RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Comparative effectiveness of pharmacological interventions for hand osteoarthritis: a systematic review and network meta-analysis of randomised trials

Anna Døssing ,[1] Sabrina Mai Nielsen,[2,3] Féline PB Kroon ,[4,5] Ida Maria Balsby,[1] Simon Tarp,[1] Margreet Kloppenburg,[4,6] Lisa Stamp ,[7] Ida K Haugen ,[8] Roy D Altman,[9] Marius Henriksen,[1] Mikael Boesen,[10] Henning Bliddal,[1] Søren Berg,[11] Robin Christensen[2,3]

To cite: Døssing A, Nielsen SM, Kroon FPB, *et al*. Comparative effectiveness of pharmacological interventions for hand osteoarthritis: a systematic review and network meta-analysis of randomised trials. *RMD Open* 2023;**9**:e003030. doi:10.1136/rmdopen-2023-003030

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2023-003030).

Nov 2022

Received 26 January 2023
Accepted 14 July 2023

Check for updates

© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to
Anna Døssing;
anna.dossing@gmail.com

ABSTRACT

Objective To explore the comparative effectiveness of pharmacological interventions for hand osteoarthritis (OA).

Methods We systematically searched Embase, MEDLINE, and the Cochrane Central Register of Controlled Trials from inception until 26 December 2021, for randomised trials of pharmacological interventions for people with hand OA. Two reviewers independently extracted study data and assessed the risk of bias. We calculated the effect sizes for pain (standardised mean differences) using Bayesian random effects models for network meta-analysis (NMA) and pairwise meta-analysis. Based on a pre-specified protocol, we prospectively registered the study at PROSPERO, CRD42021215393.

Results We included 72 trials with 7609 participants. 65 trials (n=5957) were eligible for the quantitative synthesis, investigating 29 pharmacological interventions. Oral non-steroidal anti-inflammatory drugs (NSAIDs) and oral glucocorticoids' NMA effect sizes were −0.18 (95% credible interval −0.36 to 0.02) and −0.54 (−0.83 to −0.24), respectively, compared with placebo, and the result was consistent when limiting evidence to the pairwise meta-analysis of trials without high risk of bias. Intra-articular hyaluronate, intra-articular glucocorticoids, hydroxychloroquine, and topical NSAIDs' NMA effect sizes were 0.22 (−0.08 to 0.51), 0.25 (0.00 to 0.51), −0.01 (−0.19 to 0.18), and −0.14 (−0.33 to 0.08), respectively, compared with placebo. Oral NSAIDs were inferior to oral glucocorticoids with an NMA effect size of 0.36 (0.01 to 0.72). No intervention was superior to placebo when stratifying for thumb and finger OA.

Conclusion Oral NSAIDs and glucocorticoids are apparently effective pharmacological interventions in hand OA. Intra-articular therapies and topical NSAIDs were not superior to placebo.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Hand osteoarthritis is common, and many treatment options exist.
⇒ Previous systematic reviews with meta-analyses support oral non-steroidal anti-inflammatory drugs (NSAIDs) as an effective treatment in hand osteoarthritis, but there is uncertainty regarding topical NSAIDs, oral glucocorticoids, and intra-articular glucocorticoids.
⇒ Over recent years new evidence has emerged, and there is a need for a comprehensive overview of the effectiveness of pharmacological treatments.

WHAT THIS STUDY ADDS

⇒ This network meta-analysis supports oral NSAIDs and oral glucocorticoids as effective treatments for hand osteoarthritis. We found no effectiveness of intra-articular hyaluronate, intra-articular glucocorticoids, or hydroxychloroquine. The effectiveness of topical NSAIDs remains uncertain.
⇒ The comparative analysis favoured oral glucocorticoids over oral NSAIDs.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ These findings raise questions about the evidence supporting the current treatment recommendation for intra-articular therapies and emphasise the need for future large-scale trials with a rigorous methodology to establish the efficacy of promising interventions such as topical NSAIDs.

INTRODUCTION

Hand osteoarthritis (OA) is a common disease affecting 15.9% of women and 8.2% of men between 40–84 years.[1] The incidence increases with age, and thus the burden will grow with the ageing population.[1 2] Hand

OA causes pain and impairs grip and motor function, affecting people's abilities with activities of daily living and work. The total societal cost of lost productivity per person with hand OA in a Dutch population (mean age 61 years) was estimated to be €2452 (~£2120, ~$2750) per year.[3] Evidence supports oral non-steroidal anti-inflammatory drugs (NSAIDs), yet they can have significant adverse effects, especially among the demographic groups with high OA prevalence.[4] Topical NSAIDs are the first pharmacological treatment of choice, yet the recommendation is based on a single high-quality trial.[5 6] There is conflicting evidence regarding the efficacy of oral glucocorticoids and glucocorticoid injections.[7–10] Therefore, treatment guidelines make weak recommendations for use, suggesting these therapies *may be considered*.[5 11] New evidence has been published regarding the pharmacological treatment of hand OA, and a recent meta-analysis found oral glucocorticoids effective, whereas intra-articular were not.[12] For a treating physician to navigate optimal treatment, a comprehensive overview of comparative effectiveness is needed when choosing between pharmacological interventions.

The primary objective of this study was to explore the comparative effectiveness of pharmacological interventions for hand OA pain. Secondary objectives included function, patient global assessment, health-related quality of life, grip strength, serious adverse events, and withdrawals due to adverse events.

METHODS

We conducted a systematic literature review with pairwise and network meta-analyses. The study protocol was registered at PROSPERO on 14 January 2021 (CRD42021215393).

Data sources and searches

We searched MEDLINE (via PubMed), Embase (via Ovid), and the Cochrane Central Register of Controlled Trials (CENTRAL, via the Cochrane Library) from inception to 26 December 2021. The search strategy was built on a previous systematic literature review of hand OA interventions[13]. We hand-searched reference lists from meta-analyses, systematic literature reviews, and all included studies. Unpublished data were searched from clinicaltrials.gov, the US Food and Drug Administration database, the European Medicines Agency Medicines reports, and by snowballing–contacting experts and study authors.

Study selection

We included all randomised controlled trials, including at least one pharmacological intervention for people with hand OA. Interventions were considered pharmacological if the American College of Rheumatology (ACR) treatment guideline categorises them as such.[11] Radiation was included as a pharmacological treatment as it would require a medical prescription in Denmark. Comparators were categorised as active, placebo, or care as usual. Studies were included if they reported either safety data or at least one of the Outcome Measures in Rheumatology (OMERACT) endorsed efficacy outcome domains: pain, function, patient global assessment, health-related quality of life, and/or hand strength.[14] Studies were excluded if they did not report hand OA data separately.

