)). A half-normal distribution τ ~ normal(0,1)I(0,) will be used in a sensitivity analysis for the between-trial heterogeneity. We will assess the goodness of fit of the model to the data by calculating the number of means of standardized node-based residuals within 1.96 of the standard normal distribution; visually inspecting the distribution of residuals on Q–Q plots; calculating the heterogeneity of treatment effects estimated from the posterior median between trial variance τ^2, and calculating the consistency of the network (determined by the difference in effect sizes derived from direct and indirect comparisons). The posterior probability for the effect of the experimental intervention will be the minimum clinically important difference of –0.37 SD units, with high posterior probabilities favoring the active treatment. This threshold of 0.37 SD units is based on the median minimum clinically important between-group difference reported in studies in osteoarthritis patients. An effect size of 0.37 corresponds to a difference of 9 mm on a 100 mm visual analog scale. Analyses will be done with Stata (StataCorp, College Station, TX, USA) and OpenBUGS (MRC Biostatistics Unit Cambridge, UK).

Analysis of subgroups or subsets

We will adjust the results of the primary outcome for trial characteristics (e.g., concealment of allocation, therapist blinding, completeness of outcome data) by incorporating a regression coefficient in the model. We will estimate two-sided p values for interaction between treatment effects and trial characteristics from the posterior distribution. We will conduct separate analyses per timepoint to assess whether treatment effects varied over time.

Role of the funding source

The Arthritis Society (Canada, grant YIO-17-0164) will have no role in study design, data collection, data synthesis, data interpretation, writing the report, or the decision to submit the manuscript for publication. None of the authors is affiliated with or funded by any manufacturer of any of the agents evaluated in this study.

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Change history

As of August 5th, 2021, we have added minor modifications to the initial versions of the protocol. Specifically, we have changed the following items before or during the review process:

Modification/decision made before the review process started:

1. We will change the time point "4 weeks" from 4 weeks (± 1 week) to 4 weeks (from 3 weeks to 4.5 weeks) to avoid overlap with the next time point "6 weeks (± 1 week)".
2. We will evaluate the risk of bias regarding incomplete outcome data focusing on the use of imputation methods (deterministic or probabilistic) in the trials to take into account dropouts or missing data. This domain in the risk of bias will be assessed for pain and function separately.

Modification/decision made after the review process started:

3. We will not present results for all comparisons because of the excessively high number of preparations found (>3400 head-to-head comparisons). Results will be presented comparing each intervention to a common control group, which will be the oral placebo.
4. The following outcomes will not be analyzed: all-cause mortality (because of sparse data; not enough evidence for a network meta-analysis), any dropouts, and lack of efficacy. For the latter two outcomes, the decision of not analyzing the results was based on the large amount of information already collected for safety outcomes (any adverse events (AEs), serious AEs, and dropouts due to AEs).
5. We added a sensitivity analysis focused on time point 1 week and time point 12 weeks. These analyses were anticipated in the initial protocol, but the time points had not been defined.
6. We changed the metric for the binary outcomes. Specifically, we will analyze data using rate ratio. This modification was necessary since the follow-up time varied significantly across trials. Therefore, the follow-up period was taken into account in the final analyses.
7. We revoked protocol change #6 mentioned above and went back to the original plan of analyzing binary outcomes using the odds ratio. Difficulties in estimating rate ratios due to convergence problems with Poisson likelihood and log link led to a second change of the metric used to capture binary outcomes. Specifically, after technical discussion among the statisticians and methodologists of the project on February 8, 2021, we amended the systematic review protocol. We decided to use odds ratios instead of rate ratios to summarize binary outcomes.

8. After submission, reviewers and editors requested an additional search, including Medline and Embase. Therefore, non-prespecified searches were performed in Medline+Embase (via OVID), encompassing database inception to June 28th, 2021.

Web-appendix 2. Search Strategy

The Cochrane Central Register of Controlled Trials was searched through the Cochrane library from inception to 30th of June 2021.

Cochrane Central Register of Controlled Trials (CENTRAL)	
Step	**Search Strategy**
1	(osteoarthriti* OR osteoarthro* OR gonarthriti* OR gonarthro* OR coxarthriti* OR coxarthro* OR arthros* OR arthrot*):ti,ab,kw
2	MeSH descriptor **Osteoarthritis** explode all trees
3	(#1 OR #2) in Trials

The search on Medline and Embase databases was searched through OVID inception to 28th June 2021.

MEDLINE + EMBASE (via OVID)	
Step	**Search Strategy**
1	(osteoarthriti* or osteoarthro* or gonarthriti* or gonarthro* or coxarthriti* or coxarthro* or arthros* or arthrot*).mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tn, dm, mf, dv, kw, dq]
2	osteoarthritis.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, tn, dm, mf, dv, kw, dq]
3	(#1 OR #2) in Trials Limit 3 to randomized controlled trial Limit 4 to English language Limit 5 to (buccal or intraarticular or intradermal or intramuscular or intravenous or oral or subcutaneous or sublingual or topical or transdermal)

Limit #5 is not valid in Medline (e.g., only applicable to EMBASE).

Web-appendix 3. List of 61 systematic reviews screened for trials that satisfied the eligibility criteria of the current review

Author	Year	Network meta-analysis?	Joint*	Specific to OA?	Treatments#	Trials	Period	Databases
Avouac[1]	2007	No	Mixed	Yes	Opioids	22	Between 1966 and August 2006	Medline, Embase and CENTRAL
Bannuru[2]	2014	No	Knee	Yes	NSAIDS vs IA	5	Inception until February 2013	Medline, Embase, Google Scholar, ISI Web of Science, and CENTRAL
Bannuru[3]	2015	Yes	Knee	Yes	Mixed	137	Inception through August 2014	MEDLINE, EMBASE, Web of Science, Google Scholar, Cochrane Central Register of Controlled Trials
Bannuru[4]	2015	Yes	Knee	Yes	Mixed	149	Inception through 1 June 2015	Medline, Embase, Web of Science, Google Scholar, and CENTRAL and unpublished
Beaudart[5]	2020	Yes	Knee	Yes	Mixed	80	Inception to August 2019	Medline, Scopus, and Cochrane database of systematic reviews
Berenbaum[6]	2005	No	Knee and hip	Yes	NSAIDs	9	Not described	
Biswal[7]	2006	No	Knee	Yes	NSAIDs	4	1966 to December 2004	PubMed, Medline, Embase, and CENTRAL
Bjordal[8]	2007	Yes	Knee	Yes	Mixed	63	From 1966 through November 2005	Medline, Embase, PedRo and CENTRAL
Cepeda[9]	2007	No	Hip and/or knee	Yes	Opioids	11	Up to August 2005	CENTRAL, Medline, Embase, and Lilacs
Chen[10]	2007	No	Mixed	Yes	NSAIDs	55	1966 to June 2006	Medline, Embase and CENTRAL
da Costa[11]	2014	No	Knee or hip	Yes	Opioids	22	Up to 28 July 2008, with an update performed on 15 August 2012	CENTRAL, Medline, Embase and CINAHL
da Costa[12]	2017	Yes	Knee and hip	Yes	NSAIDs + Paracetamol	76	1980 to February 2015	Medline, Embase and CENTRAL
Datto[13]	2013	Yes	Mixed	No	NSAIDs	167	Inception to April 2009	Medline, Embase and CENTRAL
De Vecchis[14]	2014	No	Mixed	No	NSAIDs	58	Inception to March 2014	PubMed, Embase and clinicalstudyresults.org
DeRogatis[15]	2019	No	Knee	Yes	Mixed	43	January 1995 to December 2018	PubMed and EBSCO Host.
Derry[16]	2016	No	Mixed	No	NSAIDs	39	Inception to February 2016	Medline, Embase and CENTRAL
Essex[17]	2013	No	Mixed	No	NSAIDs	51	Inception to July 2011	Pfizer clinical trial repository

Freynhagen[18]	2021	No	Mixed	No	Opioids	48	Up to December 2017, with an update performed in April 2019	Medline, Embase, PubMed, Cochrane databases and trial registries
Fuggle[19]	2019	No	Mixed	Yes	Opioids	17	Inception to 30 June 2017	Medline, Ovid CENTRAL, and Scopus
Garner[20]	2005	No	Mixed	No	NSAIDs	26	Inception to August 2004	Medline, Embase, Cochrane Database of Systematic Reviews, CENTRAL, National Research Register, NHS Economic Evaluation Database, Health Technology Assessment Database.
Gregori[21]	2018	No	Knee	Yes	Mixed	47	Until June 30 2018	Medline, Scopus, Embase, Web of Science, and CENTRAL
Henriksen[22]	2016	No	Knee	Yes	Mixed	54	Carried out on 31 January 2014	The Cochrane Database of systematic reviews
Honvo[23]	2019	No	Mixed	No	NSAIDs	25	Inception to August 2017	Medline, CENTRAL, and Scopus electronic databases
Huang[24]	2021	No	Knee	Yes	NSAIDs	12	Inception to September 2019	PubMed, CENTRAL, Embase, the China Biology Medicine disc (CBM), the Chinese Scientific Journal Database (VIP), China National Knowledge Infrastructure (CNKI), and the Wanfang Database
Jevsevar[25]	2018	Yes	Knee	Yes	Mixed	53	Up to October 7, 2015	PubMed, Embase, and CENTRAL
Jung[26]	2018	Yes	Knee	Yes	NSAIDs + Opioids + Paracetamol	44	Inception to June 2016	Medline, Embase and CENTRAL
Kim[27]	2017	Yes	Mixed	No	NSAIDs	10	Inception to September 2017	Medline, Embase and CENTRAL
Kongtharvonskul[28]	2015	Yes	Knee	Yes	Mixed	31	Inception to 29 August 2014	Medline and Scopus
Lee[29]	2004	No	Mixed	Yes	NSAIDs + Paracetamol	7	1966 to February 2003 (Medline)/(1991 to first quarter 2003 (Embase)	Medline and Embase
Leopoldino[30]	2019	No	Knee and hip	Yes	Paracetamol	10	Inception to October 2017	CENTRAL, Medline, Embase, AMED, CINAHL, Web of Science, LILACS, and International Pharmaceutical
Lin[31]	2004	No	Mixed	Yes	NSAIDs	13	1966 to October 2003	Medline, Embase, Scientific Citation Index, CINAHL, Cochrane Library, and abstracts from conferences
Makris[32]	2010	No	Mixed	Yes	NSAIDs	16	1950 to November 2009	Scopus, Embase, Web of Science, Cochrane

								databases, Dissertation and American College of Rheumatology meeting Abstracts.
Matchaba[33]	2005	No	Mixed	No	NSAIDs	22	Not described	Novartis Lumiracoxib Clinical Trial Database
Miller[34]	2020	No	Knee	Yes	Mixed	6	Up to March 31, 2019	Medline, Embase, and CENTRAL
Myers[35]	2014	No	Mixed	Yes	Mixed	32	Between January 1985 and March 2013	PubMed, Embase, Medline, In-Process, Cochrane Library, and ClinicalTrials.gov
Osani[36]	2020	No	Knee	Yes	NSAIDs	72	Inception to May 2018	Medline, Embase, Web of Science, Google Scholar, and the Cochrane Database
Osani[37]	2020	No	Knee or hip	Yes	Opioids	18	Inception to December 2019	Medline, Embase, PubMed Central, and CENTRAL
Patel[38]	2017	No	Mixed	Yes	NSAIDs	9	Inception to April 2016	PubMed, Google Scholar, Cochrane systematic review database, clinicaltrial registry (clinicaltrials.Gov) and bibliographies of relevant articles.
Pavelka[39]	2012	No	Mixed	Yes	NSAIDs	37	1999 to September 2010	Medline and Embase
Phleps[40]	2001	No	Mixed	No	NSAIDs	7	Not described	Not described
Puljak[41]	2017	No	Mixed	Yes	NSAIDs	36	Inception to April 2017	CENTRAL, Medline, Embase and clinical trials registers
Richy[42]	2009	No	Mixed	No	NSAIDs	75	January 1980 to August 2006	Medline and Premedline, Biosis Preview, Healthstar, Embase, CENTRAL, Current Contents, EBM reviews
Schoenfeld[43]	1999	No	Mixed	No	NSAIDs	12	1990 to 1998	Medline
Smith[44]	2016	No	Knee	Yes	Mixed	17	Between 1982 and 2015	PubMed, Web of Science – Science Citation Index Expanded, Embase, and CENTRAL
Smith[45]	2016	No	Mixed	Yes	NSAIDs	57	Inception to February 2015	Medline, Embase, AMED, CINAHL and the Cochrane library
Stewart[46]	2018	No	Mixed	Yes	Mixed	29	From 2006 through to the end of 2016	Medline
Taylor[47]	2011	No	Mixed	No	NSAIDs	37	Inception to March 2010	Medline
Toupin April[48]	2019	No	Mixed	Yes	Opioids	22	Up to February 2018	CENTRAL, Medline, Embase, US National Institutes of Health and World Health Organization trial registries
Towheed[49]	1997	No	Knee	Yes	Mixed	80	1966 to August 1994	Medline
Towheed[50]	2006	No	Knee	Yes	NSAIDs	4	1966 to February 2005	Medline, Embase, CENTRAL, Cochrane Database of Systematic Reviews (CDSR), American College of Physicians (ACP) Journal Club, Database of Abstracts of Effectiveness (DARE).
Towheed[51]	2006	No	Mixed	Yes	Paracetamol	15	Up to July 2005	Medline, Embase and CENTRAL Cochrane

								Database of Systematic Reviews (CDSR), American College of Physicians (ACP) Journal Club, Database of Abstracts of Effectiveness (DARE)
Van Walsem[52]	2015	Yes	Mixed	No	NSAIDs	176	Inception to June 2013	Medline, Embase, and Cochrane Library
Welsch[53]	2020	No	Mixed	Yes	Opioids	22	October 2013 to July 2019	Clinicaltrials.gov, CENTRAL, Medline and PsycINFO
Wiffen[54]	2020	No	Mixed	No	NSAIDs	23	Inception to November 2018	Medline, Embase and CENTRAL
Wolff[55]	2021	No	Knee	Yes	NSAIDs	18	June 2018 (Medline and Embase)/September 2020 (CENTRAL)	Medline, Embase and CENTRAL
Zeng[56]	2021	Yes	Knee	Yes	NSAIDs + Paracetamol	122	Inception to March 2021	PubMed, Embase, Cochrane Library, and Web of Science
Zeng[57]	2018	Yes	Mixed	Yes	NSAIDs	36	1966 to January 2017	PubMed, Embase, Cochrane Library and Web of Science
Zhang[58]	2008	No	Mixed	Yes	Mixed	198	Unclear (inception to January-February 2007)	Medline, Embase, Scientific Citation Index, CINAHL and Cochrane Library.
Zhang[59]	2004	No	Mixed	Yes	Paracetamol	10	1966 to July 2003	Medline, Embase, Scientific Citation Index, CINAHL, Cochrane Library, and conference Abstracts
Zhang[60]	2021	Yes	Hip and/or knee	Yes	Opioids	6	Up to May 2020	Pubmed, Embase, Cochrane Library and Web of Science
Zhu[61]	2018	Yes	Knee or hip	Yes	Mixed	61	Inception to October 23, 2017	PubMed, Embase, and Cochrane Library

* Mixed = different joints (elbow, ankle, among others) including knee and hip.
[#]Mixed = includes several modalities: exercise, IA, nutraceuticals, among others.

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Web-appendix 4. Definitions used to classify trials according to components of methodological quality

Random sequence allocation

We considered trials as being at low risk of bias for random sequence allocation when an adequate method of randomization was used: computer-generated methods, use of random number tables, drawing of lots, among others - as per Cochrane's recommendations. Trials that used one of the following methods were judged as having a high risk of bias for random sequence allocation: pseudo-randomization based on dates (birth, admission, any other), hospital/clinical record number, or any methods not considered adequate as per Cochrane's recommendations. Trials with insufficient information to judge random sequence generation methods were classified as having "unclear risk of bias" for this domain.

Concealment of allocation

We considered allocation concealment adequate if the investigators responsible for patient selection were unable to suspect before allocation which treatment was next. Methods considered adequate included central randomization, coded drugs, and sequentially numbered, sealed, opaque envelopes. Concealment was downgraded to inadequate if there was evidence of inadequate sequence generation.

Blinding of patients

We considered blinding of patients adequate if a trial was placebo-controlled, if interventions were described as indistinguishable, or if double-dummy technique was used.

Blinding of therapist

We considered blinding of therapists adequate if it was explicitly mentioned in the text that therapists were blinded.

Blinding of assessor (outcome assessor)

Pain and function scales such as the Visual Analogue Scale (VAS), WOMAC, and Lequesne are self-administered tools; that is, the patients will respond to the questionnaire. Typically, therapists will not be involved or greatly influence this assessment. If there was a "low risk of bias" in the blinding of patients, blinding of outcome assessor was considered as being at a "low risk of bias" too. If patients were not blinded and patient-reported outcomes were used, blinding of outcome assessor was considered at a "high risk of bias." Outcome assessment was considered to be blinded if self-report outcomes were employed AND

blinding of patients was considered adequate, AND there was no information to suggest that there was an investigator involved during the process of outcome assessment. Also, we will judge as in "low risk of bias" if blinding of investigators performing the outcome assessment was reported AND an attempt to blind patients was reported. We chose this option if outcome assessors (interviewers) were explicitly described as being blinded. Open-label trials were considered at a "high risk of bias" if pain/function was measured by the physician's global assessment, and they were not blinded to patient's allocation. If the information is not sufficient to judge, trials were deemed as "unclear risk of bias" for this domain.

Incomplete outcome data

Trials that performed a bona fide intention-to-treat analysis were considered at low risk of bias. We considered trials at a high-risk of bias when reports explicitly mentioned that patients were excluded after randomization or when the number of patients analyzed at six weeks (or the closest time point) differed from the number of patients randomized

Web-appendix 5. Description of the main model of analysis (Random walk)

The assumption that the standardized effects at each timepoint are fully exchangeable around a common standardized effect may be considered too restrictive, especially when the course of the disease has a potential temporal pattern. We may weaken this assumption by using a (first order) random walk. A random walk of first order assumes that any adjacent standardized effects are more similar to each other than non-adjacent standardized effects. Therefore, if there is an underlying temporal pattern, a random walk model may capture this more appropriately than a full exchangeability model.

We use the following notation:

- i denotes the study
- k denotes the study arm
- t denotes the timepoint
- $trt(i,k)$ denotes the treatment in arm k in study i
- $bsl(i)$ denotes the "baseline" treatment in study i
- $g = 1,2, \ldots,$ are the treatments
- x_i is a covariate on the study-level (e.g. adequate blinding)

In mathematical terms, the model is then written as follows:

$$seff_{itk} |\, \theta_{itk}, se_{itk} \sim N(\theta_{itk}, se_{itk}^2)$$

$$for\ t > 1$$

$$\theta_{itk} |\, \theta_{i(t-1)k}, \tau_{time} \sim N\left(\theta_{i(t-1)k}, \tau_{time}^2\right)$$

and

$$\theta_{i1k} = \begin{cases} \mu_i\ if\ trt(i,k) = bsl(i) \\ \mu_i + \delta_{ik}\ else \end{cases}$$

$$\delta_{ik} |\, d_{trt(i,k)}, d_{bsl(i)}, \tau_{RE} \sim N\left(d_{trt(i,k)} - d_{bsl(i)} + \beta * x_i, \tau_{RE}^2\right)$$

Furthermore, the following prior distributions were used:

$$\mu_i \sim N(0{,}1000)$$

$$d_g \sim N(0{,}1000)$$

$$\beta \sim N(0{,}1000)$$

$$\tau_{time} \sim U(0{,}5)$$

$$\tau_{RE}^{-2} \sim G(0.1{,}0.1) I_{(0{,}2000)}$$

We note a few points with respect to this model:

- θ_{itk} is the estimated standardized effect of arm k in study i at timepoint t
- τ^2_{time} is the variance determining how close two adjacent θ_{itk} are to each other
- μ_i is the baseline effect at time 1 in study i
- δ_{ik} is the treatment effect at time 1 in study i
- d_g is the overall (treatment) effect at timepoint 1
- An adjustment for multi-arm trials based on the approach proposed by Cooper et al was done (for simplification, this is omitted in the model formulation above)

One advantage of such (or any similar model) is that it can handle incomplete data structures, i.e. also in studies for which outcome data was reported only for some of the timepoints of interest. In a Bayesian framework, such an incomplete data structure does not pose a problem. For example, studies which only reported outcomes at later timepoints (t > 1) will contribute less to the estimated treatment effect d_g since they are naturally down-weighted through the random walk structure.
One challenge with such a model is that the estimated overall treatment effects corresponds to timepoint 1. Thus, we performed our main analysis using timepoint 4 (week 6) as the reference timepoint and performed a sensitivity analysis with timepoints 1 (week 1) and 6 (week 12) as the reference.