Studies were eligible for meta-analyses if the contrast between the intervention and comparator was a pharmacological treatment. Comparators included conventional placebo, care as usual, presumed inactive comparators, or active treatments offered to all treatment arms. Of these, studies with pain outcome data were also eligible for meta-regression. Irrespective of the contrast between the intervention and comparator, all studies with pain outcome data were eligible for network meta-analyses. Two reviewers (AD and IMB) selected the eligible studies using Covidence.[15]

Data extraction and quality assessment

Two reviewers (AD and IMB) independently extracted data and performed risk of bias assessments in a systematic, standardised way using a customised data extraction form. For each study, data extraction included design, population characteristics, interventions, outcome measures, time to the primary endpoint, length of follow-up, and contextual factors (see below). The efficacy outcomes of interest for the pairwise meta-analyses were the OMERACT-endorsed efficacy outcome domains with change from baseline until primary endpoint assessment; pain was considered the main outcome and subject to the network meta-analysis and exploration of contextual factors (see below). If no time point was prespecified as the primary endpoint, the longest possible trial period (respecting the original trial design) was used. From cross-over trials, we only included data from the first period of intervention to avoid the risk of accumulating carry-over effects.[16] Safety outcome measures of interest were discontinuation due to adverse events and the number of participants with a serious adverse event. Contextual factors included all factors suggested by the OMERACT hand OA working group[14] and factors discussed in the research group: age, sex, race, body mass index, classification criteria,[17] hand OA subset (ie, erosive or inflammatory; thumb OA, finger OA or combined thumb and finger OA), symptom and disease duration, comorbid OA, concomitant therapy, comorbidities, tender joint count, Kellgren-Lawrence score, C-reactive protein, erythrocyte sedimentation rate, smoking, exercise, alcohol consumption, and occupation with manual labour. Intention-to-treat analysis data were used whenever available. When a study reported data on more than one outcome scale, we extracted data from the scale that was highest in the protocolised prespecified hierarchy. Only data reported separately for hand OA participants were eligible, that is, data from mixed OA populations such as the knee, hip, and hand OA without separate hand OA data were not extracted. The risk of bias was

assessed using the Cochrane Risk of Bias tool version 2.0.[18] Funding was addressed as a separate bias item.[19]

For study selection, data extraction and quality assessment discrepancies were resolved by discussion and, when necessary, a third reviewer (RC) was consulted to reach a consensus.

Patient and public involvement statement

In agreement with the European Alliance of Associations for Rheumatology (EULAR) recommendation, patient research partners (PRP, including SB) were involved.[20] Two PRPs were involved in the design phase, and involvement led to an increased number of contextual factors. One of the PRPs declined to participate in the discussion of results, and a new PRP was engaged; thus, two PRPs were also involved in the discussion of the results. The PRPs were offered co-authorship of the present publication, which one PRP (SB) accepted.

Data synthesis and analysis

For continuous outcome measures, we calculated effect size as the standardised mean difference (SMD) equivalent to the mean difference (difference in mean values at the primary endpoint or change from baseline between intervention and comparator) divided by the corresponding pooled standard deviation (SD). In cases where SD was missing, it was calculated based on standard error (SE), interquartile range (IQR), confidence intervals (CI), p value, or between-group differences with CI; if this was not possible, SD was imputed by linear plotting of existing SDs against mean differences. For safety, the binary outcomes were analysed using the Peto odds ratio (OR) with the corresponding 95% CI.[21] Outcome measures from individual studies were reported for each study and summarised according to pharmacological intervention. Confidence in the cumulative estimates from the meta-analysis on pain was evaluated by the Grading Recommendations Assessment, Development and Evaluation (GRADE) as high, moderate, low, or very low, based on the evaluation of the risk of bias, risk of publication bias, imprecision, inconsistency, and indirectness.[22]

Pairwise meta-analyses

Outcomes were pooled for each intervention across trials using random-effect meta-analyses. Fixed effect analyses were used for sensitivity analyses. We used Review Manager to perform meta-analyses.[23] Heterogeneity in the pairwise meta-analyses was assessed using the I^2 inconsistency index.[24]

Network meta-analysis on pain outcome

Network meta-analysis for pain was performed using a random-effects model within a Bayesian framework using the *gemtc* package in R, version 4.0.1.[25] We used non-informative prior distributions for model parameters as the relative effectiveness of the interventions currently is uncertain. We assessed the convergence using the Gelman-Rubin statistic and by visual inspection of trace plots. Results were presented as SMD with 95% credible intervals. Intervention rankings were summarised using a rankogram (ie, rank probabilities plot).

The geometry of the network was evaluated with a network graph where nodes represent individual interventions. Network inconsistency was assessed using the node-splitting method.[26]

Meta-regression for contextual factor on pain with the effect size as the dependent variable

The effect of each possible contextual factor was explored using meta-regression stratified by a contextual factor with the SMD as the dependent variable. The statistical analyses were performed in R version 4.0.1 with the package *metafor*.[27] Heterogeneity was expressed by τ^2. Meta-regression was also used to explore the impact of the overall risk of bias evaluation and funding.

Role of the funding source

Funders had no role in the study design, data collection, data synthesis, data interpretation, writing the report, or the decision to submit the manuscript.

RESULTS

A flow diagram illustrating the study selection process is presented in figure 1. Of the 3319 references identified, 2620 were excluded through title and abstract screening. Among the 699 full-text references, 72 unique trials (n=7609) met the inclusion criteria. Of these, 65 trials (n=5957) were included in the quantitative synthesis. Of the trials included in quantitative synthesis, 60 trials (n=5246) had pain outcome data and were included in network meta-analyses, 51 trials (n between 1002 and 4352 depending on the outcome) were included in the pairwise meta-analyses, and 46 (n=4220) were included in meta-regression. A reference list of included trials is available in online supplemental file 1,2 and gives an overview of which analyses they contributed to. Two trials provided unpublished trial data,[28 29] two trials provided data only in press-release, and eight trials only had an abstract published (see online supplemental file 1).

Overall, the randomised controlled trials included in the review (k=72) were published between 1983 and 2021 and comprised 29 different pharmacological interventions. Table 1 summarises the characteristics of the included trials (k=72): 14 of the pharmacological interventions were only represented by one trial, and 17 of the pharmacological interventions had a total number of participants below 100. Eleven trials investigated intra-articular glucocorticoids. The trials evaluated triamcinolone, methylprednisolone, and betamethasone at different dosages and frequency of administration and had heterogenous comparator groups. Individual study characteristics of included trials are available in online supplemental file 3. One trial had four treatment arms, seven trials had three treatment arms, and the remainder had two (see online supplemental file 3). Most of the participants were women (mean proportion 85%), the mean age was 62 years, and white Caucasian was the most