OpenBUGS code used for random walk model (timepoint 4 as reference)[1]:

```
model {

 for(i in 1:nobs){

   # Categorical timepoint 4 corresponds to 6 weeks
   prec.t[i,4] <- pow(set[i,4],-2)
   sefft[i,4] ~ dnorm(mean.t[i,4],prec.t[i,4])
   mean.t[i,4] <- mu[trial[i]] + delta[trial[i],arm[i]]
   rest[i,4] <- (mean.t[i,4] - sefft[i,4])
   dev[i,4] <- (sefft[i,4]-mean.t[i,4])*(sefft[i,4]-mean.t[i,4])*prec.t[i,4]

   for(k in 1:3){
    prec.t[i,k] <- pow(set[i,k],-2)
```

[1] The code includes one additional prior for the between-trial heterogeneity that we used to assess sensitivity of the analysis to the prior distribution. This additional analysis showed similar results.

```
    sefft[i,k] ~ dnorm(mean.t[i,k],prec.t[i,k])
    mean.t[i,k] ~ dnorm(mean.t[i,k+1],prec.RW[k])
    rest[i,k] <- (mean.t[i,k] - sefft[i,k])
    dev[i,k] <- (sefft[i,k]-mean.t[i,k])*(sefft[i,k]-mean.t[i,k])*prec.t[i,k]
  }

  for(k in 5:n.times){
    prec.t[i,k] <- pow(set[i,k],-2)
    sefft[i,k] ~ dnorm(mean.t[i,k],prec.t[i,k])
    mean.t[i,k] ~ dnorm(mean.t[i,k-1],prec.RW[k])
    rest[i,k] <- (mean.t[i,k] - sefft[i,k])
    dev[i,k] <- (sefft[i,k]-mean.t[i,k])*(sefft[i,k]-mean.t[i,k])*prec.t[i,k]
  }
    resdev[i] <- sum(dev[i,1:n.times])
}
    totresdev <- sum(resdev[])

 for (j in 1:ns){
  mu[j] ~ dnorm(0,0.001)
  delta[j,1] <- 0
  w[j,1] <- 0

  for (k in 2:na[j]){
    delta[j,k] ~ dnorm(md[j,k],tau[j,k])
    md[j,k] <- d[t.s[j,k]] - d[t.s[j,1]] + sw[j,k] + beta*x[j]
    tau[j,k] <- 2*tau.re*(k-1)/k
    w[j,k] <- delta[j,k] - (d[t.s[j,k]] - d[t.s[j,1]] + beta*x[j])
    sw[j,k] <- sum(w[j,1:(k-1)])/(k-1)
  }
 }

 d[1] <- 0
 for (k in 2:nt){
  d[k] ~ dnorm(0,0.001)
 }

 beta ~ dnorm(0,0.001)
```

```
  prec.RW[4] <- 0
  indep[4] <- 0

  for(i in 1:3){
    sd.RW[i] <- pow(prec.RW[i], -0.5)
    prec.RW[i] <- prec.RW.which[i,indep[i]]
    prec.RW.which[i,1] <- prec.RW.common
    prec.RW.which[i,2] <- pow(sd.RW.indep[i], -2)
    sd.RW.indep[i] ~ dunif(0, 5)
  }

  for(i in 5:n.times){
    sd.RW[i] <- pow(prec.RW[i], -0.5)
    prec.RW[i] <- prec.RW.which[i,indep[i]]
    prec.RW.which[i,1] <- prec.RW.common
    prec.RW.which[i,2] <- pow(sd.RW.indep[i], -2)
    sd.RW.indep[i] ~ dunif(0, 5)
  }

  prec.RW.common <- pow(sd.RW.common, -2)
  sd.RW.common ~ dunif(0,5)

        # Gamma prior
        tau.re ~ dgamma(0.1,0.1)I(,2000)
        tausq <- 1/tau.re
}
```

In order to model a treatment specific dose-response relationship, for each preparation the maximum approved dose for the indication “osteoarthritis” was defined as the reference dose. The treatment effect d is with respect to this reference dose, and for the remaining doses of the preparation, the respective treatment effect was defined as

- $d'_g = \gamma_g \ * log\left(\frac{dose'}{referencedose}\right)$

Non-informative prior distributions (normal with mean 0 and variance 1000) were given for the parameters γ_g .

Web-appendix 6. Imputation of missing standard deviations

When summary statistics were insufficient to approximate the standard deviation, we imputed arm-specific standard deviations based on a restricted cubic spline regression model [1]. We used a large database including data from 388 large OA trials, and assumed a non-linear relationship between time point (weeks) and the magnitude of the standard deviation.

The database of large OA trials has been assembled based on previous projects conducted by our research group [2-6], and included only large OA trials selected with identical eligility criteria compared to the trials whose standard deviations were imputed. A myriad of interventions were included in this database: physical therapy, exercise, corticosteroids, hyaluronic acid, among others [2-6].

Different scales (e.g., WOMAC, Lesquene, overall pain) and approaches (e.g., visual analog scale, Likert, numeric rating scale) were used across trials to measure pain and physical function. Thus, arm-specific standard deviations were rescaled in [0,1] by dividing the standard deviation by the range of the scale. Next, assuming *n* independent trial arms, the arm-level standard deviation was modeled as:

$$\mathbf{sd} = \mathbf{C}\boldsymbol{\beta} + \mathrm{S}\boldsymbol{\gamma} + \mathrm{A}\boldsymbol{\lambda} + \mathbf{T}\boldsymbol{\pi} + \epsilon$$

where **C** is a $n \times k + 1$ matrix, in which the first column of 1's is followed by *k* columns containing the *k* cubic splines variables. **S** is the $n \times s - 1$ matrix containing dummy variables for the *s* different scales and **A** is the $n \times a - 1$ matrix containing dummy variables for the *a* different approaches. **T** is the matrix containing the values for timepoints (in weeks). β, γ, λ and π are the vectors of parameters to be estimated. Finally, ϵ is the error vector whose i^{th} element is $\overset{iid}{\sim} \mathrm{N}(0, \sigma^2_{sd})$.

We used 8 knots covering the entire distribution of time points to ensure sufficient data points in each interval [1]. Specifically, we set the knots at 0,1,4,6,12,16,25,30 and 52 weeks.

The hypothesis of non-linearity was formally using a likelihood-ratio (LR) test. Specifically, the log-likelihood of the full model (including the complete set of cubic splines variables with the linear term) was compared to the log-likelihood of the nested model with the linear term only. The LR test was obtained by -2log-likelihood$_{[\text{nested model}]}$ – 2log-likelihood$_{[\text{full model}]}$. The model with the cubic splines components improved significantly the overall fit of the model when compared to the model without the cubic splines variables (chi-squared = 111.7 on 7 degrees-of-freedom, $P<0.0001$).

We performed a sensitivity analysis in which a smaller number of knots were used. Different models with varying degrees-of-freedom (3 to 7 knots) were tested using Akaike's information criterion and Bayesian information criterion (BIC), with smaller values of AIC and

BIC preferred. Our results indicated that the model with 8 knots provided the best fit, in which the difference between the 8-knot model *vs* less complex models was > 2 in all comparisons.

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Web-appendix 7. Treatment effect estimates for pain, physical function, and adverse events, as compared to oral placebo

	No. of participants	Pain		Function	Dropouts due to AEs	Any AEs	Serious AEs
		ES (95% CrI)	Pr(MID)	ES (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)
Paracetamol							
Paracetamol <2000mg	158	-0.07 (-0.56 to 0.44)	11.8	0.04 (-0.42 to 0.50)	1.51 (0.58 to 3.72)	1.22 (0.75 to 1.98)	1.60 (0.28 to 8.71)
Paracetamol 3000mg	442	-0.21 (-0.81 to 0.39)	29.7	-0.26 (-0.80 to 0.30)	1.31 (0.56 to 3.12)	1.25 (0.71 to 2.21)	-
Paracetamol 3900-4000mg*	2614	-0.15 (-0.25 to -0.05)	0.0	-0.15 (-0.25 to -0.05)	1.35 (1.00 to 1.81)**	1.19 (0.99 to 1.42)	1.67 (0.82 to 3.52)
NSAIDs - Oral							
Aceclofenac 200mg*	1179	-0.56 (-0.78 to -0.34)	95.1	-0.54 (-0.76 to -0.31)	1.42 (0.92 to 2.21)	1.10 (0.72 to 1.66)	-
Celecoxib 100mg	419	-0.10 (-0.26 to 0.06)	0.0	-0.17 (-0.42 to 0.09)	0.83 (0.52 to 1.34)	1.12 (0.83 to 1.52)	0.18 (0.01 to 1.31)
Celecoxib 200mg	11362	-0.35 (-0.40 to -0.30)	20.0	-0.35 (-0.40 to -0.30)	1.04 (0.90 to 1.21)	1.06 (0.97 to 1.16)	0.97 (0.69 to 1.38)
Celecoxib 400mg*	661	-0.32 (-0.47 to -0.16)	24.7	-0.38 (-0.62 to -0.13)	1.08 (0.70 to 1.67)	1.08 (0.83 to 1.41)	1.19 (0.32 to 4.15)
Diclofenac ≤75mg	519	-0.42 (-0.65 to -0.18)	65.1	-0.27 (-0.77 to 0.23)	2.64 (1.53 to 4.65)	1.37 (0.71 to 2.70)	1.54 (0.32 to 7.23)
Diclofenac 100-105mg	2113	-0.47 (-0.63 to -0.31)	88.4	-0.44 (-0.65 to -0.24)	1.48 (1.12 to 1.97)	1.19 (0.93 to 1.51)	1.10 (0.52 to 2.44)
Diclofenac 114-133mg	812	-0.64 (-1.40 to 0.11)	75.9	-	1.79 (0.74 to 4.42)	1.42 (0.74 to 2.73)	-
Diclofenac 150mg*	3709	-0.56 (-0.68 to -0.45)	99.9	-0.47 (-0.59 to -0.35)	1.67 (1.31 to 2.13)	1.27 (1.03 to 1.56)	2.71 (0.93 to 8.29)
Diflunisal 750mg	139	-0.33 (-0.69 to 0.03)	41.2	-	0.94 (0.35 to 2.50)	1.22 (0.64 to 2.31)	-
Diflunisal 1000mg	140	-0.40 (-0.77 to -0.04)	57.0	-	1.97 (0.83 to 4.79)	1.34 (0.71 to 2.53)	-
Etodolac 600mg	454	-0.57 (-0.83 to -0.31)	93.1	-0.22 (-0.60 to 0.15)	1.22 (0.67 to 2.26)	0.95 (0.62 to 1.45)	-
Etoricoxib 5-10mg	231	-0.21 (-0.43 to 0.02)	7.5	-	0.65 (0.19 to 2.01)	-	1.62 (0.29 to 10.91)
Etoricoxib 30mg	1135	-0.48 (-0.63 to -0.34)	94.3	-0.43 (-0.60 to -0.26)	0.88 (0.58 to 1.33)	1.21 (0.96 to 1.51)	0.52 (0.22 to 1.21)
Etoricoxib 60mg*	939	-0.65 (-0.82 to -0.48)	99.9	-0.48 (-0.69 to -0.28)	1.02 (0.62 to 1.68)	1.56 (1.12 to 2.22)	0.89 (0.32 to 2.48)
Etoricoxib 90mg	307	-0.84 (-1.09 to -0.59)	100.0	-	1.58 (0.80 to 3.11)	-	2.92 (0.52 to 17.43)
Ibuprofen 400mg	82	-	-	-	0.44 (0.09 to 1.46)	0.89 (0.46 to 1.68)	1.91 (0.05 to 76.48)
Ibuprofen 1200mg	1055	-0.31 (-0.92 to 0.30)	42.1	-0.41 (-0.96 to 0.16)	0.99 (0.39 to 2.53)	1.07 (0.72 to 1.59)	-
Ibuprofen 2400mg*	1208	-0.37 (-0.50 to -0.25)	52.8	-0.36 (-0.49 to -0.23)	1.80 (1.23 to 2.60)	1.44 (1.10 to 1.90)	1.14 (0.36 to 3.64)
Indomethacin 75mg	356	-0.30 (-0.74 to 0.14)	37.6	-	-	-	-
Indomethacin 105mg	113	-	-	-	1.81 (1.05 to 3.20)	1.72 (1.06 to 2.81)	-
Indomethacin 150mg	123	-	-	-	2.49 (0.74 to 8.49)	-	-
Indomethacin 210mg*	110	-	-	-	3.21 (1.08 to 10.03)	1.88 (0.79 to 4.45)	-
Isoxicam 200mg¶	391	-0.59 (-1.08 to -0.09)	80.6	-	1.26 (0.58 to 2.69)	-	-
Isoxicam 300mg¶	112	-	-	-	5.61 (1.81 to 18.32)	1.67 (0.63 to 4.58)	-
Ketoprofen 200mg*	118	-0.60 (-1.06 to -0.13)	83.0	-	0.82 (0.31 to 2.09)	1.24 (0.60 to 2.55)	-
Lornoxicam 16mg*	137	-0.73 (-1.32 to -0.14)	88.1	-0.61 (-1.16 to -0.05)	-	0.96 (0.45 to 2.03)	-
Lumiracoxib 100mg	2165	-0.33 (-0.52 to -0.13)	33.8	-0.34 (-0.56 to -0.12)	0.88 (0.61 to 1.26)	1.32 (1.08 to 1.61)	1.12 (0.59 to 2.19)
Lumiracoxib 200mg*	1409	-0.36 (-0.54 to -0.19)	46.1	-0.39 (-0.57 to -0.21)	0.97 (0.66 to 1.41)	1.14 (0.91 to 1.43)	1.03 (0.49 to 2.31)
Lumiracoxib 400mg	1404	-0.39 (-0.59 to -0.18)	55.9	-0.41 (-0.66 to -0.17)	1.06 (0.71 to 1.57)	1.14 (0.90 to 1.45)	0.90 (0.40 to 2.02)
Meclofenamate sodium 300mg	211	-0.31 (-0.88 to 0.25)	41.8	-	1.82 (0.71 to 4.84)	1.50 (0.87 to 2.58)	-
Meloxicam ≤10mg	886	-0.33 (-0.52 to -0.13)	33.9	-0.27 (-0.46 to -0.08)	0.97 (0.61 to 1.52)	1.15 (0.79 to 1.66)	0.42 (0.06 to 2.41)
Meloxicam 15mg*	1184	-0.48 (-0.66 to -0.30)	88.2	-0.39 (-0.59 to -0.19)	1.13 (0.75 to 1.69)	1.16 (0.85 to 1.59)	1.37 (0.24 to 8.76)

Nabumetone 1000mg	1034	-0.22 (-0.37 to -0.08)	2.3	0.12 (-0.19 to 0.44)	1.04 (0.68 to 1.59)	0.99 (0.76 to 1.30)	1.12 (0.40 to 3.27)
Nabumetone 1327mg	191	-	-	-	1.00 (0.33 to 3.05)	1.03 (0.45 to 2.38)	-
Nabumetone 1500-1831mg	1399	-0.41 (-0.89 to 0.08)	56.3	-0.65 (-1.23 to -0.07)	1.05 (0.73 to 1.51)	1.31 (0.96 to 1.83)	-
Naproxcinod 250mg	111	0.04 (-0.21 to 0.29)	0.1	-0.04 (-0.29 to 0.21)	0.63 (0.17 to 1.82)	-	-
Naproxcinod 750mg	708	-0.31 (-0.43 to -0.19)	16.6	-0.35 (-0.48 to -0.23)	1.41 (0.80 to 2.42)	1.06 (0.79 to 1.42)	0.35 (0.09 to 1.02)
Naproxcinod 1500mg	1468	-0.44 (-0.54 to -0.34)	92.2	-0.48 (-0.58 to -0.38)	1.37 (0.93 to 1.99)	1.23 (0.99 to 1.52)	1.12 (0.56 to 2.21)
Naproxcinod 2250mg	124	-0.47 (-0.73 to -0.22)	77.9	-0.53 (-0.78 to -0.28)	-	-	0.58 (0.02 to 5.58)
Naproxen ≤750mg	2370	-0.38 (-0.63 to -0.13)	52.3	-0.31 (-0.58 to -0.05)	1.33 (0.89 to 2.02)	1.48 (1.17 to 1.87)	1.15 (0.30 to 4.41)
Naproxen 1000mg*	5869	-0.39 (-0.45 to -0.32)	68.1	-0.43 (-0.50 to -0.36)	1.50 (1.24 to 1.83)	1.39 (1.23 to 1.57)	1.03 (0.67 to 1.61)
Nimesulide 200mg*	418	-0.35 (-0.65 to -0.06)	45.7	-0.35 (-0.69 to 0.01)	1.29 (0.67 to 2.45)	1.17 (0.78 to 1.76)	2.77 (0.52 to 15.60)
Nimesulide 800mg	146	-0.44 (-0.93 to 0.05)	61.0	-0.43 (-0.90 to 0.02)	0.84 (0.28 to 2.32)	1.10 (0.57 to 2.09)	1.06 (0.03 to 48.52)
Oxaprozin 1200mg	393	-0.61 (-0.89 to -0.32)	94.6	-0.42 (-0.72 to -0.10)	1.57 (0.89 to 2.74)	1.98 (1.32 to 2.97)	0.90 (0.02 to 32.98)
Oxaprozin 1800mg*	81	-	-	-	2.02 (0.80 to 4.87)	2.92 (1.58 to 5.45)	1.96 (0.05 to 71.09)
Piroxicam 20mg	2183	-0.48 (-0.67 to -0.28)	86.4	-0.37 (-0.59 to -0.15)	1.32 (0.88 to 1.97)	1.41 (1.04 to 1.91)	1.27 (0.21 to 7.71)
Piroxicam 25.5mg	147	-0.53 (-1.43 to 0.37)	63.2	-	2.26 (0.98 to 5.19)	-	-
Polmacoxib 2mg	146	-0.28 (-0.55 to -0.02)	24.9	-0.28 (-0.54 to -0.03)	3.66 (1.28 to 11.99)	2.02 (1.12 to 3.63)	5.28 (0.93 to 47.47)
Rofecoxib 5mg¶	149	-0.34 (-0.60 to -0.09)	42.2	-0.38 (-0.63 to -0.13)	1.41 (0.44 to 3.93)	-	-
Rofecoxib 12.5mg¶	3554	-0.41 (-0.49 to -0.33)	86.3	-0.39 (-0.48 to -0.30)	1.22 (0.96 to 1.54)	1.19 (1.00 to 1.42)**	1.16 (0.63 to 2.21)
Rofecoxib 25mg*¶	3330	-0.48 (-0.55 to -0.40)	99.6	-0.49 (-0.56 to -0.41)	1.32 (1.04 to 1.68)	1.25 (1.04 to 1.50)	1.23 (0.63 to 2.39)
Rofecoxib 50mg¶	97	-0.77 (-1.05 to -0.49)	99.8	-0.62 (-0.90 to -0.33)	1.84 (0.54 to 5.35)	-	-
Tiaprofenic acid 600mg*	307	-0.27 (-0.74 to 0.22)	33.5	-	1.47 (0.84 to 2.63)	1.55 (0.98 to 2.45)	-
Tolfenamic acid 600mg	116	-0.65 (-1.45 to 0.13)	76.0	-	1.80 (0.41 to 8.37)	1.80 (0.66 to 5.22)	-
Valdecoxib 5mg¶	321	-0.29 (-0.47 to -0.11)	18.8	-0.32 (-0.49 to -0.15)	1.09 (0.43 to 2.57)	1.23 (0.72 to 2.09)	-
Valdecoxib 10mg¶	317	-0.32 (-0.50 to -0.14)	29.4	-0.41 (-0.59 to -0.24)	1.33 (0.54 to 3.12)	0.99 (0.58 to 1.68)	-
Valdecoxib 20mg¶	202	-0.37 (-0.59 to -0.14)	48.5	-0.33 (-0.55 to -0.11)	-	-	-
Zaltoprofen 240mg*	105	-0.78 (-1.39 to -0.17)	90.7	-0.56 (-1.13 to 0.01)	4.01 (0.29 to 135.37)	2.13 (1.02 to 4.49)	-
NSAIDs - Topical							
Diclofenac topical 70-81mg	987	-0.54 (-0.77 to -0.31)	92.3	-0.47 (-0.70 to -0.25)	1.14 (0.74 to 1.72)	1.03 (0.72 to 1.47)	-
Diclofenac topical 140-160mg	3124	-0.61 (-0.87 to -0.35)	96.3	-0.55 (-0.82 to -0.27)	1.58 (0.77 to 3.34)	1.17 (0.84 to 1.63)	3.35 (0.45 to 35.30)
S-flurbiprofen plaster ≤20mg	248	-0.25 (-0.92 to 0.42)	36.2	-0.31 (-0.95 to 0.31)	0.40 (0.03 to 4.14)	1.19 (0.57 to 2.53)	-
S-flurbiprofen plaster 40mg	134	-0.41 (-1.20 to 0.37)	53.9	-0.48 (-1.21 to 0.25)	0.32 (0.01 to 3.82)	1.40 (0.63 to 3.12)	-
Ibuprofen topical 1500mg	138	-0.19 (-1.03 to 0.66)	33.7	-0.43 (-1.19 to 0.35)	-	-	-
Ketoprofen topical 50mg	223	-0.15 (-0.64 to 0.33)	18.7	-0.06 (-0.52 to 0.39)	0.67 (0.25 to 1.65)	0.98 (0.61 to 1.59)	-
Ketoprofen topical 100mg	456	-0.22 (-0.49 to 0.06)	14.1	-0.18 (-0.45 to 0.09)	0.99 (0.44 to 2.15)	1.07 (0.72 to 1.61)	-
Ketoprofen topical 200-220mg	863	-0.23 (-0.39 to -0.06)	4.4	-0.21 (-0.37 to -0.05)	1.27 (0.79 to 2.02)	1.09 (0.82 to 1.45)	0.71 (0.18 to 2.66)
Piroxicam topical 15mg*	117	0.39 (-0.49 to 1.25)	4.3	-0.41 (-1.21 to 0.40)	1.32 (0.31 to 5.74)	1.31 (0.59 to 2.89)	-
Piroxicam topical 20mg	124	-	-	-	-	6.03 (0.71 to 169.69)	-
Opioids							
Buprenorphine sublingual 0.87mg	120	-0.35 (-1.39 to 0.69)	48.7	-	2.88 (1.19 to 6.88)	7.91 (3.05 to 21.14)	-
Buprenorphine transdermal 0.28-0.36mg	828	-0.36 (-0.73 to 0.01)	47.9	-	2.07 (1.19 to 3.61)	3.06 (1.96 to 4.75)	2.51 (0.44 to 15.49)
Codeine 105-127mg	263	-0.19 (-0.62 to 0.24)	19.9	-	1.51 (0.81 to 2.85)	2.14 (1.28 to 3.58)	0.64 (0.02 to 12.54)
Dextropropoxyphene 300mg	129	-	-	-	1.02 (0.43 to 2.34)	1.06 (0.55 to 2.04)	-
Fentanyl transdermal 0.6mg	216	-0.31 (-0.69 to 0.07)	37.6	-	2.76 (1.22 to 6.32)	5.43 (2.92 to 10.26)	3.14 (0.37 to 34.09)
Hydromorphone 8mg	319	-0.01 (-0.53 to 0.50)	8.7	-0.11 (-0.59 to 0.37)	4.93 (2.68 to 9.27)	2.63 (1.66 to 4.21)	1.15 (0.32 to 3.96)
Hydromorphone 13.9-16mg	469	-0.16 (-0.51 to 0.18)	12.0	-0.11 (-0.49 to 0.27)	8.72 (5.10 to 15.09)	4.79 (3.25 to 7.16)	1.46 (0.55 to 3.76)

Hydromorphone 34mg	100	-0.00 (-0.61 to 0.60)	11.6	-	-	2.41 (1.24 to 4.76)	7.64 (0.84 to 257.23)
Morphine with naltrexone 43.5mg	171	-0.25 (-0.82 to 0.32)	34.1	-0.21 (-0.75 to 0.33)	1.46 (0.62 to 3.52)	1.21 (0.71 to 2.05)	2.12 (0.44 to 12.90)
Oxycodone ≤40mg	705	-0.09 (-0.41 to 0.22)	4.5	-0.15 (-0.70 to 0.41)	7.29 (4.83 to 11.17)	4.96 (3.78 to 6.52)	1.54 (0.40 to 6.26)
Oxycodone ≥48mg	883	-0.17 (-0.33 to -0.01)	0.9	-0.24 (-0.61 to 0.13)	6.78 (4.70 to 9.66)	4.65 (3.33 to 6.55)	2.40 (1.09 to 5.60)
Oxymorphone 40mg	121	-0.23 (-0.77 to 0.30)	31.1	-0.27 (-0.83 to 0.28)	13.26 (6.53 to 27.94)	10.64 (4.80 to 26.36)	-
Oxymorphone 80mg	121	-0.32 (-0.86 to 0.22)	42.3	-0.32 (-0.87 to 0.23)	19.34 (9.47 to 40.29)	7.42 (3.57 to 16.41)	-
Tapentadol <316mg	1422	-0.34 (-0.50 to -0.17)	33.9	-0.33 (-0.62 to -0.04)	2.58 (1.84 to 3.67)	1.94 (1.55 to 2.42)	0.55 (0.19 to 1.51)
Tramadol 100-131mg	930	-0.12 (-0.25 to 0.01)	0.0	-0.07 (-0.22 to 0.08)	1.77 (1.25 to 2.51)	1.62 (1.26 to 2.09)	1.45 (0.39 to 4.57)
Tramadol 200mg	858	-0.13 (-0.26 to 0.00)	0.0	-0.17 (-0.32 to -0.03)	2.86 (2.10 to 3.89)	2.76 (2.16 to 3.53)	1.12 (0.38 to 3.13)
Tramadol 275-300mg	1319	-0.31 (-0.43 to -0.20)	18.1	-0.28 (-0.43 to -0.14)	4.73 (3.52 to 6.39)	2.88 (2.26 to 3.69)	2.23 (0.87 to 5.92)
Tramadol 400mg*	205	-0.23 (-0.46 to -0.01)	11.8	-0.24 (-0.46 to -0.01)	4.71 (2.75 to 8.02)	4.41 (2.68 to 7.34)	2.96 (0.74 to 11.42)
Tramadol/paracetamol 110-155mg	350	-0.39 (-0.88 to 0.09)	53.0	-0.21 (-0.67 to 0.24)	3.17 (1.55 to 6.84)	2.67 (1.46 to 4.99)	-
Placebos							
Topical placebo	4503	-0.23 (-0.39 to -0.06)	4.6	-0.21 (-0.38 to -0.05)	0.84 (0.55 to 1.27)	1.11 (0.85 to 1.44)	0.91 (0.28 to 2.90)
Oral and topical placebo	127	0.07 (-0.22 to 0.35)	0.2	-0.04 (-0.33 to 0.24)	1.20 (0.56 to 2.52)	0.96 (0.56 to 1.62)	1.95 (0.05 to 74.00)

All treatment effect estimates are comparisons to oral placebo. Number of participants randomized to oral placebo: 18,712

ES: effect size; Pr: probability; MID: between-group minimum clinically important difference; OR: odds ratio; 95% CrI: 95% credible interval.

Light green ES: lower bound of 95% CrI <0; dark green ES: lower bound of 95% CrI ≤-0.37 (MID); light green MID: probability of reaching MID ≥95%; dark green MID: probability to reach MID ≥99%; light red OR: lower bound of 95% CrI >1; dark red OR: lower bound of 95% CrI ≥2.

All doses are in mg per day. *Maximum daily recommended dose. ¶ Withdrawn from the market. **The lower bounds of the 95% CrI of dropouts due to adverse events for paracetamol 3900-4000mg and of any adverse event for rofecoxib 12.5mg are >1, but are shown as 1.00 due to rounding.

Pain: 84 out of 93 interventions/controls included, 170 out of 192 trials with available data; physical function: 67 out of 93 interventions/controls included, 125 out of 192 trials with available data; dropouts due to adverse events: 86 out of 93 interventions/controls included, 168 out of 192 trials with data available; any adverse event: 81 out of 93 interventions/controls included, 141 out of 192 trials with data available; and serious adverse events: 52 out of 93 interventions/controls, 95 out of 192 trials with data available.

Web-appendix 8. Number of arms and randomized participants

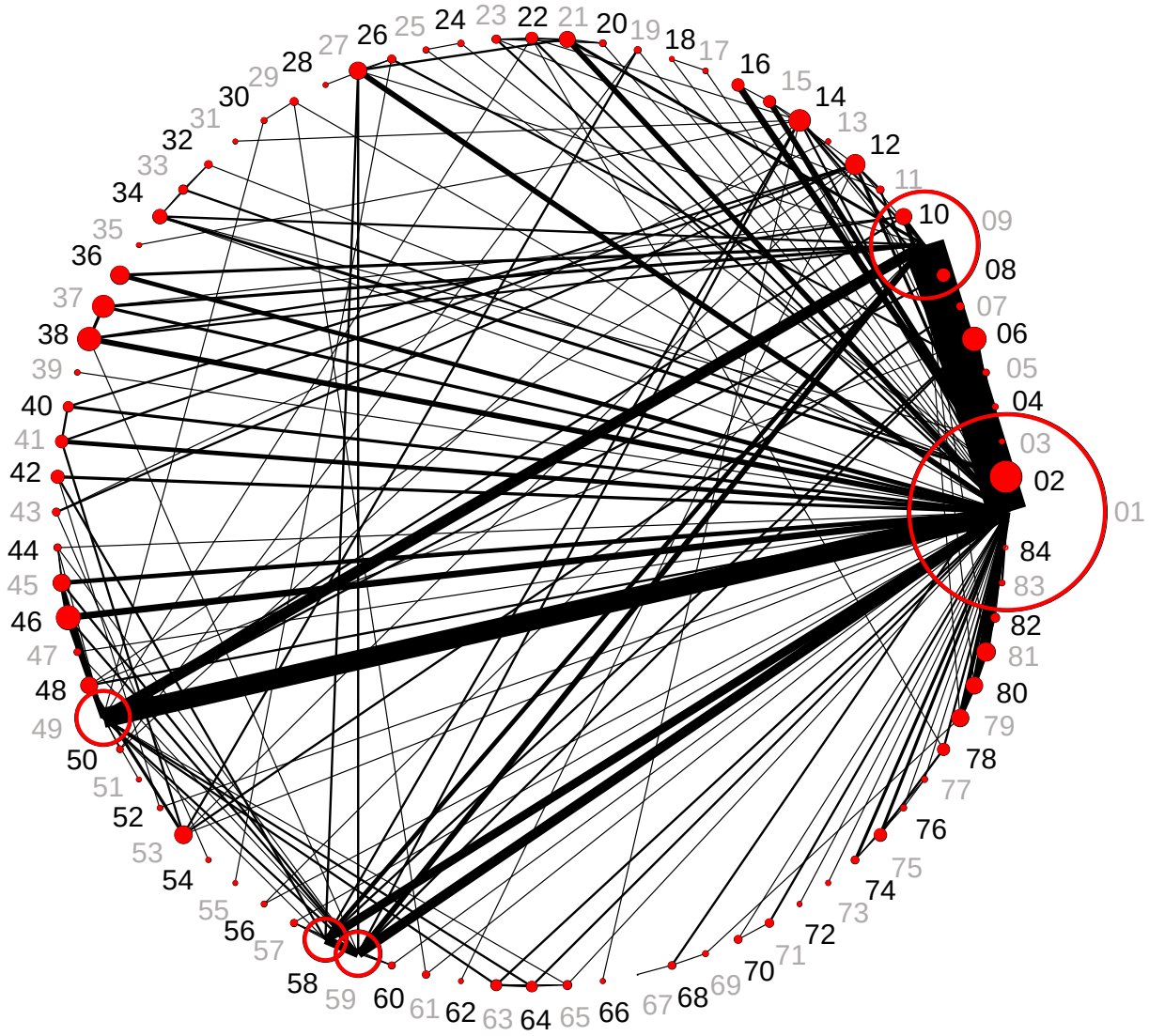
Intervention	No. of arms	No. of participants randomized
Paracetamol		
Paracetamol <2000mg	1	158
Paracetamol 3000mg	3	442
Paracetamol 3900-4000mg	11	2614
NSAIDs		
Aceclofenac 200mg	7	1179
Celecoxib 100mg	2	419
Celecoxib 200mg	44	11362
Celecoxib 400mg	4	661
Diclofenac ≤75mg	4	519
Diclofenac 100-105mg	12	2113
Diclofenac 114-133mg	3	812
Diclofenac 150mg	17	3709
Diclofenac topical 70-81mg	6	987
Diclofenac topical 140-160mg	8	3124
Diflunisal 750mg	1	0
Diflunisal 1000mg	1	140
Etodolac 600mg	4	454
Etoricoxib 5-10mg	1	231
Etoricoxib 30mg	6	1135
Etoricoxib 60mg	4	939
Etoricoxib 90mg	2	307
S-flurbiprofen plaster ≤20mg	1	248
S-flurbiprofen plaster 40mg	1	134
Ibuprofen 400mg	1	82
Ibuprofen 1200mg	6	1055
Ibuprofen 2400mg	6	1208
Ibuprofen topical 1500mg	1	138
Indomethacin 75mg	2	356
Indomethacin 105mg	1	113
Indomethacin 150mg	1	123

Indomethacin 210mg	1	110
Isoxicam 200mg	3	391
Isoxicam 300mg	1	112
Ketoprofen 200mg	1	118
Ketoprofen topical 50mg	1	223
Ketoprofen topical 100mg	2	456
Ketoprofen topical 200-220mg	4	863
Lornoxicam 16mg	1	137
Lumiracoxib 100mg	4	2165
Lumiracoxib 200mg	4	1409
Lumiracoxib 400mg	5	1404
Meclofenamate sodium 300mg	1	211
Meloxicam ≤10mg	4	886
Meloxicam 15mg	7	1184
Nabumetone 1000mg	4	1034
Nabumetone 1327mg	1	191
Nabumetone 1500-1831mg	7	1399
Naproxcinod 250mg	1	111
Naproxcinod 750mg	4	708
Naproxcinod 1500mg	6	1468
Naproxcinod 2250mg	1	124
Naproxen ≤750mg	8	2370
Naproxen 1000mg	27	5869
Nimesulide 200mg	3	418
Nimesulide 800mg	1	146
Oxaprozin 1200mg	3	393
Oxaprozin 1800mg	1	81
Piroxicam 20mg	10	2183
Piroxicam 25.5mg	1	147
Piroxicam topical 15mg	1	117
Piroxicam topical 20mg	1	124
Polmacoxib 2mg	1	146
Rofecoxib 5mg	1	149
Rofecoxib 12.5mg	13	3554
Rofecoxib 25mg	14	3330
Rofecoxib 50mg	1	97
Tiaprofenic acid 600mg	1	307

Tolfenamic acid 600mg	1	116
Valdecoxib 5mg	2	321
Valdecoxib 10mg	2	317
Valdecoxib 20mg	1	202
Zaltoprofen 240mg	1	105
Opioids		
Buprenorphine sublingual 0.87mg	1	120
Buprenorphine transdermal 0.28-0.36mg	5	828
Codeine 105-127mg	2	263
Dextropropoxyphene 300mg	1	129
Fentanyl transdermal 0.6mg	1	216
Hydromorphone 8mg	1	319
Hydromorphone 13.9-16mg	2	469
Hydromorphone 34mg	1	100
Morphine with naltrexone 43.5mg	1	171
Oxycodone ≤40mg	5	705
Oxycodone ≥48mg	3	883
Oxymorphone 40mg	1	121
Oxymorphone 80mg	1	121
Tapentadol <316mg	5	1422
Tramadol 100-131mg	5	930
Tramadol 200mg	6	858
Tramadol 275-300mg	7	1319
Tramadol 400mg	1	205
Tramadol with paracetamol 154-225mg	2	350
Placebos		
Placebo oral	109	18712
Placebo topical	22	4503
Placebo oral and topical	1	127

Web-appendix 9. Network plot

Network of comparisons included in the analysis of osteoarthritis pain.



The size of every circle is proportional to the number of randomly assigned patients and indicates the sample size. The width of the lines corresponds to the number of trials. Larger nodes were made hollow to allow the visualization of adjacent nodes. 01=placebo oral. 02=placebo topical. 03=placebo oral and topical. 04=paracetamol <2000 mg. 05=paracetamol 3000 mg. 06=paracetamol 3990-4000 mg. 07=aceclofenac 200 mg. 08=celecoxib 100 mg. 09=celecoxib 200 mg. 10=celecoxib 400 mg. 11=diclofenac ≤75 mg. 12=diclofenac 100-105 mg. 13=diclofenac 114-133 mg. 14=diclofenac 150 mg. 15=diclofenac topical 70-81 mg. 16=diclofenac topical 140-160 mg. 17=diflunisal 750 mg. 18=diflunisal 1000 mg. 19=etodolac 600 mg. 20=etoricoxib 5-10 mg. 21=etoricoxib 30 mg. 22=etoricoxib 60 mg. 23=etoricoxib 90 mg. 24=S-flurbiprofen plaster ≤20 mg. 25=S-flurbiprofen plaster 40 mg. 26=ibuprofen 1200 mg. 27=ibuprofen 2400 mg. 28=ibuprofen topical 1500 mg. 29=indomethacin 75 mg.

30=isoxicam 200 mg. 31=ketoprofen 200 mg. 32=ketoprofen topical 50 mg. 33=ketoprofen topical 100 mg. 34=ketoprofen topical 200-220 mg. 35=lornoxicam 16 mg. 36=lumarixocib 100 mg. 37=lumaricoxib 200 mg. 38=lumaricoxib 400 mg. 39=meclofenamate sodium 300 mg. 40=meloxicam ≤10 mg. 41=meloxicam 15 mg. 42=nabumetone 1000 mg. 43=nabumetone 1500-1831 mg. 44=naproxcinod 250 mg. 45=naproxcinod 750 mg. 46= naproxcinod 1500 mg. 47= naproxcinod 2250 mg. 48=naproxen ≤750 mg. 49=naproxen 1000 mg. 50=nimesulide 200 mg. 51=nimesulide 800 mg. 52=oxaprozin 1200 mg. 53=piroxicam 20 mg. 54=piroxicam 25.5 mg. 55=piroxicam topical 15 mg. 56=polmacoxib 2 mg. 57=rofecoxib 5 mg. 58=rofecoxib 12.5 mg. 59=rofecoxib 25 mg. 60=rofecoxib 50 mg. 61=tiaprofenic acid 600 mg. 62=tolfenamic acid 600 mg. 63=valdecoxib 5 mg. 64=valdecoxib 10 mg. 65=valdecoxib 20 mg. 66=zaltoprofen 240 mg. 67=buprenorphine sublingual 0.87 mg. 68=buprenorphine transdermal 0.28-0.36 mg. 69=codeine 105-127 mg. 70=hydromorphone 8 mg. 71=hydromorphone 13.9-16 mg. 72=hydromorphone 34 mg. 73=morphine with naltrexone 43.5 mg. 74=oxycodone ≤40 mg. 75=oxycodone ≥48 mg. 76=oxymorphone 40 mg. 77=oxymorphone 80 mg. 78=tapentadol <316 mg. 79=tramadol 100-131 mg. 80=tramadol 200 mg. 81=tramadol 275-300 mg. 82=tramadol 400 mg. 83=tramadol/paracetamol 154-225 mg. 84=fentanyl transdermal 0.6 mg

Web-appendix 10. Number of trials reporting efficacy estimates by drug category and timepoint

Timepoint	Drug Type					
	NSAIDs	Opioids	Paracetamol	NSAIDs vs opioids	NSAIDs vs Paracetamol	Total
Baseline	147	29	5	2	9	192
	31.89	29.29	38.46	20.00	37.50	31.63
1 week	27	15	1	1	4	48
	5.86	15.15	7.69	10.00	16.67	7.91
2 weeks	71	13	1	2	3	90
	15.40	13.13	7.69	20.00	12.50	14.83
4 weeks	72	17	1	2	2	94
	15.62	17.17	7.69	20.00	8.33	15.49
6 weeks	54	8	1	1	5	69
	11.71	8.08	7.69	10.00	20.83	11.37
12 weeks	64	17	3	2	1	87
	13.88	17.17	23.08	20.00	4.17	14.33
24 weeks	18	0	1	0	0	19
	3.90	0.00	7.69	0.00	0.00	3.13
48 weeks	7	0	0	0	0	7
	1.52	0.00	0.00	0.00	0.00	1.15
>52 weeks	1	0	0	0	0	1
	<1	0.00	0.00	0.00	0.00	<1

First row has frequencies, and second row has column percentages.
NSAIDs refer to trials that investigated the efficacy of non-steroidal anti-inflammatory drugs only.
Opioids denote trials that investigated the efficacy of opioid drugs only.