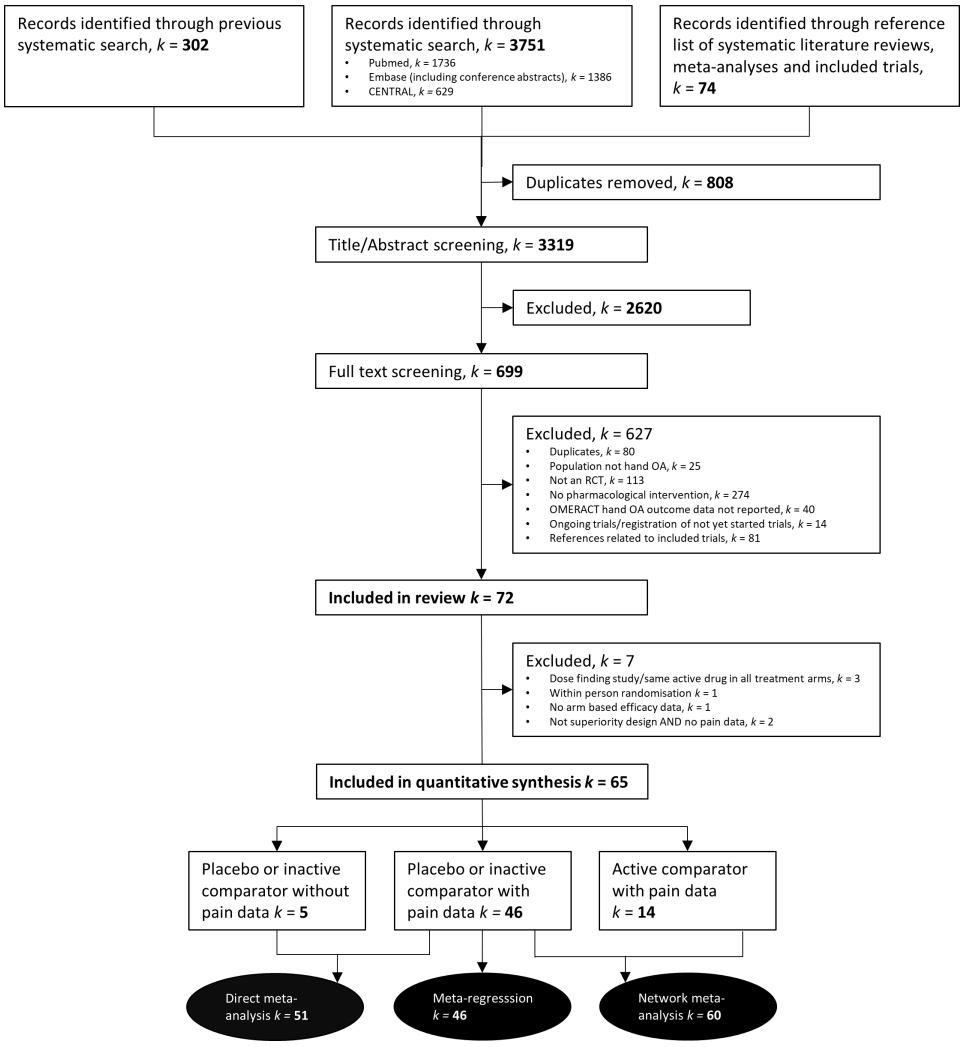

Figure 1 Flow diagram illustrating the study selection. OA, osteoarthritis; OMERACT, Outcome Measures in Rheumatology; RCT, randomised controlled trials.

frequent race (mean proportion 89%). The median time to the primary endpoint was 12 weeks (IQR 4–26 weeks). The internal validity of the included trials varied; overall 48 (67%) trials had a high risk of bias, 17 (24%) trials had some concern risk of bias, and only seven (10%) trials had a low risk of bias (see online supplemental file 4 for risk of bias summary).

The network plot for comparative effectiveness is presented in figure 2. Of the 60 trials included in the network meta-analyses, three comparisons were disconnected from the network (online supplemental file 7). As estimates from network meta-analyses are based on a connected network, comparative effectiveness could not be estimated for topical NSAIDs combined with orthoses, exercise and education versus education,[30] for perineural glucocorticoids and exercise versus exercise,[31] or for oral NSAIDs combined with glucosamine and chondroitin sulfate versus glucosamine and chondroitin sulfate.[32] However, estimates for the pairwise meta-analysis comparisons are available in online supplemental files 5–6. Non-pharmacological approaches, such as heat and leeches, were included in the network because other arms in the trial contained a pharmacological intervention and no other comparators were available. Many interventions within the network were not actively compared.

Effect sizes of pharmacological interventions compared with placebo on pain in the network meta-analyses are presented in figure 3. Please see online supplemental files 8–10 for the number of arms in the included studies, the number of comparisons per intervention, and the number of studies per intervention comparison.

Effect sizes for pain for all intervention comparisons in the network are presented in online supplemental file 11. Oral NSAIDs were inferior to oral glucocorticoids with an effect size of 0.36 (95% credible interval 0.01 to 0.72). Galactosaminoglycuronglycan sulfate, antiepileptics, and bisphosphonate were also superior to oral NSAIDs with effect sizes of –1.70 (–3.21 to –0.18), –0.97 (–1.75 to –0.14) and –1.36 (–2.36 to –0.41), respectively. Oral glucocorticoids were inferior only to bisphosphonate with an effect size for superiority of –0.99 (–2.00 to –0.02). Please see online supplemental file 12 for the ranking of interventions based on a probabilities plot. No treatment was superior to other treatments

Table 1 Summarised study characteristics, stratified by intervention class

Intervention	Number of references	Number of participants (ITT)	Number of references with data for the outcome domain							Hand OA target		
			Pain	Function	PGA	HRQoL	Grip strength	AE withdrawals	SAE	Fingers only	Thumb only	Both thumb and fingers
Capsaicin	2	73	2	1	0	0	0	2	2	0	0	2
Topical NSAID	9	1638	7	6	3	3	5	6	6	2	2	5
Topical salicylate	2	131	2	0	0	0	0	1	0	2	0	0
Glucosamine	1	50	1	0	0	0	0	0	0	0	0	1
Galactosaminoglycuronglycan sulfate	1	24	1	0	0	0	0	0	0	1	0	0
Chondroitin sulfate	3	351	1	2	1	0	1	2	2	1	1	1
Unsaponifiables*	1	261	0	0	0	0	0	0	0	0	0	1
Paracetamol	4	214	4	0	0	0	0	1	0	0	0	4
Oral NSAID	11	2172	10	3	2	1	3	6	5	4	1	6
Salicylate injection	1	40	1	1	0	0	0	1	1	0	1	0
Prolotherapy	2	87	2	1	0	0	1	2	2	0	1	1
Intra-articular platelet-rich plasma	2	78	2	2	0	0	1	1	0	0	2	0
Intra-articular hyaluronate	11	766	10	6	0	1	5	7	6	0	11	0
Intra-articular glucocorticoids	11	734	11	8	1	1	6	8	7	1	10	0
Perineural glucocorticoids	1	50	1	1	0	1	1	1	0	0	0	1
Radiation	1	56	1	1	1	1	0	1	1	0	0	1
Oral glucocorticoids	3	245	3	2	2	1	1	3	2	1	0	2
PDE4 inhibitors	1	30	1	1	1	1	0	1	1	1	0	0
Colchicine	1	64	1	1	0	0	1	1	1	0	0	1
SNRI	1	65	1	1	0	0	0	1	0	0	0	1
Antiepileptics	1	65	1	1	0	0	0	1	0	0	0	1
Cannabidiol	1	77	1	0	0	0	0	0	0	0	0	1
Bisphosphonates	2	78	2	2	1	0	1	2	2	1	0	1
Hydroxychloroquine	6	747	6	3	2	2	2	6	5	2	0	4
Methotrexate	1	64	1	1	1	0	0	1	0	1	0	0
TNF inhibitor	4	271	4	2	1	0	1	4	4	1	0	3
IL-1 inhibitor	4	395	2	2	2	2	1	2	4	0	0	4
IL-6 inhibitor	1	91	1	1	1	0	0	1	1	1	0	0
GM-CSF inhibitor	1	44	1	1	0	0	0	1	1	1	0	0
Total	72	7609	64	40	17	12	21	51	45	17	19	36