Web-appendix 11. Trial characteristics

Author (year)	Interventions	Number of participants	% of Women	Age	Joints	LOCF	Risk of Bias				
							Allocation concealment	Blinding of Patient	Blinding of Therapist	Blinding of Outcome Assessor	Incomplete outcome data
Afilalo (2010)	Placebo oral Oxycodone (48.2 mg/day) Tapentadol (299.3 mg/day)	1030	60	58	Knee	Yes	Low	Low	Low	Low	High
Agrawal (1999)	Placebo oral Diclofenac (150 mg/day)/misoprostol Nabumetone (1500 mg/day) Naproxen (1000 mg/day)	1398	58	62	Knee and hip	Unclear	Unclear	Low	Low	Low	Unclear
Alho (1988)	Naproxen (750 mg/day) Piroxicam (20 mg/day)	252	72	70	Hip	Unclear	Unclear	Low	Low	Low	Low
Altman (1998)	Placebo oral Naproxen (1000 mg/day)	495	38	63	Knee	Yes	Unclear	High	Unclear	High	High
Altman (2007)	Placebo oral Paracetamol (1950 mg/day) Paracetamol (3900 mg/day)	483	67	62	Knee and hip	Unclear	Unclear	Low	Low	Low	Low
Altman (2015)	Placebo oral Meloxicam (5 mg/day) Meloxicam (10 mg/day)	403	66	61	Knee and hip	Unclear	Unclear	Low	Unclear	Low	High
Ardia (1994)	Diclofenac (100 mg/day) Tolfenamic acid (600 mg/day)	228	67	60	Knee and hip	No	Unclear	Low	Low	Low	High
Asmus (2014)	Placebo oral Celecoxib (200 mg/day)	380	61	60	Knee	Yes	Unclear	Low	Low	Low	High
Asmus (2014)	Placebo oral Celecoxib (200 mg/day)	388	68	59	Knee	Yes	Unclear	Low	Low	Low	High
Babul (2004)	Placebo oral Tramadol (276 mg/day)	246	62	61	Knee	Unclear	Unclear	Low	Low	Low	Low
Baer (2005)	Placebo topical Diclofenac_Topical (77.04 mg/day)	216	56	65	Knee	Yes	Low	Low	Low	Low	High
Baerwald (2010)	Placebo oral Naproxcinod (1500 mg/day) Naproxen (1000 mg/day)	810	66	63	Hip	Yes	Unclear	Low	Unclear	Low	Low
Bakshi (1991)	Placebo oral Diclofenac (150 mg/day)	314	59	69	Knee and hip	Unclear	Unclear	Low	Low	Low	High
Bakshi (1996)	Diclofenac (100 mg/day)	216	63	64	Knee	Yes	Unclear	Low	Low	Low	High

	Diclofenac (75 mg/day)				and hip						
Banerjee (2016)	Etoricoxib (60 mg/day) Tapentadol (200 mg/day)	244	43	54	Knee	Yes	Unclear	High	High	High	High
Baraf (2010)	Placebo topical Diclofenac topical (160 mg/day)	420	64	61	Knee	Yes	Low	Low	Low	Low	High
Barthel (2010)	Placebo topical Diclofenac topical (160 mg/day)	492	66	59	Knee	Yes	Unclear	Low	Low	Low	High
Becvar (1999)	Diclofenac (100 mg/day) Nabumetone (1500 mg/day)	394	77	61	Knee and hip	Unclear	Unclear	High	High	High	High
Behrens (1985)	Diclofenac (75 mg/day) Isoxicam (300 mg/day)	240	61	63	Knee and hip	Unclear	Unclear	Low	Low	Low	High
Bellamy (1995)	Diclofenac (125 mg/day) Nabumetone (1327 mg/day)	382	70	62	Knee and hip	Unclear	Unclear	Low	Low	Low	Unclear
Benevolenskaya (2003)	Placebo oral Lumiracoxib (100 mg/day)	244	NR	NR	Knee and hip	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Bensen (1999)	Placebo oral Celecoxib (100 mg/day) Celecoxib (200 mg/day) Celecoxib (400 mg/day) Naproxen (1000 mg/day)	1004	72	62	Knee	Yes	Unclear	Low	Low	Low	High
Bierma-Zeinstra (2017)	Ibuprofen (1200 mg/day) Ibuprofen (2400 mg/day)	464	41	52	Knee	No	Low	Low	Low	Low	High
Bihlet (2020)	Placebo topical Diclofenac topical (70.4 mg/day) Diclofenac topical (140.8 mg/day) Diclofenac topical (160 mg/day)	444	67	64	Knee	Unclear	Low	Low	Low	Low	High
Bin (2007)	Celecoxib (200 mg/day) Lumiracoxib (200 mg/day)	703	85	61	Knee	Yes	Unclear	Low	Low	Low	Low
Bingham (2007)	Placebo oral Celecoxib (200 mg/day) Etoricoxib (30 mg/day)	599	67	62	Knee and hip	Yes	Unclear	Low	Low	Low	High
Bingham (2007)	Placebo oral Celecoxib (200 mg/day) Etoricoxib (30 mg/day)	608	66	62	Knee and hip	Yes	Unclear	Low	Low	Low	High
Birbara (2006)	Placebo oral Celecoxib (200 mg/day) Rofecoxib (12.5 mg/day)	395	72	60	Knee	Yes	Unclear	Low	Low	Low	High
Birbara (2006)	Placebo oral Celecoxib (200 mg/day)	413	65	61	Knee	Yes	Unclear	Low	Low	Low	High

	Rofecoxib (12.5 mg/day)										
Bocanegra (1998)	Placebo oral Diclofenac (150 mg/day) Diclofenac (150 mg/day)/misoprostol	572	69	62	Knee and hip	Unclear	Unclear	Low	Low	Low	Low
Bolnot-Delmas (1996)	Placebo oral Piroxicam (20 mg/day)	522	70	60	Knee and hip	Unclear	Unclear	Low	Unclear	Low	Low
Boswell (2008)	Placebo oral Celecoxib (200 mg/day)	649	65	63	Knee	Yes	Unclear	Low	Low	Low	High
Boswell (2008)	Placebo oral Celecoxib (200 mg/day)	1331	68	60	Knee	Yes	Unclear	Low	Low	Low	High
Boureau (2004)	Paracetamol (3000 mg/day) Ibuprofen (1200 mg/day)	222	73	66	Knee and hip	Unclear	Unclear	Low	Low	Low	High
Burch (2007)	Placebo oral Tramadol (275 mg/day)	646	63	62	Knee	Unclear	Low	Low	Low	Low	High
Busquier (1997)	Aceclofenac (200 mg/day) Piroxicam (20 mg/day)	240	91	59	Knee	Unclear	Unclear	Low	Low	Low	High
Cannon (2000)	Diclofenac (150 mg/day) Rofecoxib (12.5 mg/day) Rofecoxib (25 mg/day)	784	67	64	Knee and hip	Unclear	Unclear	Low	Low	Low	Low
Cardoe (1986)	Naproxen (1000 mg/day) Isoxicam (200 mg/day)	230	68	63	Knee and hip	Unclear	Unclear	Low	Low	Low	High
Caruso (1987)	Placebo oral Naproxen (750 mg/day)	734	74	59	Knee and hip	No	Unclear	Low	Low	Low	High
Clegg (2006)	Placebo oral Celecoxib (200 mg/day)	1583	64	59	Knee	Yes	Unclear	Low	Low	Low	Low
Conaghan (2011)	Codeine (127.2 mg/day) Buprenorphine transdermal (.30 mg/day)	220	66	71	Knee and hip	Yes	Unclear	High	High	High	High
Conaghan (2013)	Placebo oral Placebo topical Celecoxib (200 mg/day) Ketoprofen topical (200 mg/day)	928	67	61	Knee	Yes	Unclear	High	High	High	High
Conaghan (2013)	Placebo topical Ketoprofen topical (100 mg/day)	471	64	61	Knee	Yes	Unclear	High	High	High	Low
Dahlberg (2009)	Diclofenac (100 mg/day) Celecoxib (200 mg/day)	925	69	71	Knee and hip	Yes	Low	Low	Low	Low	High
Day (2000)	Placebo oral Ibuprofen (2400 mg/day) Rofecoxib (12.5 mg/day) Rofecoxib (25 mg/day)	809	80	64	Knee and hip	No	Unclear	Low	Low	Low	Low
DeLemos (2011)	Placebo oral	1011	63	60	Knee	Yes	Unclear	Low	Low	Low	High

	Celecoxib (200 mg/day) Tramadol (100 mg/day) Tramadol (200 mg/day) Tramadol (300 mg/day)				and hip						
Dickson (1991)	Ibuprofen (1200 mg/day) Piroxicam topical (15 mg/day)	235	66	62	Knee	Unclear	Unclear	Low	Low	Low	High
Doherty (1992)	Diclofenac (117 mg/day) Diclofenac (116 mg/day)/misoprostol	455	63	62	Knee and hip	Unclear	Unclear	Low	Low	Low	High
Doherty (2011)	Paracetamol (3000 mg/day) Ibuprofen (1200 mg/day)	892	49	61	Knee	Yes	Unclear	Low	Low	Low	High
Eberl (1982)	Indomethacin (150 mg/day) Isoxicam (200 mg/day)	246	63	63	Knee and hip	Unclear	Unclear	Low	Low	Low	Unclear
Ehrich (2001)	Placebo oral Rofecoxib (5 mg/day) Rofecoxib (12.5 mg/day) Rofecoxib (25 mg/day) Rofecoxib (50 mg/day)	672	71	62	Knee and hip	Yes	Unclear	Low	Low	Low	High
Ekman (2014)	Placebo oral Naproxen (1000 mg/day)	849	63	61	Knee and hip	Yes	Unclear	Low	Low	Low	High
Ekman (2014)	Placebo oral Naproxen (1000 mg/day)	832	60	61	Knee	Yes	Unclear	Low	Low	Low	High
Emery (2008)	Celecoxib (200 mg/day) Diclofenac (150 mg/day)	249	22	64	Hip	Yes	Unclear	Low	Low	Low	High
Emkey (2004)	Placebo oral Tramadol (154mg/day) with Paracetamol	307	68	61	Knee and hip	Yes	Unclear	Low	Low	Low	High
Essex (2012)	Celecoxib (200 mg/day) Naproxen (1000 mg/day)	589	66	60	Knee	Unclear	Unclear	Low	Unclear	Low	High
Essex (2012)	Placebo oral Celecoxib (200 mg/day) Naproxen (1000 mg/day)	322	80	58	Knee	Unclear	Unclear	Low	Unclear	Low	High
Essex (2014)	Placebo oral Celecoxib (200 mg/day) Naproxen (1000 mg/day)	318	66	60	Knee	Unclear	Unclear	Low	Low	Low	High
Essex (2016)	Placebo oral Celecoxib (200 mg/day) Naproxen (1000 mg/day)	367	67	65	Knee	Unclear	Unclear	Low	Unclear	Low	High
Etropolski (2011)	Placebo oral Oxycodone (31 mg/day) Tapentadol (192 mg/day) Tapentadol (278 mg/day)	596	58	58	Knee and hip	Yes	Unclear	Low	Low	Low	High

Fioravanti (2002)	Naproxen (1000 mg/day) Nimesulide (800 mg/day)	287	75	66	Knee and hip	Unclear	Low	Low	Low	Low	High
Fishman (2007)	Placebo oral Tramadol (100 mg/day) Tramadol (200 mg/day) Tramadol (300 mg/day)	552	60	61	Knee	Yes	Low	Low	Low	Low	High
Fleischmann (2005)	Placebo oral Celecoxib (200 mg/day) Lumiracoxib (200 mg/day) Lumiracoxib (400 mg/day)	1608	66	61	Knee	Yes	Unclear	Low	Low	Low	High
Fraenkel (2020)	Placebo oral Meloxicam (15 mg/day)	364	13	58	Knee	Yes	Unclear	Low	Low	Low	High
Friedmann (2011)	Placebo oral Oxycodone (55 mg/day)	412	70	58	Knee and hip	Yes	Unclear	Low	Unclear	Low	High
Gana (2006)	Placebo oral Tramadol (100 mg/day) Tramadol (200 mg/day) Tramadol (300 mg/day) Tramadol (400 mg/day)	1020	62	58	Knee and hip	Yes	Low	Low	Low	Low	High
Ghosh (2007)	Placebo oral Diclofenac (75 mg/day) Etoricoxib (90 mg/day)	585	63	55	Knee	Unclear	Unclear	Low	Low	Low	High
Gibofsky (2003)	Placebo oral Celecoxib (200 mg/day) Rofecoxib (25 mg/day)	477	67	63	Knee	Yes	Unclear	Low	Low	Low	High
Gibofsky (2014)	Placebo oral Diclofenac (70 mg/day) Diclofenac (105 mg/day)	305	67	62	Knee and hip	Yes	Unclear	Low	Low	Low	Low
Golden (2004)	Placebo oral Paracetamol (4000 mg/day) Naproxen (550 mg/day)	465	69	61	Knee	Unclear	Unclear	Low	Low	Low	High
Gordo (2017)	Placebo oral Celecoxib (200 mg/day) Ibuprofen (2400 mg/day)	388	73	63	Knee	Unclear	Unclear	Low	Low	Low	High
Goregaonkar (2009)	Diclofenac (150 mg/day) Lornoxicam (16 mg/day)	273	42	48	Knee and hip	No	Low	Low	Low	Low	High
Gottesdiener (2002)	Placebo oral Etoricoxib (5 mg/day) Etoricoxib (10 mg/day) Etoricoxib (30 mg/day) Etoricoxib (60 mg/day)	617	72	61	Knee	Yes	Unclear	Low	Low	Low	Unclear

	Etoricoxib (90 mg/day)										
Hartrick (2009)	Placebo oral Oxycodone (33 mg/day) Tapentadol (189 mg/day) Tapentadol (272 mg/day)	674	48	61	Knee and hip	Yes	Unclear	Low	Low	Low	High
Herrero-Beaumont (2007)	Placebo oral Paracetamol (3000 mg/day)	325	86	64	Knee	Yes	Low	Low	Low	Low	High
Hochberg (2011)	Placebo oral Celecoxib (200 mg/day) Naproxen (1000 mg/day) with esomeprazole	615	63	62	Knee	Yes	Low	Low	Unclear	Low	High
Hochberg (2011)	Placebo oral Celecoxib (200 mg/day) Naproxen (1000 mg/day) with esomeprazole	619	63	62	Knee	Yes	Low	Low	Unclear	Low	High
Hosie (1996)	Diclofenac (100 mg/day) Meloxicam (7.5 mg/day)	336	59	64	Knee and hip	Unclear	Unclear	Low	Low	Low	High
Hosie (1997)	Meloxicam (15 mg/day) Piroxicam (20 mg/day)	455	57	65	Knee and hip	Yes	Unclear	Low	Low	Low	Low
Husby (1986)	Naproxen (750 mg/day) Piroxicam (20 mg/day)	2035	70	67	Knee and hip	Unclear	Unclear	Low	Low	Low	Low
Huskisson (1999)	Diclofenac (150 mg/day) Nimesulide (200 mg/day)	279	65	65	Knee and hip	Unclear	Unclear	Low	Low	Low	Low
James (2010)	Buprenorphine sublingual (.87 mg/day) Buprenorphine transdermal (.30 mg/day)	238	63	64	Knee and hip	Unclear	Unclear	Low	Low	Low	High
Jensen (1994)	Dextropropoxyphene (300 mg/day) Tramadol (300 mg/day)	264	79	67	Knee and hip	Unclear	Unclear	Low	Low	Low	Unclear
Kageyama (1987)	Placebo topical Piroxicam topical (20 mg/day)	246	82	NR	Knee	Unclear	Unclear	Low	Low	Low	Unclear
Karlsson (2009)	Placebo oral Naproxcinod (750 mg/day) Naproxcinod (1500 mg/day) Naproxcinod (2250 mg/day) Rofecoxib (25 mg/day)	543	65	62	Knee and hip	Yes	Unclear	Low	Low	Low	High
Katz (2010)	Placebo oral Morphine (43.5 mg/day) with naltrexone	344	58	55	Knee and hip	Yes	Low	Low	Low	Low	Low
Kennedy (1994)	Diclofenac (150 mg/day)	239	70	64	Knee	Unclear	Unclear	Low	Low	Low	High

	Ketoprofen (200 mg/day)				and hip						
Kivitz (2001)	Placebo oral Ibuprofen (400 mg/day) Oxaprozin (1200 mg/day) Oxaprozin (1800 mg/day)	491	70	60	Knee	Yes	Unclear	Low	Low	Low	Unclear
Kivitz (2001)	Placebo oral Celecoxib (100 mg/day) Celecoxib (200 mg/day) Celecoxib (400 mg/day) Naproxen (1000 mg/day)	1061	66	63	Hip	Yes	Unclear	Low	Low	Low	High
Kivitz (2002)	Placebo oral Naproxen (1000 mg/day) Valdecoxib (5 mg/day) Valdecoxib (10 mg/day) Valdecoxib (20 mg/day)	1019	65	60	Knee	Yes	Unclear	Low	Low	Low	High
Kivitz (2004)	Placebo oral Nabumetone (1000 mg/day) Rofecoxib (12.5 mg/day)	1042	68	63	Knee	Yes	Unclear	Low	Low	Low	Unclear
Kneer (2013)	Placebo topical Ketoprofen topical (50 mg/day) Ketoprofen topical (100 mg/day) Ketoprofen topical (200 mg/day)	867	68	62	Knee	Yes	Unclear	Low	Low	Low	High
Kornasoff (1997)	Aceclofenac (200 mg/day) Naproxen (1000 mg/day)	374	64	61	Knee	Unclear	Unclear	Low	Low	Low	Unclear
Kriegel (2001)	Naproxen (750 mg/day) Nimesulide (200 mg/day)	370	72	65	Knee and hip	Yes	Unclear	Low	Low	Low	Low
Langford (2006)	Placebo transdermal Fentanyl transdermal (.6 mg/day)	416	64	66	Knee and hip	Yes	Low	Low	Low	Low	High
Laws (1990)	Diclofenac (100 mg/day) Nabumetone (1000 mg/day)	243	56	64	Knee and hip	No	Unclear	Low	Low	Low	Unclear
Lee (1985)	Placebo oral Diflunisal (750 mg/day) Diflunisal (1000 mg/day)	422	67	61	Knee	No	Unclear	Unclear	Unclear	Unclear	High
Lee (2017)	Placebo oral Celecoxib (200 mg/day) Polmacoxib (2 mg/day)	362	85	62	Knee and hip	Yes	Low	Low	Low	Low	Low
Lehmann (2005)	Placebo oral Celecoxib (200 mg/day) Lumiracoxib (100 mg/day)	1684	70	62	Knee	Yes	Unclear	Low	Low	Low	Low
Levenstein (1985)	Indomethacin (75 mg/day) Isoxicam (200 mg/day)	309	72	59	Knee and hip	Unclear	Unclear	Low	Low	Low	High

Linden (1996)	Meloxicam (15 mg/day) Piroxicam (20 mg/day)	285	56	67	Hip	Yes	Unclear	Low	Low	Low	Low
Lohmander (2005)	Placebo oral Naproxcinod (1500 mg/day) Naproxen (1000 mg/day)	970	73	59	Knee and hip	Unclear	Unclear	Low	Low	Low	High
Lucker (1994)	Etodolac (600 mg/day) Nimesulide (200 mg/day)	200	67	64	Knee	Unclear	Unclear	Low	Low	Low	High
Lund (1998)	Placebo oral Meloxicam (7.5 mg/day) Meloxicam (15 mg/day)	513	58	68	Knee	Yes	Unclear	Low	Low	Low	Low
Makarowski (1996)	Placebo oral Nabumetone (1500 mg/day) Oxaprozin (1200 mg/day)	347	68	61	Knee	Unclear	Unclear	Low	Low	Low	Unclear
Makarowski (2002)	Placebo oral Naproxen (1000 mg/day) Valdecoxib (5 mg/day) Valdecoxib (10 mg/day)	467	68	62	Hip	Yes	Unclear	Low	Low	Low	High
Malonne (2004)	Placebo oral Tramadol (200 mg/day)	231	72	67	Knee and hip	Unclear	Unclear	Low	Low	Low	High
Matsumoto (2005)	Placebo oral Oxycodone (40 mg/day) Oxymorphone (40 mg/day) Oxymorphone (80 mg/day)	491	60	62	Knee and hip	Yes	Unclear	Low	Low	Low	High
McKenna (2001)	Placebo oral Celecoxib (200 mg/day) Diclofenac (150 mg/day)	600	65	62	Knee	Unclear	Unclear	Low	Low	Low	High
Melo-Gomes (1993)	Diclofenac (100 mg/day)/misoprostol Naproxen (750 mg/day) Piroxicam (20 mg/day)	643	76	60	Knee and hip	Unclear	Unclear	Low	Low	Low	Low
Miceli-Richard (2004)	Placebo oral Paracetamol (4000 mg/day)	779	75	70	Knee	Yes	Unclear	Low	Low	Low	Low
Morgan (2001)	Diclofenac (133 mg/day) Nabumetone (1596 mg/day)	335	70	72	Knee and hip	Unclear	Unclear	Low	Low	Low	High
Mullican (2001)	Codeine (105 mg/day) Tramadol (131 mg/day)	462	62	58	Knee and hip	Yes	Unclear	Low	Low	Low	High
Munera (2010)	Placebo transdermal Buprenorphine transdermal (.30 mg/day)	315	67	61	Knee and hip	Yes	Unclear	Low	Low	Low	High
Myllykangas-Luosujarvi (2002)	Naproxen (1000 mg/day) Rofecoxib (12.5 mg/day)	944	78	62	Knee and hip	No	Unclear	Low	Low	Low	Low