Traffic light colours indicate completeness of reporting (0–33% red, 34–66% yellow, 67–100% green).
*The trial reported overall data and were therefore included; however, no arm-based data were available.
.AE, adverse event; GM-CSF, granulocyte-macrophage colony-stimulating factor; HRQoL, health-related quality of life; IL, interleukin; ITT, intention-to-treat; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; PDE4, phosphodiesterase-4; PGA, patient global assessment; SAE, serious adverse event; SNRI, selective norepinephrine reuptake inhibitors; TNF, tumour necrosis factor.

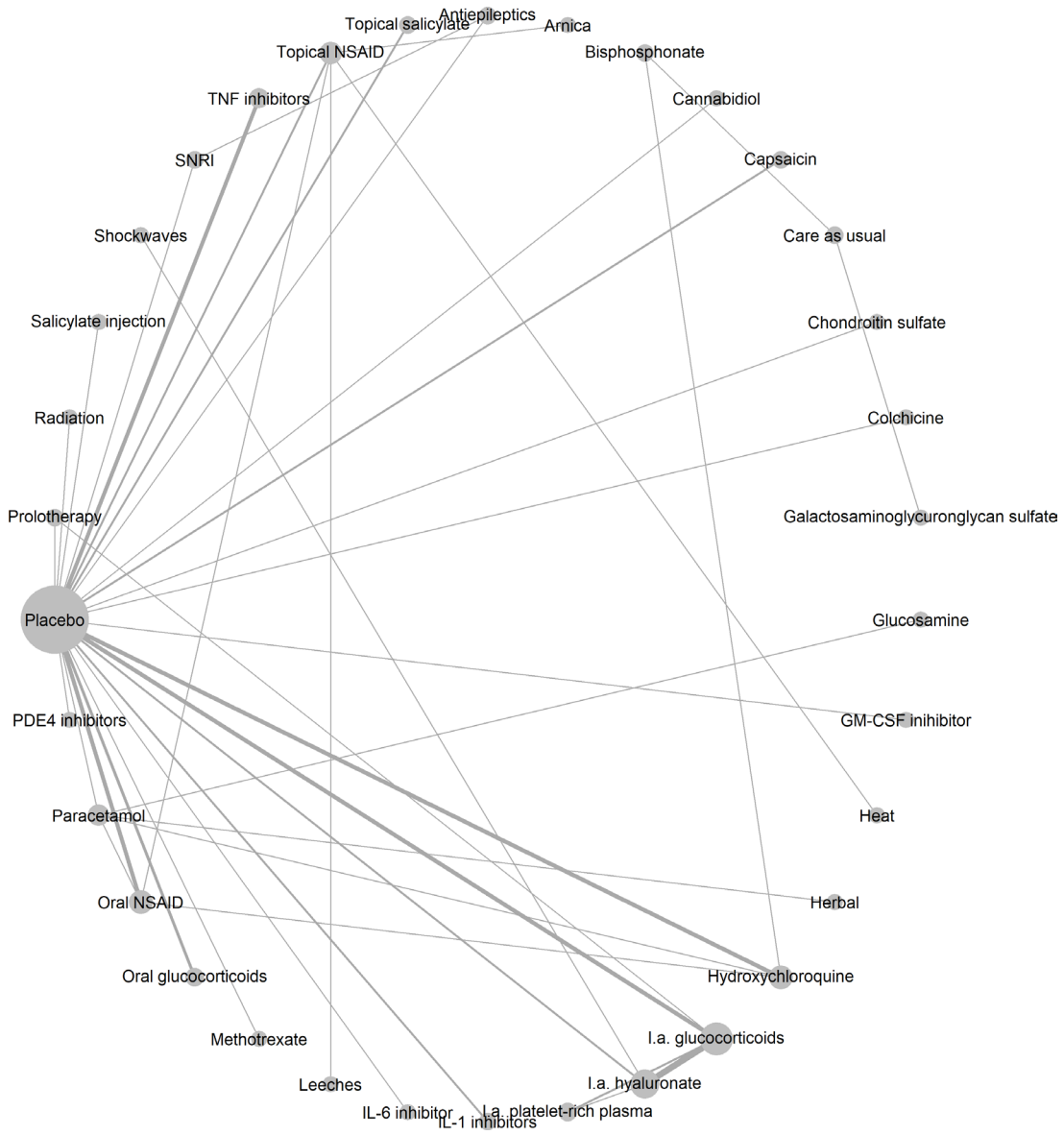

Figure 2 Network of treatment comparisons for pain. Circle size reflects number of participants, and the line width reflects the number of direct comparisons. No connecting line between two treatments indicate that there was no direct comparison. GM-CSF, granulocyte-macrophage colony-stimulating factor; I.a., intra-articular; IL, interleukin; NSAID, non-steroidal anti-inflammatory drugs; PDE4, phosphodiesterase-4; SNRI, selective norepinephrine reuptake inhibitors; TNF, tumour necrosis factor.

or placebo when limiting the network meta-analysis to trials without high risk of bias (see online supplemental files 14–18). To account for potential different treatment benefits based on anatomical site, we also did two subgroup network meta-analyses based on participants with thumb OA and participants with finger OA (see online supplemental files 19–28). In the network meta-analysis of participants with thumb OA, no pharmacological treatment was superior to placebo. Intra-articular glucocorticoid was inferior to placebo with an effect size of −0.45 (−0.99 to −0.02), and there were no significant differences between intra-articular glucocorticoids, hyaluronate, and platelet-rich plasma (online supplemental file 23). In the network meta-analysis of participants with finger OA, no pharmacological treatment was superior to placebo (online supplemental file 28).

Estimates from pairwise meta-analysis and pairwise meta-analysis without high risk of bias trials (including a quality of evidence table) are available in table 2. All pairwise meta-analyses, including sensitivity analyses and funnel plots, are available in online supplemental file 5, and pairwise meta-analyses for pain limited to trials with low or some concern risk of bias are available in online supplemental file 6.