NCT00531427 (2010)	Placebo topical Buprenorphine_Transdermal (.36 mg/day)	570	62	59	Knee	Unclear	Unclear	Low	Unclear	Low	Low
NCT00631319 (2009)	Placebo oral Hydromorphone (34 mg/day)	200	54	56	Knee and hip	Yes	Unclear	Low	Unclear	Low	Low
NCT00832416 (2009)	Placebo oral Tramadol (100 mg/day) Tramadol (200 mg/day) Tramadol (300 mg/day)	565	60	60	Knee	Yes	Unclear	Unclear	Unclear	Unclear	High
NCT00979953 (2010)	Placebo oral Oxycodone (40 mg/day)	408	59	57	Knee	Yes	Unclear	Low	Unclear	Low	High
NCT01430559 (2020)	Placebo oral Meloxicam (15 mg/day)	293	78	NR	Knee	Yes	Unclear	Low	Low	Low	High
NCT01768520 (2019)	Placebo oral Celecoxib (200 mg/day)	338	77	62	Knee	Yes	Unclear	Unclear	Unclear	Unclear	High
NCT01967550 (2015)	Placebo topical Diclofenac topical (160 mg/day)	304	64	65	Knee	Unclear	Unclear	Unclear	Unclear	Unclear	High
NCT02121002 (2021)	Placebo topical Diclofenac topical (160 mg/day)	1176	64	52	Knee	Yes	Unclear	Low	Low	Low	High
NCT02596451 (2017)	Placebo topical Diclofenac topical (160 mg/day)	1164	63	56	Knee	Unclear	Unclear	Low	Low	Low	High
NCT02913521 (2021)	Placebo topical Diclofenac topical (160 mg/day)	934	62	57	Knee	Unclear	Unclear	Low	Low	Low	High
Niethard (2005)	Placebo topical Diclofenac topical (160 mg/day)	238	63	66	Knee	Yes	Low	Low	Low	Low	High
Novartis (2002)	Placebo oral Lumiracoxib (400 mg/day) Rofecoxib (25 mg/day)	511	NR	NR	Hip	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Novartis [CCOX189A2303] (2002)	Placebo oral Celecoxib (400 mg/day) Lumiracoxib (200 mg/day) Lumiracoxib (400 mg/day)	408	59	65	Knee	Yes	Unclear	Low	Low	Low	Low
Pareek (2006)	Diclofenac (150 mg/day) Aceclofenac (200 mg/day)	247	67	53	Knee	No	Low	Low	Low	Low	High
Pareek (2011)	Diclofenac (150 mg/day) Zaltoprofen (240 mg/day)	213	59	53	Knee	Yes	Unclear	Low	Low	Low	High
Pareek (2013)	Aceclofenac (200 mg/day) Diclofenac (150 mg/day)	591	66	53	Knee	Yes	Unclear	Low	Low	Low	High
Paul (2009)	Placebo oral Aceclofenac (200 mg/day) Nabumetone (1500 mg/day)	423	55	53	Knee	Unclear	Unclear	Low	Low	Low	High
Paulsen (1991)	Etodolac (600 mg/day) Piroxicam (20 mg/day)	220	77	58	Knee	Unclear	Unclear	Low	Low	Low	High

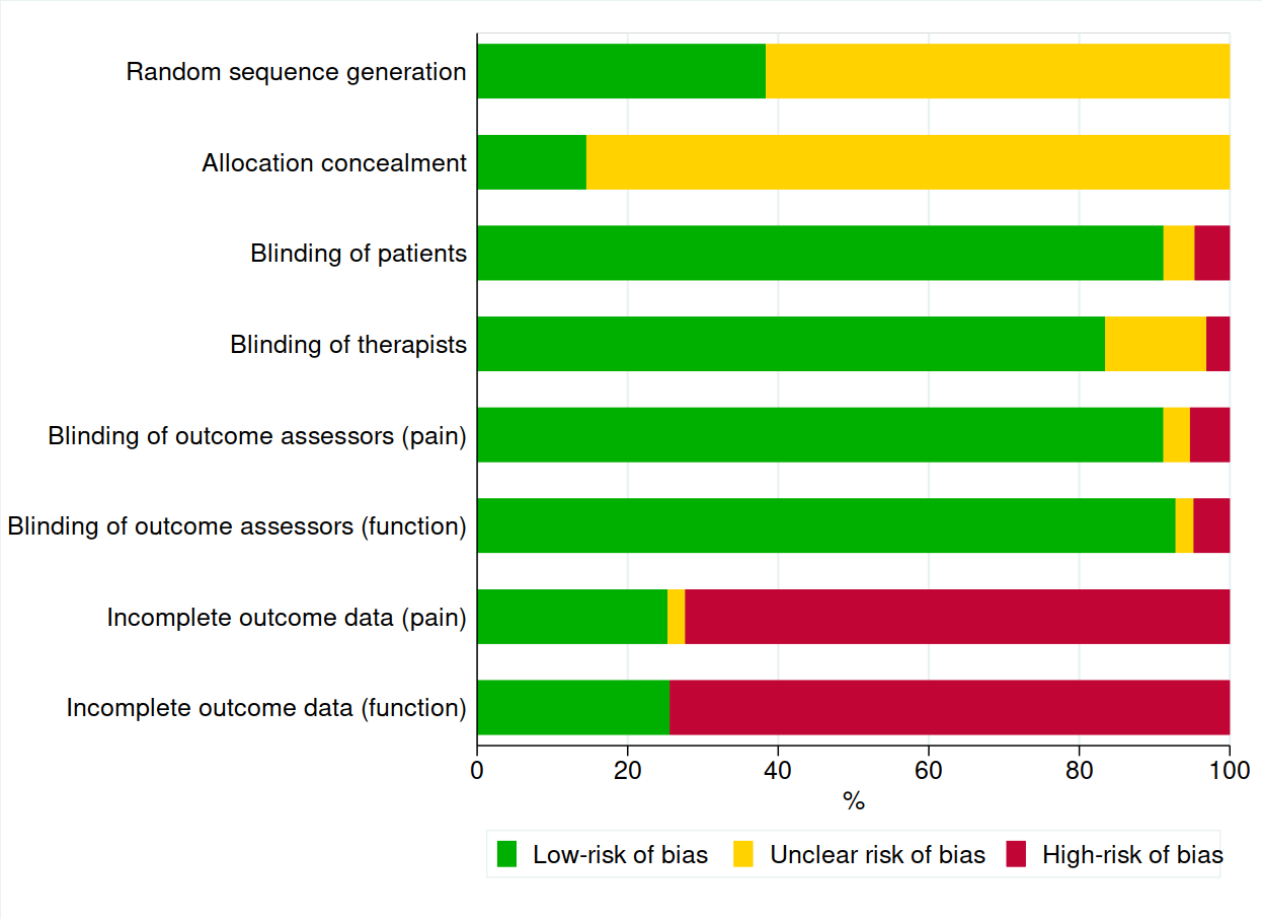
Petrick (1983)	Placebo oral Meclofenamate (300 mg/day)	417	69	65	Knee and hip	Unclear	Unclear	Low	Low	Low	Low
Pincus (2001)	Paracetamol (4000 mg/day) Diclofenac (150 mg/day)/misoprostol	227	70	61	Knee and hip	Unclear	Unclear	Low	Low	Low	High
Pincus (2004)	Placebo oral Paracetamol (4000 mg/day) Celecoxib (200 mg/day)	524	63	63	Knee and hip	Yes	Unclear	Low	Low	Low	Low
Pincus (2004)	Placebo oral Paracetamol (4000 mg/day) Celecoxib (200 mg/day)	556	66	63	Knee and hip	Yes	Unclear	Low	Low	Low	Low
Prior (2014)	Placebo oral Paracetamol (3900 mg/day)	542	74	62	Knee and hip	Unclear	Unclear	Low	Low	Low	Low
Puopolo (2007)	Placebo oral Etoricoxib (30 mg/day) Ibuprofen (2400 mg/day)	548	76	63	Knee and hip	Unclear	Low	Low	Low	Low	High
Rauck (2013)	Placebo oral Hydromorphone (8 mg/day) Hydromorphone (16 mg/day)	990	63	60	Knee and hip	Yes	Unclear	Low	Low	Low	High
Reed (2018)	Placebo oral Paracetamol (3990 mg/day) Paracetamol (4000 mg/day)	708	60	61	Knee and hip	Yes	Low	Low	Low	Low	High
Reginster (2007)	Placebo oral Etoricoxib (60 mg/day) Naproxen (1000 mg/day)	997	72	63	Knee and hip	Unclear	Unclear	Low	Low	Low	High
Reginster (2017)	Placebo oral Celecoxib (200 mg/day)	604	77	65	Knee	No	Unclear	Low	Unclear	Low	High
Rogind (1997)	Etodolac (600 mg/day) Piroxicam (20 mg/day)	271	79	67	Knee and hip	Unclear	Unclear	Low	Low	Low	High
Roth (2004)	Placebo topical Diclofenac_Topical (77.04 mg/day)	326	68	64	Knee	Unclear	Low	Low	Low	Low	High
Rother (2007)	Placebo oral and topical Celecoxib (200 mg/day) Ketoprofen topical (220 mg/day)	397	60	63	Knee	Unclear	Low	Low	Low	Low	Low
Rother (2013)	Placebo topical Ketoprofen topical (200 mg/day)	555	62	62	Knee	Yes	Unclear	Low	Low	Low	Low
Saag (2000)	Placebo oral Ibuprofen (2400 mg/day) Rofecoxib (12.5 mg/day) Rofecoxib (25 mg/day)	736	74	61	Knee and hip	Unclear	Unclear	Low	Low	Low	Low
Saag (2000)	Diclofenac (150 mg/day)	693	80	62	Knee	Unclear	Unclear	Low	Low	Low	Low

	Rofecoxib (12.5 mg/day) Rofecoxib (25 mg/day)				and hip							
Schiff (1996)	Placebo oral Naproxen (1000 mg/day)	347	69	64	Knee	Unclear	Unclear	Low	Low	Low	Unclear
Schiff (2004)	Placebo oral Ibuprofen (1200 mg/day) Naproxen (550 mg/day)	461	69	61	Knee	Unclear	Unclear	Low	Low	Low	High
Schnitzer (1999)	Placebo oral Tramadol (200 mg/day)	240	61	61	Knee	Unclear	Unclear	Low	Low	Low	Unclear
Schnitzer (2005)	Placebo oral Naproxcinod (250 mg/day) Naproxcinod (750 mg/day) Naproxcinod (1500 mg/day) Naproxen (1000 mg/day) Rofecoxib (25 mg/day)	672	62	60	Knee	Yes	Unclear	Low	Low	Low	High
Schnitzer (2005)	Paracetamol (4000 mg/day) Celecoxib (200 mg/day) Rofecoxib (12.5 mg/day) Rofecoxib (25 mg/day)	1578	67	62	Knee	Yes	Unclear	Low	Low	Low	High
Schnitzer (2009)	Paracetamol (3900 mg/day) Rofecoxib (12.5 mg/day) Rofecoxib (25 mg/day)	403	58	60	Knee	Unclear	Unclear	Low	Low	Low	High
Schnitzer (2010)	Placebo oral Naproxcinod (750 mg/day) Naproxcinod (1500 mg/day) Naproxen (1000 mg/day)	918	70	61	Knee	Yes	Unclear	Low	Unclear	Low	High
Schnitzer (2011)	Placebo oral Naproxcinod (750 mg/day) Naproxcinod (1500 mg/day) Naproxen (1000 mg/day)	1020	70	60	Knee	Yes	Unclear	Low	Unclear	Low	High
Schnitzer (2011)	Placebo oral Celecoxib (200 mg/day) Lumiracoxib (100 mg/day)	1262	62	62	Hip	Yes	Unclear	Low	Low	Low	Low
Schnitzer (2015)	Celecoxib (200 mg/day) Naproxen (1000 mg/day)	1424	NR	NR	Knee and hip	Yes	Unclear	Low	Low	Low	High
Scott (2000)	Diclofenac (100 mg/day) Nabumetone (1500 mg/day)	399	57	63	Knee and hip	Unclear	Unclear	Low	Low	Low	High
Scott (2000)	Nabumetone (1831 mg/day) Piroxicam (25.5 mg/day)	295	48	63	Knee and hip	Unclear	Unclear	Low	Low	Low	High
Scott (2000)	Placebo oral Indomethacin (75 mg/day) Tiaprofenic acid (600 mg/day)	812	70	61	Knee	Unclear	Unclear	High	Low	High	Unclear

Serrie (2017)	Placebo oral Oxycodone (54.1 mg/day) Tapentadol (315.2 mg/day)	990	71	62	Knee	Yes	Low	Low	Low	Low	High
Shannon (2005)	Placebo topical Buprenorphine transdermal (.30 mg/day)	327	67	61	Knee and hip	Unclear	Unclear	Low	Unclear	Unclear	High
Sheldon (2005)	Placebo oral Celecoxib (200 mg/day) Lumiracoxib (100 mg/day)	1551	62	61	Knee	Yes	Unclear	Low	Low	Low	Low
Silverfield (2002)	Placebo oral Tramadol (225 mg/day) with Paracetamol	308	72	60	Knee and hip	Yes	Unclear	Low	Low	Low	High
Simon (2009)	Placebo oral Diclofenac_Topical (77.04 mg/day) Diclofenac (100 mg/day) Placebo topical	775	62	62	Knee	Yes	Unclear	Low	Low	Low	High
Smugar (2006)	Placebo oral Celecoxib (200 mg/day) Rofecoxib (12.5 mg/day) Rofecoxib (25 mg/day)	1521	68	62	Knee and hip	Yes	Unclear	Low	Low	Low	High
Smugar (2006)	Placebo oral Celecoxib (200 mg/day) Rofecoxib (25 mg/day)	1082	66	62	Knee and hip	Yes	Unclear	Low	Low	Low	High
Sowers (2005)	Naproxen (1000 mg/day) Celecoxib (200 mg/day) Rofecoxib (25 mg/day)	404	60	63	Knee and hip	Yes	Unclear	Low	Low	Low	High
Spierings (2013)	Placebo oral Oxycodone (25.8 mg/day)	614	62	57	Knee and hip	Yes	Unclear	High	Unclear	High	High
Tannenbaum (2004)	Placebo oral Celecoxib (200 mg/day) Lumiracoxib (200 mg/day) Lumiracoxib (400 mg/day)	1702	69	64	Knee	Yes	Unclear	Low	Low	Low	Low
Temple (2006)	Paracetamol (4000 mg/day) Naproxen (750 mg/day)	581	68	59	Knee and hip	Unclear	Unclear	Low	Low	Low	Unclear
The (1997)	Diclofenac (100 mg/day) Meloxicam (15 mg/day)	258	81	71	Knee	Yes	Unclear	Low	Low	Low	Low
Torri (1994)	Aceclofenac (200 mg/day) Piroxicam (20 mg/day)	205	62	57	Knee	Unclear	Unclear	Low	Low	Low	High
Tugwell (2004)	Diclofenac (150 mg/day) Diclofenac topical (75 mg/day)	622	57	64	Knee	Yes	Low	Low	Low	Low	High
Underwood (2008)	Ibuprofen (1200 mg/day)	282	54	63	Knee	Yes	Low	High	High	High	High

	Ibuprofen topical (1500mg/day)										
Vojtassak (2011)	Placebo oral Hydromorphone (13.9 mg/day)	288	72	67	Knee and hip	Unclear	Low	Low	Low	Low	High
Wadsworth (2016)	Placebo topical Diclofenac topical (80.8 mg/day)	260	67	61	Knee	Yes	Low	Unclear	Unclear	Unclear	High
Ward (1995)	Aceclofenac (200 mg/day) Diclofenac (150 mg/day)	397	56	62	Knee	Yes	Unclear	Low	Low	Low	Unclear
Weaver (1995)	Placebo oral Nabumetone (1000 mg/day) Oxaprozin (1200 mg/day)	328	71	63	Knee	Yes	Unclear	Low	Low	Low	Low
Weaver (2006)	Placebo oral Nabumetone (1000 mg/day) Rofecoxib (12.5 mg/day)	978	70	63	Knee	Yes	Unclear	Low	Low	Low	Unclear
Wiesenhutter (2005)	Placebo oral Etoricoxib (30 mg/day) Ibuprofen (2400 mg/day)	528	70	62	Knee and hip	Unclear	Unclear	Low	Low	Low	High
Williams (1989)	Placebo oral Etodolac (600 mg/day)	210	55	63	Knee and hip	Unclear	Unclear	Low	Low	Low	High
Williams (2000)	Placebo oral Celecoxib (200 mg/day)	686	66	63	Knee	Yes	Unclear	Low	Low	Low	High
Williams (2001)	Placebo oral Celecoxib (200 mg/day)	718	70	62	Knee	Yes	Unclear	Low	Low	Low	High
Wittenberg (2006)	Placebo oral Celecoxib (400 mg/day) Lumiracoxib (400 mg/day)	364	58	65	Knee	Unclear	Unclear	Low	Low	Low	Low
Yataba (2017)	Placebo topical S-Flurbiprofen (10mg/day) S-Flurbiprofen (20mg/day) S-Flurbiprofen (40mg/day)	509	84	67	Knee	Yes	Unclear	Low	Low	Low	High
Yocum (2000)	Placebo oral Diclofenac (100 mg/day) Meloxicam (3.75 mg/day) Meloxicam (7.5 mg/day) Meloxicam (15 mg/day)	779	65	63	Knee and hip	Yes	Unclear	Low	Low	Low	High
Yoo (2014)	Celecoxib (200 mg/day) Etoricoxib (30 mg/day)	239	90	63	Knee	Unclear	Unclear	Low	Low	Low	High
Young (1983)	Indomethacin (105 mg/day) Indomethacin (210 mg/day)	223	59	62	Hip	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Zacher (2003)	Diclofenac (150 mg/day) Etoricoxib (60 mg/day)	516	80	63	Knee and hip	Unclear	Unclear	Low	Low	Low	High

Web-appendix 12. Summary risk of bias



Web-appendix 13. Dose-response analysis

Intervention	P for linear dose-effect*
Paracetamol	
Paracetamol <2000mg	0.80
Paracetamol 3000mg	
Paracetamol 3900-4000mg	
NSAIDS - Oral	
Aceclofenac 200mg	-
Celecoxib 100mg	0.030
Celecoxib 200mg	
Celecoxib 400mg	
Diclofenac ≤75mg	0.17
Diclofenac 100-105mg	
Diclofenac 114-133mg	
Diclofenac 150mg	
Diflunisal 750mg	0.69
Diflunisal 1000mg	
Etodolac 600mg	-
Etoricoxib 5-10mg	0.014
Etoricoxib 30mg	
Etoricoxib 60mg	
Etoricoxib 90mg	
Ibuprofen 1200mg	0.44
Ibuprofen 1500-1600mg	
Ibuprofen 2400mg	
Isoxicam 200mg	0.98
Isoxicam 300mg	
Ketoprofen 200mg	-
Lornoxicam 16mg	-
Lumiracoxib 100mg	0.95
Lumiracoxib 200mg	
Lumiracoxib 400mg	
Meloxicam ≤10mg	0.23
Meloxicam 15mg	
Nabumetone 1000mg	0.56
Nabumetone 1500-1830mg	
Naproxcinod 250mg	0.015
Naproxcinod 750mg	
Naproxcinod 1500mg	
Naproxcinod 2250mg	

Naproxen ≤750mg	0.89
Naproxen 1000mg	
Nimesulide 200mg	0.75
Nimesulide 800mg	
Piroxicam 20mg	0.98
Piroxicam 25.5mg	
Polmacoxib 2mg	-
Rofecoxib 5mg	0.44
Rofecoxib 12.5mg	
Rofecoxib 25mg	
Rofecoxib 50mg	
Tiaprofenic acid 600mg	-
Valdecoxib 5mg	0.68
Valdecoxib 10mg	
Valdecoxib 20mg	
Zaltoprofen 240mg	-
NSAIDS - Topical	
Diclofenac topical 70-81mg	0.63
Diclofenac topical 140-160mg	
S-flurbiprofen plaster ≤20mg	0.63
S-flurbiprofen plaster 40mg	
Ketoprofen topical 50mg	0.89
Ketoprofen topical 100mg	
Ketoprofen topical 200-220mg	
Piroxicam topical 15mg	-
Opioids	
Buprenorphine sublingual 0.87mg	-
Buprenorphine transdermal 0.30-0.36mg	-
Codeine 100-130mg	-
Dextropropoxyphene 300mg	-
Fentanyl transdermal 0.6mg	-
Hydromorphone 8mg	0.54
Hydromorphone 13.9-16mg	
Hydromorphone 34mg	
Morphine with naltrexone 43.5mg	-
Oxycodone ≤40mg	0.66
Oxycodone ≥48mg	
Oxymorphone 40mg	0.80
Oxymorphone 80mg	
Tapentadol <316mg	-
Tramadol 100-131mg	0.035

Tramadol 200mg	
Tramadol 275-300mg	
Tramadol 400mg	
Tramadol/paracetamol 154-225mg	-
Placebos	
Placebo topical	-
Placebo oral and topical	-

*Lower p-values indicate stronger evidence of a linear association between drug dose and treatment effects (i.e. association between higher doses and larger treatment effects).

Web-appendix 14. Differences in pain intensity expressed as effect sizes comparing each intervention to oral placebo over time

	Effect size (95% CrI)/Pr(MID)		
	Week 1	Week 6	Week 12
Paracetamol			
Paracetamol <2000mg	-0.05 (-0.92 to 0.79) / 23.8	-0.07 (-0.56 to 0.44) / 11.8	-0.05 (-0.30 to 0.20) / 0.6
Paracetamol 3000mg	-0.25 (-0.65 to 0.16) / 28.4	-0.21 (-0.81 to 0.39) / 29.7	-0.17 (-0.69 to 0.34) / 22.9
Paracetamol 3900-4000mg	-0.14 (-0.28 to -0.01) / 0.1	-0.15 (-0.25 to -0.05) / 0.0	-0.12 (-0.24 to 0.01) / 0.0
NSAIDs - Oral			
Aceclofenac 200mg	-0.61 (-0.87 to -0.35) / 96.4	-0.56 (-0.78 to -0.34) / 95.1	-0.56 (-0.78 to -0.33) / 95.1
Celecoxib 100mg	-0.11 (-0.43 to 0.21) / 5.4	-0.10 (-0.26 to 0.06) / 0.0	-0.07 (-0.23 to 0.09) / 0.0
Celecoxib 200mg	-0.34 (-0.43 to -0.26) / 27.5	-0.35 (-0.40 to -0.30) / 20.0	-0.32 (-0.37 to -0.26) / 2.5
Celecoxib 400mg	-0.39 (-0.58 to -0.20) / 58.1	-0.32 (-0.47 to -0.16) / 24.7	-0.26 (-0.41 to -0.10) / 7.5
Diclofenac ≤75mg	-0.59 (-0.93 to -0.23) / 88.2	-0.42 (-0.65 to -0.18) / 65.1	-0.36 (-0.59 to -0.14) / 46.7
Diclofenac 100-105mg	-0.53 (-0.80 to -0.26) / 87.8	-0.47 (-0.63 to -0.31) / 88.4	-0.42 (-0.54 to -0.30) / 76.8
Diclofenac 114-133mg	-0.66 (-1.90 to 0.56) / 68.2	-0.64 (-1.40 to 0.11) / 75.9	-0.65 (-1.06 to -0.25) / 91.2
Diclofenac 150mg	-0.59 (-0.77 to -0.40) / 98.7	-0.56 (-0.68 to -0.45) / 99.9	-0.53 (-0.65 to -0.40) / 99.4
Diflunisal 750mg	-0.45 (-1.18 to 0.29) / 58.4	-0.33 (-0.69 to 0.03) / 41.2	-0.33 (-0.92 to 0.27) / 44.7
Diflunisal 1000mg	-0.42 (-1.17 to 0.32) / 55.4	-0.40 (-0.77 to -0.04) / 57.0	-0.40 (-1.01 to 0.21) / 54.2
Etodolac 600mg	-0.89 (-1.14 to -0.64) / 100.0	-0.57 (-0.83 to -0.31) / 93.1	-0.44 (-0.69 to -0.18) / 69.2
Etoricoxib 5-10mg	-0.18 (-0.42 to 0.06) / 5.4	-0.21 (-0.43 to 0.02) / 7.5	-0.16 (-0.54 to 0.22) / 13.8
Etoricoxib 30mg	-0.51 (-0.69 to -0.33) / 93.5	-0.48 (-0.63 to -0.34) / 94.3	-0.44 (-0.56 to -0.32) / 86.0
Etoricoxib 60mg	-0.70 (-0.92 to -0.48) / 99.9	-0.65 (-0.82 to -0.48) / 99.9	-0.46 (-0.63 to -0.29) / 84.6
Etoricoxib 90mg	-0.89 (-1.15 to -0.62) / 100.0	-0.84 (-1.09 to -0.59) / 100.0	-0.88 (-1.27 to -0.49) / 99.5
Ibuprofen 1200mg	-0.50 (-0.84 to -0.17) / 78.5	-0.31 (-0.92 to 0.30) / 42.1	-0.30 (-0.85 to 0.26) / 39.9
Ibuprofen 2400mg	-0.51 (-0.73 to -0.29) / 89.0	-0.37 (-0.50 to -0.25) / 52.8	-0.32 (-0.47 to -0.16) / 24.6
Indomethacin 75mg	-0.59 (-1.07 to -0.11) / 81.2	-0.30 (-0.74 to 0.14) / 37.6	-0.20 (-0.69 to 0.30) / 23.9
Isoxicam 200mg	-0.45 (-0.91 to 0.02) / 62.5	-0.59 (-1.08 to -0.09) / 80.6	-0.47 (-1.09 to 0.14) / 63.2
Ketoprofen 200mg	-0.59 (-0.96 to -0.23) / 88.6	-0.60 (-1.06 to -0.13) / 83.0	-0.63 (-1.01 to -0.25) / 91.5
Lornoxicam 16mg	-0.74 (-1.34 to -0.14) / 88.9	-0.73 (-1.32 to -0.14) / 88.1	-0.70 (-1.45 to 0.06) / 80.1
Lumiracoxib 100mg	-0.35 (-0.62 to -0.08) / 43.1	-0.33 (-0.52 to -0.13) / 33.8	-0.31 (-0.43 to -0.19) / 15.3
Lumiracoxib 200mg	-0.40 (-0.62 to -0.18) / 59.6	-0.36 (-0.54 to -0.19) / 46.1	-0.33 (-0.48 to -0.18) / 29.4
Lumiracoxib 400mg	-0.45 (-0.64 to -0.26) / 78.8	-0.39 (-0.59 to -0.18) / 55.9	-0.33 (-0.46 to -0.20) / 26.0
Meclofenamate sodium 300mg	-0.43 (-0.97 to 0.11) / 59.0	-0.31 (-0.88 to 0.25) / 41.8	-0.31 (-1.05 to 0.43) / 43.8
Meloxicam ≤10mg	-0.28 (-0.51 to -0.05) / 22.5	-0.33 (-0.52 to -0.13) / 33.9	-0.27 (-0.42 to -0.12) / 9.8
Meloxicam 15mg	-0.33 (-0.54 to -0.12) / 36.3	-0.48 (-0.66 to -0.30) / 88.2	-0.44 (-0.59 to -0.29) / 82.2
Nabumetone 1000mg	-0.24 (-0.42 to -0.05) / 7.8	-0.22 (-0.37 to -0.08) / 2.3	-0.19 (-0.48 to 0.11) / 10.7
Nabumetone 1500-1831mg	-0.43 (-1.20 to 0.34) / 56.3	-0.41 (-0.89 to 0.08) / 56.3	-0.42 (-0.71 to -0.13) / 62.7

Naproxcinod 250mg	-0.02 (-0.28 to 0.24) / 0.3	0.04 (-0.21 to 0.29) / 0.1	0.08 (-0.37 to 0.53) / 2.6
Naproxcinod 750mg	-0.40 (-0.57 to -0.23) / 62.9	-0.31 (-0.43 to -0.19) / 16.6	-0.28 (-0.43 to -0.13) / 11.0
Naproxcinod 1500mg	-0.50 (-0.66 to -0.35) / 95.2	-0.44 (-0.54 to -0.34) / 92.2	-0.38 (-0.51 to -0.26) / 57.2
Naproxcinod 2250mg	-0.58 (-0.84 to -0.32) / 94.1	-0.47 (-0.73 to -0.22) / 77.9	-0.45 (-0.90 to 0.02) / 62.5
Naproxen ≤750mg	-0.43 (-0.64 to -0.22) / 71.4	-0.38 (-0.63 to -0.13) / 52.3	-0.37 (-0.59 to -0.15) / 51.4
Naproxen 1000mg	-0.42 (-0.54 to -0.31) / 81.7	-0.39 (-0.45 to -0.32) / 68.1	-0.32 (-0.39 to -0.25) / 7.0
Nimesulide 200mg	-0.54 (-0.89 to -0.20) / 84.4	-0.35 (-0.65 to -0.06) / 45.7	-0.26 (-0.49 to -0.03) / 16.9
Nimesulide 800mg	-0.50 (-0.83 to -0.17) / 78.6	-0.44 (-0.93 to 0.05) / 61.0	-0.37 (-0.70 to -0.04) / 49.5
Oxaprozin 1200mg	-0.50 (-0.78 to -0.21) / 81.9	-0.61 (-0.89 to -0.32) / 94.6	-0.59 (-1.11 to -0.08) / 79.4
Piroxicam 20mg	-0.53 (-0.72 to -0.33) / 94.4	-0.48 (-0.67 to -0.28) / 86.4	-0.49 (-0.67 to -0.30) / 88.6
Piroxicam 25.5mg	-0.55 (-1.88 to 0.81) / 60.0	-0.53 (-1.43 to 0.37) / 63.2	-0.53 (-1.19 to 0.12) / 68.8
Polmacoxib 2mg	-0.32 (-0.94 to 0.32) / 43.4	-0.28 (-0.55 to -0.02) / 24.9	-0.26 (-0.75 to 0.25) / 33.1
Rofecoxib 5mg	-0.36 (-1.08 to 0.35) / 49.0	-0.34 (-0.60 to -0.09) / 42.2	-0.32 (-0.79 to 0.16) / 41.5
Rofecoxib 12.5mg	-0.42 (-0.54 to -0.30) / 79.1	-0.41 (-0.49 to -0.33) / 86.3	-0.38 (-0.51 to -0.26) / 58.4
Rofecoxib 25mg	-0.53 (-0.65 to -0.40) / 99.4	-0.48 (-0.55 to -0.40) / 99.6	-0.45 (-0.56 to -0.34) / 92.4
Rofecoxib 50mg	-0.79 (-1.51 to -0.07) / 87.2	-0.77 (-1.05 to -0.49) / 99.8	-0.75 (-1.23 to -0.27) / 93.9
Tiaprofenic acid 600mg	-0.39 (-1.06 to 0.28) / 52.0	-0.27 (-0.74 to 0.22) / 33.5	-0.24 (-0.76 to 0.29) / 30.8
Tolfenamic acid 600mg	-0.69 (-1.12 to -0.27) / 93.2	-0.65 (-1.45 to 0.13) / 76.0	-0.62 (-1.51 to 0.28) / 70.3
Valdecoxib 5mg	-0.26 (-0.61 to 0.08) / 27.4	-0.29 (-0.47 to -0.11) / 18.8	-0.26 (-0.44 to -0.08) / 11.7
Valdecoxib 10mg	-0.36 (-0.71 to -0.03) / 48.7	-0.32 (-0.50 to -0.14) / 29.4	-0.28 (-0.46 to -0.10) / 16.7
Valdecoxib 20mg	-0.42 (-0.87 to 0.04) / 58.2	-0.37 (-0.59 to -0.14) / 48.5	-0.32 (-0.52 to -0.12) / 31.1
Zaltoprofen 240mg	-0.72 (-1.10 to -0.34) / 96.6	-0.78 (-1.39 to -0.17) / 90.7	-0.75 (-1.53 to 0.02) / 83.6
NSAIDs - Topical			
Diclofenac topical 70-81mg	-0.43 (-0.77 to -0.08) / 63.1	-0.54 (-0.77 to -0.31) / 92.3	-0.44 (-0.60 to -0.27) / 78.9
Diclofenac topical 140-160mg	-0.35 (-0.66 to -0.02) / 44.0	-0.61 (-0.87 to -0.35) / 96.3	-0.51 (-0.71 to -0.31) / 91.9
S-flurbiprofen plaster ≤20mg	-0.20 (-0.60 to 0.20) / 20.6	-0.25 (-0.92 to 0.42) / 36.2	-0.19 (-0.94 to 0.62) / 32.8
S-flurbiprofen plaster 40mg	-0.30 (-0.73 to 0.13) / 38.0	-0.41 (-1.20 to 0.37) / 53.9	-0.35 (-1.24 to 0.58) / 48.4
Ibuprofen topical 1500mg	-0.38 (-1.41 to 0.64) / 50.9	-0.19 (-1.03 to 0.66) / 33.7	-0.18 (-0.80 to 0.44) / 27.2
Ketoprofen topical 50mg	-0.16 (-1.00 to 0.67) / 31.3	-0.15 (-0.64 to 0.33) / 18.7	-0.10 (-0.35 to 0.16) / 1.9
Ketoprofen topical 100mg	-0.48 (-1.01 to 0.04) / 65.4	-0.22 (-0.49 to 0.06) / 14.1	-0.20 (-0.42 to 0.02) / 6.3
Ketoprofen topical 200-220mg	-0.17 (-0.51 to 0.18) / 12.0	-0.23 (-0.39 to -0.06) / 4.4	-0.19 (-0.36 to -0.02) / 2.0
Piroxicam topical 15mg	0.19 (-0.63 to 1.03) / 9.0	0.39 (-0.49 to 1.25) / 4.3	0.40 (-0.54 to 1.33) / 5.6
Opioids			
Buprenorphine sublingual 0.87mg	-0.19 (-0.75 to 0.37) / 26.3	-0.35 (-1.39 to 0.69) / 48.7	-0.34 (-1.42 to 0.76) / 47.8
Buprenorphine transdermal 0.28-0.36mg	-0.19 (-0.51 to 0.13) / 13.9	-0.36 (-0.73 to 0.01) / 47.9	-0.35 (-0.61 to -0.08) / 43.5
Codeine 105-127mg	-0.04 (-0.33 to 0.25) / 1.3	-0.19 (-0.62 to 0.24) / 19.9	-0.21 (-0.58 to 0.16) / 19.9
Fentanyl transdermal 0.6mg	-0.36 (-0.76 to 0.04) / 47.8	-0.31 (-0.69 to 0.07) / 37.6	-0.24 (-0.85 to 0.37) / 33.9
Hydromorphone 8mg	-0.04 (-0.88 to 0.83) / 21.7	-0.01 (-0.53 to 0.50) / 8.7	-0.03 (-0.26 to 0.21) / 0.2

Hydromorphone 13.9-16mg	-0.20 (-0.49 to 0.09) / 12.3	-0.16 (-0.51 to 0.18) / 12.0	-0.19 (-0.39 to -0.00) / 4.0
Hydromorphone 34mg	-0.00 (-0.99 to 0.98) / 23.4	-0.00 (-0.61 to 0.60) / 11.6	-0.00 (-0.34 to 0.33) / 1.6
Morphine with naltrexone 43.5mg	-0.25 (-1.21 to 0.71) / 40.2	-0.25 (-0.82 to 0.32) / 34.1	-0.24 (-0.53 to 0.05) / 19.8
Oxycodone ≤40mg	-0.08 (-0.42 to 0.27) / 4.9	-0.09 (-0.41 to 0.22) / 4.5	-0.03 (-0.29 to 0.24) / 0.6
Oxycodone ≥48mg	-0.26 (-0.43 to -0.08) / 10.1	-0.17 (-0.33 to -0.01) / 0.9	-0.13 (-0.28 to 0.02) / 0.1
Oxymorphone 40mg	-0.22 (-0.88 to 0.45) / 32.9	-0.23 (-0.77 to 0.30) / 31.1	-0.21 (-0.86 to 0.46) / 31.2
Oxymorphone 80mg	-0.30 (-0.95 to 0.37) / 41.6	-0.32 (-0.86 to 0.22) / 42.3	-0.29 (-0.95 to 0.38) / 40.3
Tapentadol <316mg	-0.13 (-0.31 to 0.04) / 0.5	-0.34 (-0.50 to -0.17) / 33.9	-0.33 (-0.49 to -0.18) / 31.9
Tramadol 100-131mg	-0.12 (-0.29 to 0.04) / 0.2	-0.12 (-0.25 to 0.01) / 0.0	-0.07 (-0.21 to 0.06) / 0.0
Tramadol 200mg	-0.26 (-0.41 to -0.11) / 7.9	-0.13 (-0.26 to 0.00) / 0.0	-0.12 (-0.25 to 0.01) / 0.0
Tramadol 275-300mg	-0.28 (-0.43 to -0.13) / 11.2	-0.31 (-0.43 to -0.20) / 18.1	-0.29 (-0.41 to -0.18) / 9.0
Tramadol 400mg	-0.20 (-0.45 to 0.05) / 8.4	-0.23 (-0.46 to -0.01) / 11.8	-0.20 (-0.43 to 0.03) / 7.7
Tramadol/paracetamol 154-225mg	-0.63 (-0.94 to -0.32) / 95.0	-0.39 (-0.88 to 0.09) / 53.0	-0.31 (-0.59 to -0.02) / 33.1
Placebos			
Placebo topical	-0.10 (-0.38 to 0.19) / 3.1	-0.23 (-0.39 to -0.06) / 4.6	-0.15 (-0.30 to -0.01) / 0.2
Placebo oral and topical	0.09 (-0.67 to 0.87) / 12.2	0.07 (-0.22 to 0.35) / 0.2	0.11 (-0.40 to 0.61) / 3.3

MID: between-group minimum clinically important difference; 95% CrI: 95% credible interval
Light green ES: lower bound of 95% CrI <0; dark green ES: lower bound of 95% CrI ≤-0.37

Web-appendix 15. Treatment effect estimates for pain (effect sizes [95% CrI]) adjusted by risk of bias

	Unadjusted	Adjustment for risk of bias regarding				
		Allocation concealment	Blinding of patients	Blinding of therapist	Blinding of outcome assessor	Incomplete outcome data
Paracetamol						
Paracetamol <2000mg	-0.07 (-0.56 to 0.44)	-0.03 (-0.54 to 0.47)	-0.07 (-0.56 to 0.44)	-0.07 (-0.57 to 0.42)	-0.07 (-0.57 to 0.43)	-0.06 (-0.56 to 0.44)
Paracetamol 3000mg	-0.21 (-0.81 to 0.39)	-0.21 (-0.81 to 0.39)	-0.21 (-0.83 to 0.37)	-0.21 (-0.81 to 0.38)	-0.22 (-0.82 to 0.38)	-0.21 (-0.80 to 0.39)
Paracetamol 3900-4000mg	-0.15 (-0.25 to -0.05)	-0.13 (-0.24 to -0.02)	-0.15 (-0.26 to -0.05)	-0.16 (-0.26 to -0.05)	-0.16 (-0.26 to -0.05)	-0.15 (-0.25 to -0.05)
NSAIDs - Oral						
Aceclofenac 200mg	-0.56 (-0.78 to -0.34)	-0.54 (-0.76 to -0.32)	-0.56 (-0.78 to -0.33)	-0.56 (-0.78 to -0.34)	-0.55 (-0.78 to -0.34)	-0.57 (-0.78 to -0.35)
Celecoxib 100mg	-0.10 (-0.26 to 0.06)	-0.06 (-0.23 to 0.11)	-0.10 (-0.26 to 0.06)	-0.11 (-0.27 to 0.05)	-0.10 (-0.26 to 0.06)	-0.05 (-0.22 to 0.11)
Celecoxib 200mg	-0.35 (-0.40 to -0.30)	-0.32 (-0.39 to -0.24)	-0.35 (-0.40 to -0.31)	-0.36 (-0.41 to -0.31)	-0.35 (-0.40 to -0.30)	-0.31 (-0.38 to -0.25)
Celecoxib 400mg	-0.32 (-0.47 to -0.16)	-0.28 (-0.45 to -0.11)	-0.32 (-0.47 to -0.17)	-0.33 (-0.48 to -0.17)	-0.32 (-0.47 to -0.17)	-0.28 (-0.43 to -0.11)
Diclofenac ≤75mg	-0.42 (-0.65 to -0.18)	-0.39 (-0.63 to -0.16)	-0.42 (-0.65 to -0.19)	-0.42 (-0.65 to -0.19)	-0.42 (-0.65 to -0.19)	-0.40 (-0.63 to -0.16)
Diclofenac 100-105mg	-0.47 (-0.63 to -0.31)	-0.45 (-0.62 to -0.27)	-0.47 (-0.64 to -0.31)	-0.48 (-0.64 to -0.31)	-0.47 (-0.64 to -0.31)	-0.43 (-0.60 to -0.25)
Diclofenac 114-133mg	-0.64 (-1.40 to 0.11)	-0.63 (-1.38 to 0.13)	-0.70 (-1.46 to 0.07)	-0.67 (-1.44 to 0.08)	-0.70 (-1.45 to 0.06)	-0.60 (-1.36 to 0.15)
Diclofenac 150mg	-0.56 (-0.68 to -0.45)	-0.53 (-0.66 to -0.40)	-0.56 (-0.68 to -0.45)	-0.57 (-0.68 to -0.46)	-0.56 (-0.68 to -0.45)	-0.53 (-0.65 to -0.40)
Diflunisal 750mg	-0.33 (-0.69 to 0.03)	-0.29 (-0.66 to 0.07)	-0.42 (-0.80 to -0.04)	-0.38 (-0.75 to -0.00)	-0.42 (-0.80 to -0.04)	-0.28 (-0.64 to 0.08)
Diflunisal 1000mg	-0.40 (-0.77 to -0.04)	-0.36 (-0.73 to 0.00)	-0.49 (-0.88 to -0.10)	-0.45 (-0.83 to -0.07)	-0.49 (-0.88 to -0.10)	-0.35 (-0.72 to 0.02)
Etodolac 600mg	-0.57 (-0.83 to -0.31)	-0.54 (-0.81 to -0.27)	-0.57 (-0.84 to -0.31)	-0.57 (-0.84 to -0.31)	-0.57 (-0.83 to -0.31)	-0.57 (-0.84 to -0.31)
Etoricoxib 5-10mg	-0.21 (-0.43 to 0.02)	-0.16 (-0.40 to 0.07)	-0.20 (-0.43 to 0.02)	-0.21 (-0.43 to 0.02)	-0.20 (-0.43 to 0.02)	-0.15 (-0.39 to 0.08)
Etoricoxib 30mg	-0.48 (-0.63 to -0.34)	-0.44 (-0.61 to -0.28)	-0.49 (-0.63 to -0.34)	-0.49 (-0.63 to -0.34)	-0.48 (-0.63 to -0.34)	-0.43 (-0.59 to -0.27)