Effect sizes from pairwise meta-analyses for function, patient global assessment, health-related quality of life, and hand strength are available in online supplemental files 5,6. Oral NSAIDs were effective across outcomes

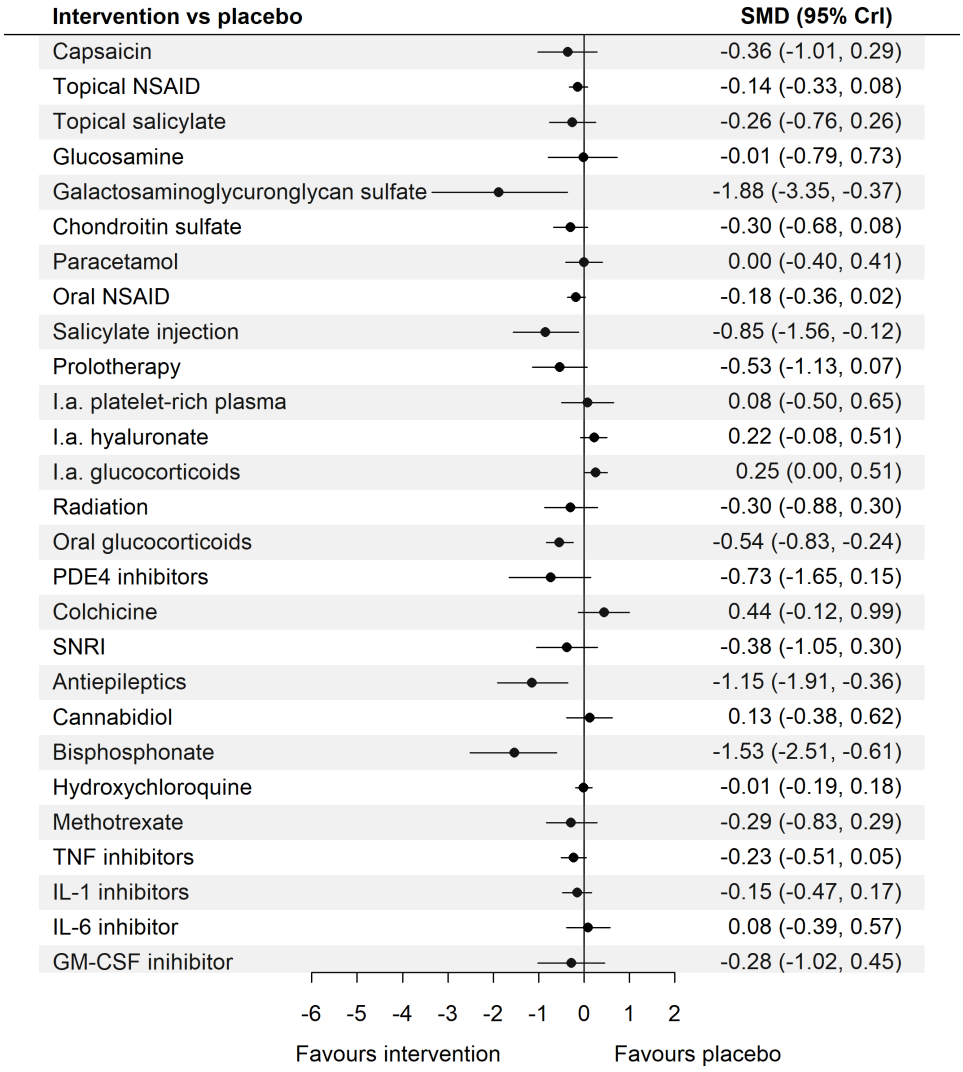

Figure 3 Estimates of the treatment effects of pharmacological interventions compared with placebo on pain in network meta-analyses. All studies included in the network meta-analysis connected to the network contributed to the estimates. An overview of studies contributing to the analysis is available in online supplemental file 2. Number of comparisons per treatment and studies per treatment comparison in the network meta-analyses are available in online supplemental files 9,10. CrI, credible interval; GM-CSF, granulocyte-macrophage colony-stimulating factor; I.a., intra-articular; IL, interleukin; NSAID, non-steroidal anti-inflammatory drugs; PDE4, phosphordiesterase-4; SMD, standardised mean difference; SNRI, selective norepinephrine reuptake inhibitors; TNF, tumour necrosis factor.

with effect estimates −0.19 (−0.37 to 0.00) for function, −0.31 (−0.51 to −0.11) for patient global assessment, and 0.71 (0.07 to 1.34) for grip strength (no data for health-related quality of life). Likewise, oral glucocorticoids were effective with effect estimates of −0.34 (−0.63 to −0.05) for function, −0.60 (−0.90 to 0.29) for patient global assessment, and 0.52 (0.10 to 0.93) for health-related quality of life. Oral glucocorticoids were not superior to comparators for grip strength, with an effect estimate of 0.27 (−0.14 to 0.68) (online supplemental file 5).

Treatment with pharmacological interventions led to more discontinuations due to adverse events than treatment with placebo (Peto OR 1.99, 95% CI 1.41 to 2.82), but overall, pharmacological interventions appeared safe, with no difference in the occurrence of serious adverse events (Peto OR 0.85, 95% CI 0.56 to 1.31) (online supplemental file 5).

The impact of contextual factors on pain, irrespective of pharmacological intervention, is presented in online supplemental file 13. A higher mean joint count yielded better pain reduction with an increase in effect size of 0.04 (95% CI 0.02 to 0.07) for every increase in the number of tender joints (p=0.002). Stratifying by hand OA location (ie, thumb, fingers, or both) showed that trials concerning isolated thumb OA reported no significant effect of intervention with effect size −0.04 (−0.46 to 0.37), whereas trials concerning finger OA or combined finger and thumb OA did with effect sizes −0.41 (−0.75 to −0.08) and −0.31 (−0.54 to −0.09); however, stratifying by hand OA location was not significant (p=0.376) (online supplemental file 13). Four trials studied inflammatory hand OA, and seven studied erosive hand OA. Stratifying by the subset of OA (ie, erosive, inflammatory, or other) did not significantly reduce heterogeneity.

Table 2 Pairwise meta-analysis with grade evidence profile of pharmacological interventions versus placebo for pain

Intervention	Number of trials (number of participants)	Primary endpoint, weeks	Serious risk of bias?*	Inconsistency	Indirectness	Imprecision	SMD (95% CI)†	Quality of evidence‡	SMD (95% CI), high risk of bias trials excluded†
Capsaicin	2 (55)	4 to 9	Yes	No	No	Yes§¶	−0.54 (−1.25 to 0.17)	Low	–
Topical NSAIDs	5 (905)	1 to 6	Yes	Yes	No	Yes§	0.15 (−0.19 to 0.49)	Very low	**−0.23 (−0.39 to −0.06)**
Topical salicylate	2 (113)	0.01 to 1	Yes	No	No	Yes¶	**−0.41 (−0.78 to −0.04)**	Low	–
Glucosamine	0 (0)	–	–	–	–	–	–	–	–
Galactosaminoglycuronglycan sulfate	1 (24)	104	Yes	No	No	Yes¶	**−0.94 (−1.79 to −0.09)**	Low	–
Chondroitin sulfate	3 (162)	26 to 156	Yes	No	No	**Yes¶**	**−0.35 (−0.66 to −0.04)**	Low	**−0.35 (−0.66 to −0.04)**
Unsaponifiables	0 (0)	–	–	–	–	–	–	–	–
Paracetamol	2 (99)	6 to 24	Yes	No	No	Yes§¶	0.14 (−0.25 to 0.54)	Low	–
Per oral NSAIDs	6 (577)	2 to 4	Yes	Yes	No	**No**	**−0.55 (−0.89 to −0.21)**	Low	**−0.43 (−0.62 to −0.25)**
Salicylate injection	1 (40)	13	Yes	No	No	Yes§¶	−0.84 (−1.49 to −0.19)	Low	–
Prolotherapy	1 (25)	26	No	No	No	Yes¶	**−0.94 (−1.78 to −0.10)**	Moderate	**−0.94 (−1.78 to −0.10)**
Intra-articular platelet-rich plasma	0 (0)	–	–	–	–	–	–	–	–
Intra-articular hyaluronate	2 (163)	26	Yes	No	No	Yes§¶	0.08 (−0.23 to 0.39)	Low	−0.11 (−0.75 to 0.53)
Intra-articular glucocorticoids	4 (265)	12 to 26	No	Yes	No	Yes§¶	0.44 (−0.37 to 1.26)	Low	0.62 (−0.70 to 1.95)
Perineural glucocorticoids	1 (46)	4	Yes (double)	No	Yes**	No	**−5.22 (−6.48 to −3.96)**	Very low	–
Radiation	1 (55)	14	No	No	No	Yes§¶	−0.10 (−0.63 to 0.43)	Moderate	−0.10 (−0.63 to 0.43)
Per oral glucocorticoids	3 (245)	4 to 6	No	Yes	No	Yes§¶	**−0.49 (−0.81 to −0.17)**	Low	−0.44 (−0.98 to 0.10)
PDE4 inhibitors	1 (28)	12	Yes	No	No	Yes§¶	−0.44 (−1.24 to 0.37)	Low	–
Colchicine	1 (64)	12	No	No	No	Yes¶	0.43 (−0.07 to 0.93)	Moderate	–
SNRI	1 (43)	13	Yes	No	No	Yes§¶	−0.48 (−1.09 to 0.13)	Low	–
Antiepileptics	1 (44)	13	Yes	No	No	No	**−0.81 (−1.43 to −0.19)**	Moderate	–
Cannabidiol	1 (74)	12	No	No	No	Yes§¶	0.10 (−0.35 to 0.56)	Moderate	0.10 (−0.35 to 0.56)
Bisphosphonates	1 (31)	26	Yes (double)	No	No	Yes¶	−0.62 (−1.39 to 0.15)	Very low	–
Hydroxychloroquine	4 (640)	24 to 52	No	No	No	No	0.01 (−0.15 to 0.16)	High	0.03 (−0.23 to 0.29)
Methotrexate	1 (64)	12	No	No	No	Yes§¶	−0.36 (−0.85 to 0.14)	Moderate	−0.36 (−0.85 to 0.14)
TNF inhibitors	4 (272)	6 to 52	No	Yes	No	Yes§¶	−0.21 (−0.45 to 0.03)	Low	−0.12 (−0.41 to 0.18)
IL-1 inhibitors	4 (196)	4 to 16	Yes	No	Yes††	Yes¶	−0.13 (−0.42 to 0.15)	Low	−0.12 (−0.50 to 0.26)
IL-6 inhibitor	1 (83)	6	No	No	No	Yes§¶	0.10 (−0.33 to 0.53)	Moderate	0.10 (−0.33 to 0.53)
GM-CSF inhibitor	1 (44)	6	No	No	No	Yes¶	−0.24 (−0.83 to 0.36)	Moderate	−0.24 (−0.83 to 0.36)

Grade evidence profile of pharmacological interventions for pain. Significant effect estimates are in bold.
*Please see online supplemental file 4 for risk of bias summary.
†Negative values favour interventions; positive values favour comparators.
‡It was not feasible to judge funnel plot asymmetry, because all groups contained <10 trials; no intervention was degraded further because of publication bias.
§95% CI includes appreciable benefit or harm.
¶Small sample size.
**Exercise comparator not an appropriate pharmacological placebo.
††Interventions differ in administration.
.CI, confidence interval; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; NSAID, non-steroidal anti-inflammatory drug; PDE4, phosphodiesterase-4; SMD, standardised mean difference; SNRI, selective norepinephrine reuptake inhibitors; TNF, tumour necrosis factor.

DISCUSSION

Our network meta-analyses and pairwise meta-analyses provide evidence-based estimates of the efficacy of pharmacological interventions used for hand OA. For some interventions, the effect estimates differed between the network meta-analysis, the pairwise meta-analysis, and the pairwise meta-analysis without high risk of bias trials.

Oral glucocorticoids were consistently effective across analyses for pain and were effective in function, patient global assessment, and health-related quality of life. In the network meta-analysis, the confidence interval to the effect estimate for oral NSAIDs overlapped zero (−0.36 to 0.02). A beneficial effect of oral NSAIDs was supported by consistent effectiveness in the pairwise meta-analyses on pain, function, patient global assessment, and grip strength; and effectiveness in the pairwise meta-analysis without high risk of bias trials on pain. Therefore, we believe oral NSAIDs have an actual effect on pain. Oral NSAIDs and oral glucocorticoid were not superior to other treatments, including placebo when excluding trials with high risk of bias from the network meta-analysis. Both oral glucocorticoids and oral NSAIDs appear safe in our analysis, but caution should be taken to apply them, as we only assessed withdrawals due to adverse events and serious adverse events without addressing long-term safety. For oral glucocorticoids, a dose effect was not investigated. Oral glucocorticoids were superior to placebo in two out of three trials when assessing individual trial results (online supplemental file 5). One trial administered oral glucocorticoid as a combination therapy with dipyridamole. The other administered prednisolone 10 mg daily, and was not superior to placebo after drug tapering.[13] Thus there was only a beneficial effect while maintaining the treatment.

The network meta-analysis and pairwise meta-analysis on pain suggested the efficacy of galactosaminoglycuronglycan sulfate, salicylate injection, prolotherapy, perineural glucocorticoids, antiepileptics, and bisphosphonate. Notably, only one to two high risk of bias trials contributed data for each intervention, which made sample size a major limitation. We therefore question the confidence in the estimate and refrain from making any conclusions on effectiveness. Chondroitin sulfate and topical salicylate had positive effects on pain compared with placebo in the pairwise meta-analysis, which the network meta-analysis did not support. There were no data on other outcomes for topical salicylate, and the inconsistency warrants more studies before making any final conclusion. A positive effect on function, patient global assessment, and health-related quality of life supported the effectiveness of chondroitin sulfate. However, only one trial provided data for effectiveness on pain, and adding the divergent results in the pain analyses, we believe more evidence is needed to claim effectiveness.