Etoricoxib 60mg	-0.65 (-0.82 to -0.48)	-0.60 (-0.79 to -0.42)	-0.64 (-0.81 to -0.47)	-0.65 (-0.82 to -0.48)	-0.64 (-0.81 to -0.47)	-0.59 (-0.77 to -0.40)
Etoricoxib 90mg	-0.84 (-1.09 to -0.59)	-0.80 (-1.06 to -0.54)	-0.83 (-1.09 to -0.59)	-0.84 (-1.09 to -0.59)	-0.84 (-1.09 to -0.59)	-0.79 (-1.05 to -0.53)
Ibuprofen 1200mg	-0.31 (-0.92 to 0.30)	-0.28 (-0.88 to 0.34)	-0.32 (-0.94 to 0.28)	-0.31 (-0.92 to 0.29)	-0.32 (-0.93 to 0.29)	-0.26 (-0.86 to 0.34)
Ibuprofen 2400mg	-0.37 (-0.50 to -0.25)	-0.34 (-0.48 to -0.20)	-0.38 (-0.50 to -0.25)	-0.38 (-0.50 to -0.25)	-0.38 (-0.50 to -0.25)	-0.34 (-0.47 to -0.20)
Indomethacin 75mg	-0.30 (-0.74 to 0.14)	-0.26 (-0.71 to 0.17)	-0.37 (-0.83 to 0.08)	-0.30 (-0.74 to 0.13)	-0.37 (-0.83 to 0.09)	-0.27 (-0.71 to 0.17)
Isoxicam 200mg	-0.59 (-1.08 to -0.09)	-0.56 (-1.07 to -0.07)	-0.62 (-1.13 to -0.12)	-0.60 (-1.10 to -0.11)	-0.62 (-1.11 to -0.12)	-0.56 (-1.05 to -0.06)
Ketoprofen 200mg	-0.60 (-1.06 to -0.13)	-0.53 (-1.01 to -0.05)	-0.60 (-1.07 to -0.14)	-0.60 (-1.07 to -0.13)	-0.60 (-1.06 to -0.13)	-0.51 (-0.98 to -0.03)
Lornoxicam 16mg	-0.73 (-1.32 to -0.14)	-0.70 (-1.29 to -0.11)	-0.74 (-1.32 to -0.14)	-0.74 (-1.33 to -0.15)	-0.73 (-1.31 to -0.14)	-0.65 (-1.25 to -0.04)
Lumiracoxib 100mg	-0.33 (-0.52 to -0.13)	-0.29 (-0.50 to -0.08)	-0.34 (-0.54 to -0.14)	-0.34 (-0.54 to -0.14)	-0.34 (-0.54 to -0.14)	-0.31 (-0.51 to -0.12)
Lumiracoxib 200mg	-0.36 (-0.54 to -0.19)	-0.31 (-0.51 to -0.11)	-0.37 (-0.54 to -0.19)	-0.37 (-0.54 to -0.19)	-0.36 (-0.54 to -0.19)	-0.33 (-0.51 to -0.15)
Lumiracoxib 400mg	-0.39 (-0.59 to -0.18)	-0.35 (-0.57 to -0.13)	-0.40 (-0.61 to -0.19)	-0.40 (-0.61 to -0.19)	-0.40 (-0.61 to -0.19)	-0.36 (-0.57 to -0.15)
Meclofenamate sodium 300mg	-0.31 (-0.88 to 0.25)	-0.28 (-0.84 to 0.30)	-0.32 (-0.88 to 0.25)	-0.31 (-0.88 to 0.27)	-0.31 (-0.88 to 0.25)	-0.31 (-0.88 to 0.26)
Meloxicam ≤10mg	-0.33 (-0.52 to -0.13)	-0.29 (-0.50 to -0.08)	-0.33 (-0.52 to -0.14)	-0.36 (-0.56 to -0.16)	-0.33 (-0.52 to -0.13)	-0.28 (-0.49 to -0.08)
Meloxicam 15mg	-0.48 (-0.66 to -0.30)	-0.44 (-0.63 to -0.25)	-0.48 (-0.66 to -0.30)	-0.49 (-0.67 to -0.30)	-0.48 (-0.66 to -0.30)	-0.44 (-0.62 to -0.25)
Nabumetone 1000mg	-0.22 (-0.37 to -0.08)	-0.18 (-0.34 to -0.03)	-0.23 (-0.37 to -0.08)	-0.23 (-0.37 to -0.08)	-0.22 (-0.36 to -0.08)	-0.19 (-0.33 to -0.04)
Nabumetone 1500-1831mg	-0.41 (-0.89 to 0.08)	-0.36 (-0.86 to 0.14)	-0.47 (-0.97 to 0.03)	-0.44 (-0.94 to 0.05)	-0.47 (-0.97 to 0.04)	-0.32 (-0.83 to 0.18)
Naproxcinod 250mg	0.04 (-0.21 to 0.29)	0.08 (-0.18 to 0.34)	0.04 (-0.21 to 0.29)	0.03 (-0.23 to 0.28)	0.04 (-0.21 to 0.29)	0.09 (-0.18 to 0.35)
Naproxcinod 750mg	-0.31 (-0.43 to -0.19)	-0.27 (-0.41 to -0.13)	-0.31 (-0.44 to -0.19)	-0.33 (-0.46 to -0.20)	-0.31 (-0.44 to -0.19)	-0.26 (-0.40 to -0.13)
Naproxcinod 1500mg	-0.44 (-0.54 to -0.34)	-0.40 (-0.52 to -0.29)	-0.45 (-0.55 to -0.35)	-0.47 (-0.57 to -0.36)	-0.44 (-0.55 to -0.34)	-0.40 (-0.51 to -0.29)
Naproxcinod 2250mg	-0.47 (-0.73 to -0.22)	-0.43 (-0.70 to -0.17)	-0.47 (-0.73 to -0.22)	-0.48 (-0.75 to -0.23)	-0.47 (-0.73 to -0.21)	-0.42 (-0.69 to -0.16)

Naproxen ≤750mg	-0.38 (-0.63 to -0.13)	-0.34 (-0.60 to -0.08)	-0.38 (-0.63 to -0.13)	-0.38 (-0.63 to -0.13)	-0.38 (-0.63 to -0.13)	-0.33 (-0.59 to -0.08)
Naproxen 1000mg	-0.39 (-0.45 to -0.32)	-0.35 (-0.44 to -0.26)	-0.39 (-0.46 to -0.32)	-0.40 (-0.48 to -0.33)	-0.39 (-0.46 to -0.32)	-0.34 (-0.43 to -0.25)
Nimesulide 200mg	-0.35 (-0.65 to -0.06)	-0.28 (-0.61 to 0.03)	-0.36 (-0.65 to -0.06)	-0.36 (-0.65 to -0.06)	-0.36 (-0.65 to -0.06)	-0.31 (-0.61 to -0.01)
Nimesulide 800mg	-0.44 (-0.93 to 0.05)	-0.41 (-0.90 to 0.09)	-0.45 (-0.94 to 0.05)	-0.46 (-0.96 to 0.04)	-0.44 (-0.95 to 0.06)	-0.34 (-0.85 to 0.17)
Oxaprozin 1200mg	-0.61 (-0.89 to -0.32)	-0.57 (-0.87 to -0.27)	-0.61 (-0.89 to -0.32)	-0.61 (-0.89 to -0.32)	-0.61 (-0.89 to -0.32)	-0.59 (-0.87 to -0.30)
Piroxicam 20mg	-0.48 (-0.67 to -0.28)	-0.41 (-0.64 to -0.18)	-0.48 (-0.68 to -0.28)	-0.49 (-0.69 to -0.29)	-0.48 (-0.67 to -0.28)	-0.43 (-0.64 to -0.23)
Piroxicam 25.5mg	-0.53 (-1.43 to 0.37)	-0.44 (-1.37 to 0.51)	-0.58 (-1.51 to 0.32)	-0.55 (-1.46 to 0.37)	-0.59 (-1.49 to 0.33)	-0.39 (-1.35 to 0.55)
Polmacoxib 2mg	-0.28 (-0.55 to -0.02)	-0.26 (-0.52 to 0.01)	-0.28 (-0.55 to -0.02)	-0.28 (-0.54 to -0.02)	-0.28 (-0.55 to -0.02)	-0.26 (-0.52 to 0.01)
Rofecoxib 5mg	-0.34 (-0.60 to -0.09)	-0.31 (-0.57 to -0.04)	-0.35 (-0.60 to -0.09)	-0.35 (-0.60 to -0.09)	-0.35 (-0.60 to -0.09)	-0.30 (-0.56 to -0.03)
Rofecoxib 12.5mg	-0.41 (-0.49 to -0.33)	-0.37 (-0.48 to -0.27)	-0.42 (-0.49 to -0.34)	-0.42 (-0.50 to -0.34)	-0.42 (-0.50 to -0.34)	-0.37 (-0.47 to -0.28)
Rofecoxib 25mg	-0.48 (-0.55 to -0.40)	-0.44 (-0.54 to -0.33)	-0.48 (-0.56 to -0.40)	-0.48 (-0.56 to -0.41)	-0.48 (-0.56 to -0.40)	-0.44 (-0.53 to -0.34)
Rofecoxib 50mg	-0.77 (-1.05 to -0.49)	-0.73 (-1.02 to -0.44)	-0.77 (-1.05 to -0.49)	-0.77 (-1.05 to -0.49)	-0.77 (-1.05 to -0.49)	-0.73 (-1.01 to -0.43)
Tiaprofenic acid 600mg	-0.27 (-0.74 to 0.22)	-0.23 (-0.71 to 0.26)	-0.34 (-0.84 to 0.16)	-0.27 (-0.75 to 0.22)	-0.34 (-0.84 to 0.16)	-0.22 (-0.71 to 0.26)
Tolfenamic acid 600mg	-0.65 (-1.45 to 0.13)	-0.61 (-1.40 to 0.18)	-0.67 (-1.46 to 0.12)	-0.68 (-1.46 to 0.13)	-0.68 (-1.46 to 0.12)	-0.58 (-1.37 to 0.23)
Valdecoxib 5mg	-0.29 (-0.47 to -0.11)	-0.25 (-0.44 to -0.06)	-0.29 (-0.47 to -0.11)	-0.30 (-0.47 to -0.12)	-0.29 (-0.47 to -0.12)	-0.24 (-0.42 to -0.05)
Valdecoxib 10mg	-0.32 (-0.50 to -0.14)	-0.29 (-0.47 to -0.10)	-0.32 (-0.50 to -0.15)	-0.33 (-0.51 to -0.15)	-0.32 (-0.50 to -0.15)	-0.27 (-0.46 to -0.08)
Valdecoxib 20mg	-0.37 (-0.59 to -0.14)	-0.33 (-0.56 to -0.09)	-0.37 (-0.59 to -0.14)	-0.37 (-0.60 to -0.15)	-0.37 (-0.59 to -0.13)	-0.32 (-0.55 to -0.08)
Zaltoprofen 240mg	-0.78 (-1.39 to -0.17)	-0.71 (-1.34 to -0.09)	-0.78 (-1.39 to -0.17)	-0.79 (-1.39 to -0.17)	-0.78 (-1.40 to -0.17)	-0.69 (-1.31 to -0.07)
NSAIDs - Topical						
Diclofenac topical 70-81mg	-0.54 (-0.77 to -0.31)	-0.52 (-0.76 to -0.28)	-0.57 (-0.81 to -0.34)	-0.56 (-0.80 to -0.33)	-0.57 (-0.81 to -0.33)	-0.46 (-0.72 to -0.21)

Diclofenac topical 140-160mg	-0.61 (-0.87 to -0.35)	-0.57 (-0.85 to -0.30)	-0.64 (-0.90 to -0.37)	-0.62 (-0.89 to -0.36)	-0.64 (-0.90 to -0.36)	-0.52 (-0.81 to -0.25)
S-flurbiprofen plaster ≤20mg	-0.25 (-0.92 to 0.42)	-0.18 (-0.88 to 0.50)	-0.28 (-0.95 to 0.40)	-0.27 (-0.94 to 0.40)	-0.28 (-0.96 to 0.41)	-0.17 (-0.86 to 0.53)
S-flurbiprofen plaster 40mg	-0.41 (-1.20 to 0.37)	-0.35 (-1.14 to 0.44)	-0.45 (-1.22 to 0.35)	-0.44 (-1.20 to 0.34)	-0.44 (-1.21 to 0.34)	-0.34 (-1.13 to 0.47)
Ibuprofen topical 1500mg	-0.19 (-1.03 to 0.66)	-0.16 (-0.99 to 0.68)	-0.29 (-1.12 to 0.55)	-0.24 (-1.09 to 0.60)	-0.28 (-1.14 to 0.57)	-0.09 (-0.93 to 0.76)
Ketoprofen topical 50mg	-0.15 (-0.64 to 0.33)	-0.10 (-0.59 to 0.39)	-0.20 (-0.69 to 0.29)	-0.18 (-0.68 to 0.31)	-0.20 (-0.69 to 0.30)	-0.09 (-0.58 to 0.40)
Ketoprofen topical 100mg	-0.22 (-0.49 to 0.06)	-0.16 (-0.46 to 0.13)	-0.31 (-0.63 to -0.00)	-0.27 (-0.56 to 0.02)	-0.31 (-0.62 to -0.00)	-0.18 (-0.46 to 0.10)
Ketoprofen topical 200-220mg	-0.23 (-0.39 to -0.06)	-0.19 (-0.37 to -0.01)	-0.26 (-0.43 to -0.09)	-0.25 (-0.41 to -0.08)	-0.26 (-0.43 to -0.08)	-0.19 (-0.36 to -0.01)
Piroxicam topical 15mg	0.39 (-0.49 to 1.25)	0.46 (-0.41 to 1.32)	0.38 (-0.49 to 1.23)	0.38 (-0.48 to 1.24)	0.38 (-0.48 to 1.23)	0.49 (-0.36 to 1.35)
Opioids						
Buprenorphine sublingual 0.87mg	-0.35 (-1.39 to 0.69)	-0.38 (-1.40 to 0.65)	-0.38 (-1.38 to 0.66)	-0.39 (-1.42 to 0.63)	-0.36 (-1.40 to 0.68)	-0.39 (-1.43 to 0.64)
Buprenorphine transdermal 0.28-0.36mg	-0.36 (-0.73 to 0.01)	-0.33 (-0.72 to 0.05)	-0.37 (-0.75 to 0.01)	-0.39 (-0.76 to -0.01)	-0.37 (-0.74 to 0.01)	-0.33 (-0.71 to 0.05)
Codeine 105-127mg	-0.19 (-0.62 to 0.24)	-0.15 (-0.59 to 0.29)	-0.25 (-0.69 to 0.19)	-0.24 (-0.67 to 0.20)	-0.25 (-0.69 to 0.19)	-0.14 (-0.57 to 0.29)
Fentanyl transdermal 0.6mg	-0.31 (-0.69 to 0.07)	-0.30 (-0.67 to 0.09)	-0.34 (-0.72 to 0.04)	-0.33 (-0.71 to 0.06)	-0.34 (-0.72 to 0.04)	-0.23 (-0.62 to 0.17)
Hydromorphone 8mg	-0.01 (-0.53 to 0.50)	0.02 (-0.49 to 0.54)	-0.01 (-0.53 to 0.50)	-0.01 (-0.53 to 0.50)	-0.01 (-0.53 to 0.49)	0.04 (-0.48 to 0.56)
Hydromorphone 13.9-16mg	-0.16 (-0.51 to 0.18)	-0.14 (-0.49 to 0.20)	-0.16 (-0.50 to 0.18)	-0.16 (-0.50 to 0.19)	-0.16 (-0.50 to 0.18)	-0.11 (-0.46 to 0.23)
Hydromorphone 34mg	-0.00 (-0.61 to 0.60)	0.03 (-0.56 to 0.64)	0.00 (-0.60 to 0.60)	-0.04 (-0.66 to 0.57)	-0.00 (-0.61 to 0.60)	-0.00 (-0.60 to 0.60)
Morphine with naltrexone 43.5mg	-0.25 (-0.82 to 0.32)	-0.24 (-0.80 to 0.34)	-0.24 (-0.82 to 0.33)	-0.24 (-0.83 to 0.33)	-0.24 (-0.81 to 0.34)	-0.25 (-0.83 to 0.32)
Oxycodone ≤40mg	-0.09 (-0.41 to 0.22)	-0.05 (-0.38 to 0.27)	-0.14 (-0.47 to 0.19)	-0.13 (-0.45 to 0.19)	-0.14 (-0.47 to 0.19)	-0.05 (-0.37 to 0.28)
Oxycodone ≥48mg	-0.17 (-0.33 to -0.01)	-0.16 (-0.32 to -0.00)	-0.18 (-0.34 to -0.02)	-0.18 (-0.34 to -0.02)	-0.18 (-0.34 to -0.02)	-0.12 (-0.29 to 0.06)
Oxymorphone 40mg	-0.23 (-0.77 to 0.30)	-0.20 (-0.75 to 0.36)	-0.26 (-0.80 to 0.28)	-0.25 (-0.79 to 0.28)	-0.26 (-0.79 to 0.29)	-0.19 (-0.73 to 0.36)
Oxymorphone 80mg	-0.32 (-0.86 to	-0.28 (-0.81 to	-0.33 (-0.87 to	-0.33 (-0.86 to	-0.34 (-0.88 to	-0.26 (-0.80 to

	0.22)	0.26)	0.19)	0.21)	0.20)	0.28)
Tapentadol <316mg	-0.34 (-0.50 to -0.17)	-0.32 (-0.49 to -0.16)	-0.35 (-0.51 to -0.18)	-0.34 (-0.51 to -0.18)	-0.34 (-0.51 to -0.19)	-0.28 (-0.46 to -0.10)
Tramadol 100-131mg	-0.12 (-0.25 to 0.01)	-0.09 (-0.23 to 0.04)	-0.14 (-0.27 to -0.00)	-0.13 (-0.26 to -0.00)	-0.14 (-0.27 to -0.00)	-0.07 (-0.21 to 0.08)
Tramadol 200mg	-0.13 (-0.26 to 0.00)	-0.11 (-0.24 to 0.03)	-0.15 (-0.28 to -0.02)	-0.14 (-0.27 to -0.01)	-0.14 (-0.28 to -0.01)	-0.08 (-0.23 to 0.06)
Tramadol 275-300mg	-0.31 (-0.43 to -0.20)	-0.29 (-0.42 to -0.17)	-0.33 (-0.45 to -0.21)	-0.32 (-0.44 to -0.20)	-0.33 (-0.45 to -0.21)	-0.27 (-0.40 to -0.14)
Tramadol 400mg	-0.23 (-0.46 to -0.01)	-0.22 (-0.44 to 0.01)	-0.25 (-0.47 to -0.02)	-0.24 (-0.47 to -0.02)	-0.25 (-0.47 to -0.02)	-0.19 (-0.42 to 0.05)
Tramadol/Paracetamol 154-225mg	-0.39 (-0.88 to 0.09)	-0.35 (-0.85 to 0.14)	-0.39 (-0.88 to 0.10)	-0.39 (-0.88 to 0.09)	-0.39 (-0.89 to 0.10)	-0.34 (-0.84 to 0.16)
Placebos						
Placebo topical	-0.23 (-0.39 to -0.06)	-0.21 (-0.38 to -0.04)	-0.25 (-0.42 to -0.08)	-0.24 (-0.41 to -0.07)	-0.25 (-0.42 to -0.08)	-0.19 (-0.37 to -0.02)
Placebo oral and topical	0.07 (-0.22 to 0.35)	0.11 (-0.18 to 0.41)	0.05 (-0.23 to 0.34)	0.06 (-0.23 to 0.34)	0.05 (-0.24 to 0.34)	0.11 (-0.19 to 0.40)