The effect estimates from the network meta-analysis for intra-articular hyaluronate, intra-articular glucocorticoids, and hydroxychloroquine were close to zero or favouring placebo, and the credible intervals were above −0.2, which we interpret as ineffectiveness. The pairwise meta-analysis showed similar effect sizes. The lack of efficacy of intra-articular glucocorticoids echoes previous meta-analyses,[11–13 33] but conflicts with guidelines: the ACR/Arthritis Foundation guideline for managing hand OA conditionally recommends intra-articular glucocorticoids, and EULAR guidelines state that intra-articular glucocorticoids can be considered in people with painful interphalangeal hand OA.[5 11] Subgroup network meta-analysis for trials of participants with thumb OA confirmed the ineffectiveness of intra-articular glucocorticoid. Trials of intra-articular glucocorticoid were heterogeneous concerning drug, dosage, and frequency of administration, and our network meta-analysis did not account for this. No trial of intra-articular glucocorticoid investigated the effectiveness of inflammatory or erosive hand, thumb, or finger OA, which future trials could target. Intra-articular glucocorticoids may have a role in treatment to circumvent systemic exposure and potential side effects of oral glucocorticoids.

The remaining interventions had uncertain efficacy on pain (capsaicin, topical NSAIDs, glucosamine, paracetamol, intra-articular platelet-rich plasma, radiation, phosphodiesterase-4 inhibitors, colchicine, selective norepinephrine reuptake inhibitors, cannabidiol, methotrexate, tumour necrosis factor inhibitors, interleukin-1 inhibitors, interleukin-6 inhibitors, and granulocyte-macrophage colony-stimulating factor). Topical NSAIDs were comparable to placebo in the pairwise meta-analysis on pain, function, health-related quality of life, and grip strength. However, they were superior to placebo in the pairwise meta-analysis without the high risk of bias trials on pain and the pairwise meta-analysis on patient global assessment. EULAR recommends topical NSAIDs as a first-line pharmacological treatment in hand OA.[6] The ACR/Arthritis Foundation guideline for managing hand OA limits the recommendation to *conditional* given practical considerations and lack of direct evidence.[11] The inconsistent result in our analysis emphasises that the actual treatment effect is uncertain and more high-quality placebo-controlled studies are needed to support guidelines.

Clinically, a treating physician can use our findings to avoid harm by deselecting ineffective and potentially harmful interventions such as hydroxychloroquine and intra-articular glucocorticoids for the thumb. To select the proper intervention for the patient, the treating physician must address comparability to the participants included in the meta-analyses, that is, Caucasian 62-year-old females. Thus, results may not be directly transferred for people with erosive and inflammatory OA as these subgroups were only included in a few trials.

Our study is the first to explore the effect of contextual factors on pain for pharmacological interventions in hand OA. We found a markedly better pain reduction with an increasing mean number of tender joints. It supports transitivity as a central limitation in hand OA

meta-analyses.[34 35] We also found different effect sizes for the thumb, finger, and combined thumb-finger OA; thus, clinically, it may be essential to deal with thumb and finger OA separately. For some interventions, we expect a difference in treatment response for subtypes of hand OA, such as erosive or inflammatory OA. We did not reduce heterogeneity when stratifying for these subtypes, which could be due to limited reporting of these features or treatment-specific effects that are lost when pooling data across interventions. Reporting of efficacy results in subgroups could clarify the impact of contextual factors in future meta-analyses, but there is no reporting standard for contextual factors.[36]

This study has several limitations, some of which we inherited from the included studies. Poor outcome-reporting forced us to exclude 40 trials because they did not report safety or efficacy data. Again, we emphasise that high risk of bias was an issue in many trials, and the number of trials and participants for each intervention was low, which calls for future high-quality large trials to establish the efficacy of promising interventions. Also, we have focused network meta-analyses on pain, as this is the most important complaint of people with hand OA,[14 37] and we only investigated the remaining outcome domains using pairwise meta-analyses. In hand OA, there is a need for more validated questionnaires to reflect the aspect of pain versus function. Confidence in the estimates from the network meta-analysis was not systematically addressed but is generally restricted by indirectness (a key judgement in network meta-analysis evaluation) led by poor connection in the network and transitivity,[38] and few studies for each intervention. Heterogeneity is also a limitation with the pooling of hand OA types and the pooling of interventions with different doses and routes of administration.

The strengths of our study include our rigorous search strategy, which minimised the risk of missing eligible studies, and an active and extensive search that identified unpublished trial data and trials not previously included in systematic reviews. Nevertheless, we cannot completely rule out publication bias, so our results must be interpreted cautiously (see funnel plots online supplemental file 5).

CONCLUSION

Many pharmacological treatments for hand OA pain are available, of which most have no proven efficacy. For hand OA, oral NSAIDs and oral glucocorticoids appear effective, whereas the efficacy of topical NSAIDs remains questionable. Current intra-articular therapies are ineffective for thumb OA.

Author affiliations
[1]Bispebjerg and Frederiksberg Hospital, University of Copenhagen, The Parker Institute, Copenhagen, Denmark
[2]Section for Biostatistics and Evidence-Based Research, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, The Parker Institute, Copenhagen, Denmark
[3]Research Unit of Rheumatology, Department of Clinical Research, Odense University Hospital, University of Southern Denmark, Odense, Denmark
[4]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands
[5]Department of Rheumatology, Zuyderland Medical Center, Heerlen, Netherlands
[6]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, Netherlands
[7]Department of Medicine, Christchurch, University of Otago, Christcurch, Christcurch, New Zealand
[8]Center for Treatment of Rheumatic and Musculoskeletal Diseases (REMEDY), Diakonhjemmet Hospital, Oslo, Norway
[9]Division of Rheumatology and Immunology, the University of California at Los Angeles (UCLA), David Geffen School of Medicine, Los Angeles, California, USA
[10]Department of Radiology, University of Copenhagen, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark
[11]Bispebjerg and Frederiksberg Hospital, The Parker Institute, Copenhagen, Denmark

Twitter Anna Døssing @AnnaDossing

Acknowledgements Juergen Rech: for sharing data from the ACCOST Study (EudraCT Number 2008-005365-61). Jonathan Vela: for sharing data from the NordCan study. The patient research partners: for valuable input in both the design and interpretation phases. To all authors who replied to emails requesting results.

Contributors AD and RC conceived and designed the study and contributed to the development of the protocol. AD developed the search strategy. AD and IMB sorted the references and extracted all the data. AD and SMN conducted statistical analyses. All authors assisted in the final manuscript and agreed to its final approval before submission. AD is responsible for the overall content as guarantor, AD accepts full responsibility for the finished work and the conduct of the study, had access to the data, and controlled the decision to publish.

Funding The Parker Institute is supported by a core grant from the Oak Foundation (OCAY-18-774-OFIL). This project was supported by IMK Almene Fond, Minister Erna Hamilton's Scholarship for Science and Art, the A.P. Møller and Wife Chastine McKinney Møllers Foundation, Aase and Ejnar Danielsen's Foundation, and the Velux Foundation. Funders had no role in study design, data collection, data synthesis, data interpretation, writing the report, or decision to submit the manuscript.