95% CrI: 95% credible interval
Light green ES: lower bound of 95% CrI <0; dark green ES: lower bound of 95% CrI ≤-0.37

Web-appendix 16. Results for the primary outcome (pain) based on different prior distributions for the between-trial heterogeneity

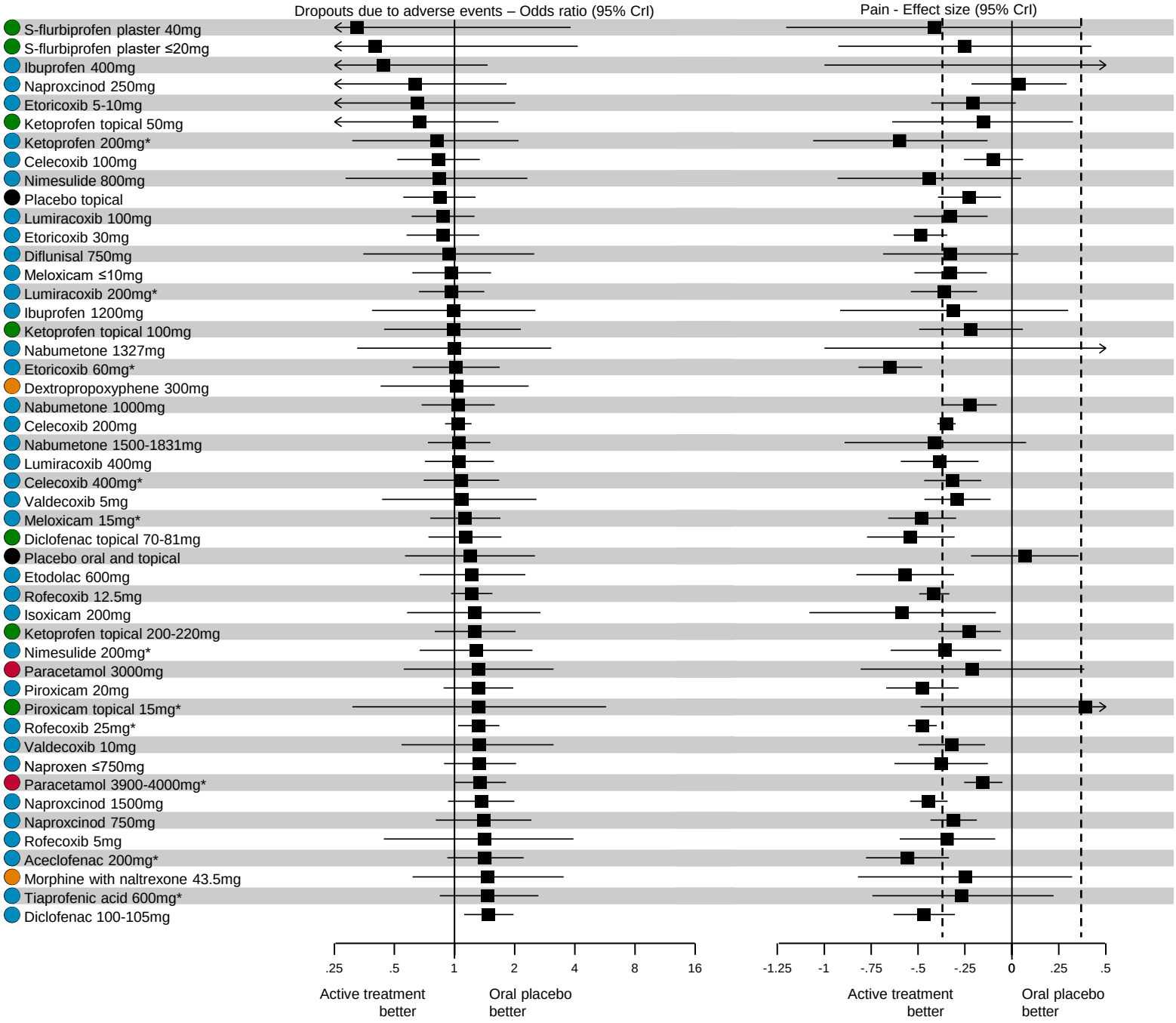
	Effect size (95% CI)	
	Gamma prior	Normal prior
Paracetamol		
Paracetamol <2000mg	-0.07 (-0.56 to 0.44)	-0.05 (-0.54 to 0.41)
Paracetamol 3000mg	-0.21 (-0.81 to 0.39)	-0.23 (-0.84 to 0.31)
Paracetamol 3900-4000mg	-0.15 (-0.25 to -0.05)	-0.15 (-0.23 to -0.07)
NSAIDs - Oral		
Aceclofenac 200mg	-0.56 (-0.78 to -0.34)	-0.54 (-0.73 to -0.35)
Celecoxib 100mg	-0.10 (-0.26 to 0.06)	-0.10 (-0.22 to 0.02)
Celecoxib 200mg	-0.35 (-0.40 to -0.30)	-0.36 (-0.40 to -0.32)
Celecoxib 400mg	-0.32 (-0.47 to -0.16)	-0.32 (-0.44 to -0.20)
Diclofenac ≤75mg	-0.42 (-0.65 to -0.18)	-0.38 (-0.58 to -0.18)
Diclofenac 100-105mg	-0.47 (-0.63 to -0.31)	-0.47 (-0.61 to -0.32)
Diclofenac 114-133mg	-0.64 (-1.40 to 0.11)	-0.66 (-1.38 to 0.08)
Diclofenac 150mg	-0.56 (-0.68 to -0.45)	-0.56 (-0.66 to -0.47)
Diflunisal 750mg	-0.33 (-0.69 to 0.03)	-0.33 (-0.64 to -0.01)
Diflunisal 1000mg	-0.40 (-0.77 to -0.04)	-0.40 (-0.72 to -0.08)
Etodolac 600mg	-0.57 (-0.83 to -0.31)	-0.57 (-0.81 to -0.32)
Etoricoxib 5-10mg	-0.21 (-0.43 to 0.02)	-0.20 (-0.39 to -0.00)
Etoricoxib 30mg	-0.48 (-0.63 to -0.34)	-0.49 (-0.61 to -0.35)
Etoricoxib 60mg	-0.65 (-0.82 to -0.48)	-0.65 (-0.79 to -0.51)
Etoricoxib 90mg	-0.84 (-1.09 to -0.59)	-0.81 (-1.02 to -0.59)
Ibuprofen 1200mg	-0.31 (-0.92 to 0.30)	-0.32 (-0.91 to 0.24)
Ibuprofen 2400mg	-0.37 (-0.50 to -0.25)	-0.38 (-0.48 to -0.27)
Indomethacin 75mg	-0.30 (-0.74 to 0.14)	-0.28 (-0.71 to 0.13)
Isoxicam 200mg	-0.59 (-1.08 to -0.09)	-0.60 (-1.07 to -0.14)
Ketoprofen 200mg	-0.60 (-1.06 to -0.13)	-0.60 (-1.03 to -0.15)
Lornoxicam 16mg	-0.73 (-1.32 to -0.14)	-0.74 (-1.29 to -0.16)
Lumiracoxib 100mg	-0.33 (-0.52 to -0.13)	-0.33 (-0.51 to -0.15)
Lumiracoxib 200mg	-0.36 (-0.54 to -0.19)	-0.37 (-0.51 to -0.23)
Lumiracoxib 400mg	-0.39 (-0.59 to -0.18)	-0.39 (-0.58 to -0.20)
Meclofenamate sodium 300mg	-0.31 (-0.88 to 0.25)	-0.32 (-0.87 to 0.22)
Meloxicam ≤10mg	-0.33 (-0.52 to -0.13)	-0.33 (-0.50 to -0.17)
Meloxicam 15mg	-0.48 (-0.66 to -0.30)	-0.48 (-0.65 to -0.32)
Nabumetone 1000mg	-0.22 (-0.37 to -0.08)	-0.24 (-0.35 to -0.13)
Nabumetone 1500-1831mg	-0.41 (-0.89 to 0.08)	-0.41 (-0.88 to 0.06)
Naproxcinod 250mg	0.04 (-0.21 to 0.29)	0.04 (-0.17 to 0.25)
Naproxcinod 750mg	-0.31 (-0.43 to -0.19)	-0.31 (-0.40 to -0.21)
Naproxcinod 1500mg	-0.44 (-0.54 to -0.34)	-0.44 (-0.52 to -0.36)
Naproxcinod 2250mg	-0.47 (-0.73 to -0.22)	-0.47 (-0.68 to -0.25)
Naproxen ≤750mg	-0.38 (-0.63 to -0.13)	-0.37 (-0.60 to -0.14)
Naproxen 1000mg	-0.39 (-0.45 to -0.32)	-0.39 (-0.45 to -0.34)
Nimesulide 200mg	-0.35 (-0.65 to -0.06)	-0.35 (-0.63 to -0.08)
Nimesulide 800mg	-0.44 (-0.93 to 0.05)	-0.45 (-0.90 to 0.02)
Oxaprozin 1200mg	-0.61 (-0.89 to -0.32)	-0.61 (-0.86 to -0.37)
Piroxicam 20mg	-0.48 (-0.67 to -0.28)	-0.47 (-0.65 to -0.29)
Piroxicam 25.5mg	-0.53 (-1.43 to 0.37)	-0.53 (-1.42 to 0.35)
Polmacoxib 2mg	-0.28 (-0.55 to -0.02)	-0.29 (-0.50 to -0.07)
Rofecoxib 5mg	-0.34 (-0.60 to -0.09)	-0.35 (-0.56 to -0.13)
Rofecoxib 12.5mg	-0.41 (-0.49 to -0.33)	-0.42 (-0.48 to -0.35)
Rofecoxib 25mg	-0.48 (-0.55 to -0.40)	-0.48 (-0.54 to -0.41)
Rofecoxib 50mg	-0.77 (-1.05 to -0.49)	-0.77 (-1.02 to -0.53)
Tiaprofenic acid 600mg	-0.27 (-0.74 to 0.22)	-0.26 (-0.71 to 0.20)
Tolfenamic acid 600mg	-0.65 (-1.45 to 0.13)	-0.66 (-1.40 to 0.14)
Valdecoxib 5mg	-0.29 (-0.47 to -0.11)	-0.30 (-0.43 to -0.15)
Valdecoxib 10mg	-0.32 (-0.50 to -0.14)	-0.32 (-0.46 to -0.18)
Valdecoxib 20mg	-0.37 (-0.59 to -0.14)	-0.37 (-0.54 to -0.19)
Zaltoprofen 240mg	-0.78 (-1.39 to -0.17)	-0.79 (-1.37 to -0.20)

NSAIDs - Topical		
Diclofenac topical 70-81mg	-0.54 (-0.77 to -0.31)	-0.57 (-0.78 to -0.36)
Diclofenac topical 140-160mg	-0.61 (-0.87 to -0.35)	-0.64 (-0.87 to -0.41)
S-flurbiprofen plaster ≤20mg	-0.25 (-0.92 to 0.42)	-0.27 (-0.95 to 0.36)
S-flurbiprofen plaster 40mg	-0.41 (-1.20 to 0.37)	-0.45 (-1.22 to 0.30)
Ibuprofen topical 1500mg	-0.19 (-1.03 to 0.66)	-0.20 (-1.03 to 0.59)
Ketoprofen topical 50mg	-0.15 (-0.64 to 0.33)	-0.17 (-0.62 to 0.29)
Ketoprofen topical 100mg	-0.22 (-0.49 to 0.06)	-0.24 (-0.46 to 0.00)
Ketoprofen topical 200-220mg	-0.23 (-0.39 to -0.06)	-0.24 (-0.37 to -0.11)
Piroxicam topical 15mg	0.39 (-0.49 to 1.25)	0.38 (-0.47 to 1.17)
Opioids		
Buprenorphine sublingual 0.87mg	-0.35 (-1.39 to 0.69)	-0.40 (-1.40 to 0.63)
Buprenorphine transdermal 0.28-0.36mg	-0.36 (-0.73 to 0.01)	-0.38 (-0.73 to -0.03)
Codeine 105-127mg	-0.19 (-0.62 to 0.24)	-0.20 (-0.61 to 0.19)
Fentanyl transdermal 0.6mg	-0.31 (-0.69 to 0.07)	-0.34 (-0.66 to -0.02)
Hydromorphone 8mg	-0.01 (-0.53 to 0.50)	-0.01 (-0.50 to 0.49)
Hydromorphone 13.9-16mg	-0.16 (-0.51 to 0.18)	-0.16 (-0.49 to 0.16)
Hydromorphone 34mg	-0.00 (-0.61 to 0.60)	0.01 (-0.57 to 0.59)
Morphine with naltrexone 43.5mg	-0.25 (-0.82 to 0.32)	-0.25 (-0.79 to 0.29)
Oxycodone ≤40mg	-0.09 (-0.41 to 0.22)	-0.09 (-0.39 to 0.21)
Oxycodone ≥48mg	-0.17 (-0.33 to -0.01)	-0.16 (-0.28 to -0.04)
Oxymorphone 40mg	-0.23 (-0.77 to 0.30)	-0.23 (-0.76 to 0.28)
Oxymorphone 80mg	-0.32 (-0.86 to 0.22)	-0.32 (-0.84 to 0.20)
Tapentadol <316mg	-0.34 (-0.50 to -0.17)	-0.31 (-0.44 to -0.19)
Tramadol 100-131mg	-0.12 (-0.25 to 0.01)	-0.12 (-0.22 to -0.01)
Tramadol 200mg	-0.13 (-0.26 to 0.00)	-0.13 (-0.24 to -0.03)
Tramadol 275-300mg	-0.31 (-0.43 to -0.20)	-0.31 (-0.41 to -0.22)
Tramadol 400mg	-0.23 (-0.46 to -0.01)	-0.23 (-0.41 to -0.06)
Tramadol/Paracetamol 154-225mg	-0.39 (-0.88 to 0.09)	-0.39 (-0.87 to 0.08)
Placebos		
Placebo topical	-0.23 (-0.39 to -0.06)	-0.26 (-0.39 to -0.12)
Placebo oral and topical	0.07 (-0.22 to 0.35)	0.06 (-0.18 to 0.30)

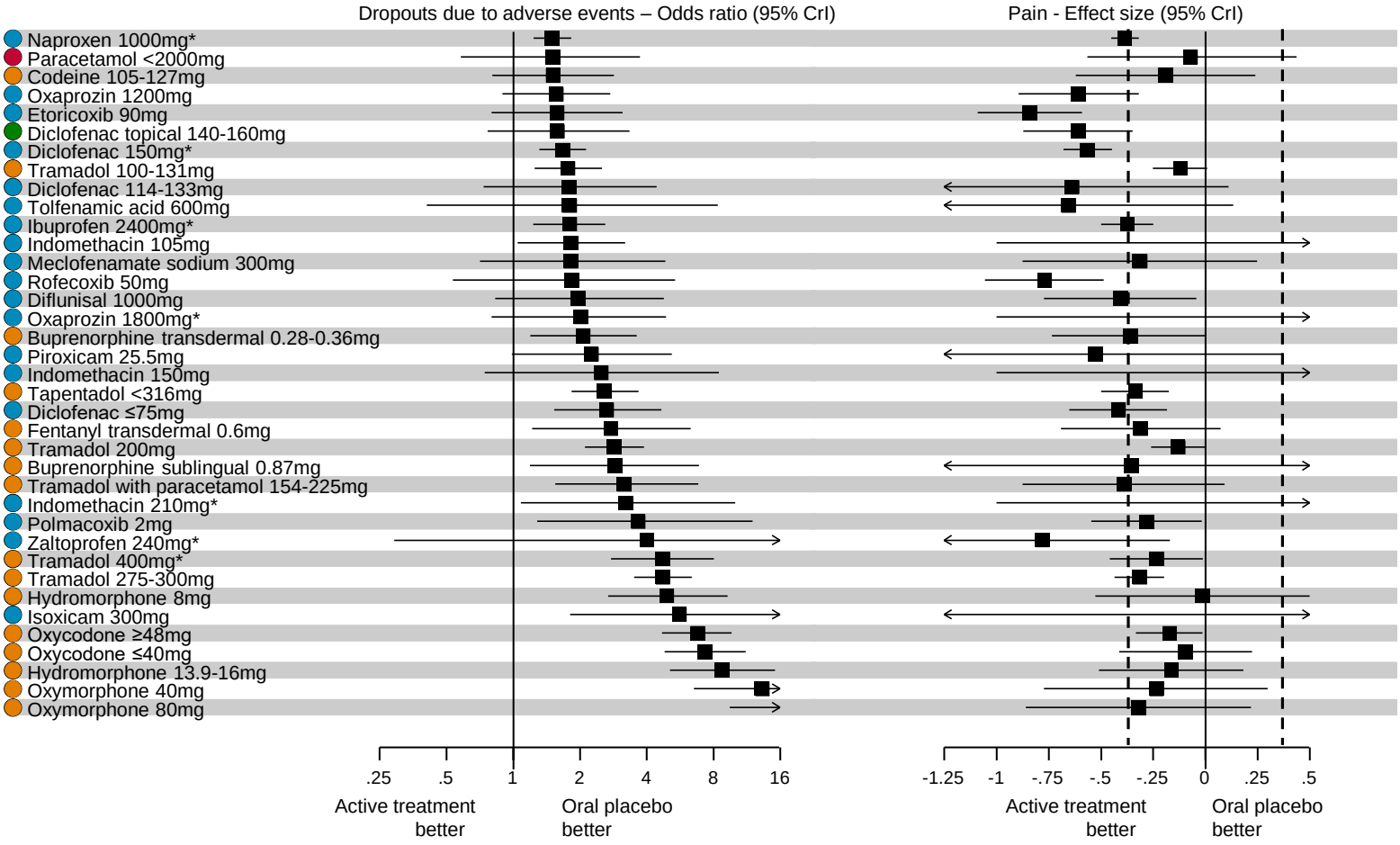
All treatment effect estimates are comparisons to oral placebo. Negative values suggest that the intervention is better than the oral placebo. ES: effect size; 95% CrI: 95% credible interval. Light green ES: lower bound of 95% CrI <0; dark green ES: lower bound of 95% CrI ≤ -0.37

For the gamma prior, $1/\tau^2 \sim$ gamma(0.1,0.1)I(0,2000). For the half-normal prior, $\tau \sim$ normal(0,1)I(0,).

Web-appendix 17. Dropouts due to adverse events and treatment effect on osteoarthritis pain as compared to oral placebo, ordered according to the odds ratio of dropouts due to adverse events.



Web-appendix 17 – Continued



95% CrI: 95% credible interval. *Maximum daily recommended dose. Blue: oral non-steroidal anti-inflammatory drugs; green: topical non-steroidal anti-inflammatory drugs; orange: opioids; red: paracetamol; black: placebo. Area between dashed lines shows treatment effect estimates below the minimum clinically important difference. See Figures 2-3 for caterpillar plot ordered according to the treatment effect size on osteoarthritis pain. See Tables 2-3 for specific estimates with 95% CrI and additional outcomes.

Web-appendix 18. Model fit for pain and function

	Data points	Residuals Number (%) within 1.96 SND	Q-Q plots
Pain	1080	1069 (99%)	Adequate
Function	735	731 (99%)	Adequate

SND: Standard normal distribution

Web-appendix 19. Model fit for safety outcomes

	Data points	Mean residual deviance
Dropouts due to adverse events	439	452
Any adverse event	364	382
Serious adverse events	253	274

Web-appendix 20. Assessment of inconsistency

	DIC
Pain	
Consistency model	-1678
Inconsistency model	-1670
Function	
Consistency model	-1125
Inconsistency model	-1119
Dropouts due to adverse events	
Consistency model	2603
Inconsistency model	2626
Any adverse event	
Consistency model	2634
Inconsistency model	2651
Serious adverse events	
Consistency model	1078
Inconsistency model	1087