Competing interests This study had no competing financial interests. Interests disclosed in the International Committee of Medical Journal Editors (ICMJE) conflict of interest forms are as follows: LKS has received grants from the Health Research Council of New Zealand, royalties/licenses from UpToDate and consulting fees from Pharmac NZ. AD has received grants for the research project disclosed as funding. IKH has received consulting fees from Novartis and GSK and is a member of the OARSI executive committee. MK has received grants from IMI APPROACH and the Dutch Arthritis Society, royalties/licences from Wolters Kluwer and Springer Verlag, and consulting fees from Abbvie, Pfizer, Kiniksa Flexion, Galapagos, CHDR, Novartis and UCB, and she is a member of the OARSI board, the EULAR council and President of the Dutch Society for Rheumatology.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Template data collection forms, extracted data, data used for analysis, and analytic code are not publicly available. Published extracted data that underlie the results reported in this article and analytic code will be available from Robin Christensen (robin.christensen@regionh.dk) once all planned analyses have been completed and published. We will consider the request on an individual basis. We will not share unpublished data explicitly provided for this study. In these cases, we recommend contacting the authors of the original work.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which

permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Anna Døssing http://orcid.org/0000-0002-8388-9735
Féline PB Kroon http://orcid.org/0000-0002-8940-0582
Lisa Stamp http://orcid.org/0000-0003-0138-2912
Ida K Haugen http://orcid.org/0000-0001-7810-2216

REFERENCES

1 Haugen IK, Englund M, Aliabadi P, *et al*. Prevalence, incidence and progression of hand osteoarthritis in the general population: the Framingham osteoarthritis study. *Ann Rheum Dis* 2011;70:1581–6.
2 Zhang Y, Niu J, Kelly-Hayes M, *et al*. Prevalence of symptomatic hand osteoarthritis and its impact on functional status among the elderly: the Framingham study. *Am J Epidemiol* 2002;156:1021–7.
3 Terpstra S, van de Stadt LA, Boonen AE, *et al*. The association of hand osteoarthritis with paid and unpaid work impairment and related costs: the HOSTAS cohort. *Osteoarthritis and Cartilage* 2022;30:S217–8.
4 McGettigan P, Henry D. Use of non-steroidal anti-inflammatory drugs that elevate cardiovascular risk: an examination of sales and essential medicines lists in low-, middle-, and high-income countries. *PLoS Med* 2013;10:e1001388.
5 Kloppenburg M, Kroon FP, Blanco FJ. SP0161 2018 EULAR recommendations for the management of hand osteoarthritis. Annual European Congress of Rheumatology, EULAR 2018, Amsterdam, 13–16 June 2018; June 2018:16–24
6 Altman RD, Dreiser R-L, Fisher CL, *et al*. Diclofenac sodium GEL in patients with primary hand osteoarthritis: a randomized, double-blind, placebo-controlled trial. *J Rheumatol* 2009;36:1991–9.
7 Meenagh GK, Patton J, Kynes C, *et al*. A randomised controlled trial of intra-articular corticosteroid injection of the carpometacarpal joint of the thumb in osteoarthritis. *Ann Rheum Dis* 2004;63:1260–3.
8 Kvien TK, Fjeld E, Slatkowsky-Christensen B, *et al*. Efficacy and safety of a novel synergistic drug candidate, Crx-102, in hand osteoarthritis. *Ann Rheum Dis* 2008;67:942–8.
9 Wenham CYJ, Hensor EMA, Grainger AJ, *et al*. A randomized, double-blind, placebo-controlled trial of low-dose oral prednisolone for treating painful hand osteoarthritis. *Rheumatology (Oxford)* 2012;51:2286–94.
10 Spolidoro Paschoal N de O, Natour J, Machado FS, *et al*. Effectiveness of triamcinolone hexacetonide intraarticular injection in interphalangeal joints: a 12-week randomized controlled trial in patients with hand osteoarthritis. *J Rheumatol* 2015;42:1869–77.
11 Kolasinski SL, Neogi T, Hochberg MC, *et al*. American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Rheumatol* 2020;72:220–33.
12 Estee MM, Cicuttini FM, Page MJ, *et al*. Efficacy of corticosteroids for hand osteoarthritis-a systematic review and meta-analysis of randomized controlled trials. *BMC Musculoskelet Disord* 2022;23:665:665.:.
13 Kroon FPB, Carmona L, Schoones JW, *et al*. Efficacy and safety of non-pharmacological, pharmacological and surgical treatment for hand osteoarthritis: a systematic literature review informing the 2018 update of the EULAR recommendations for the management of hand osteoarthritis. *RMD Open* 2018;4:e000734.
14 Kloppenburg M, Bøyesen P, Visser AW, *et al*. Report from the OMERACT hand osteoarthritis working group: set of core domains and preliminary set of instruments for use in clinical trials and observational studies. *J Rheumatol* 2015;42:2190–7.
15 Veritas Health Innovation, Melbourne, Australia. 2020. Available: www.covidence.org
16 Elbourne DR, Altman DG, Higgins JPT, *et al*. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol* 2002;31:140–9.
17 Altman R, Alarcón G, Appelrouth D, *et al*. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheumatol* 1990;33:1601–10.
18 Sterne JAC, Savović J, Page MJ, *et al*. n.d. Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*:l4898.
19 Lundh A, Sismondo S, Lexchin J, *et al*. Industry sponsorship and research outcome. *Cochrane Database Syst Rev* 2012;12:MR000033.
20 de Wit MPT, Berlo SE, Aanerud GJ, *et al*. European League Against Rheumatism recommendations for the inclusion of patient representatives in scientific projects. *Ann Rheum Dis* 2011;70:722–6.
21 Bradburn MJ, Deeks JJ, Berlin JA, *et al*. Much ado about nothing: a comparison of the performance of Meta-Analytical methods with rare events. *Stat Med* 2007;26:53–77.
22 Guyatt GH, Oxman AD, Vist GE, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
23 RevMan. Computer program]. version 5.3. Copenhagen: the Nordic Cochrane centre. The Cochrane Collaboration [program]; 2014.
24 Higgins JPT, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
25 Gemtc: network meta-analysis using Bayesian methods [R package version 0.8-6]. 2020. Available: https://CRAN.R-project.org/package=gemtc
26 Dias S, Welton NJ, Caldwell DM, *et al*. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010;29:932–44.
27 Viechtbauer W. Conducting meta-analyses in R with the Metafor package. *J Stat Softw* 2010;36:1–48.
28 Rech J, Faustini F, Hueber AJ, *et al*. A phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy study of apremilast (CC-10004) in subjects with erosive hand osteoarthritis. *Arthritis Rheumatol* 2014;66:S971–2.
29 Vela J, Dreyer L, Petersen KK, *et al*. Cannabidiol treatment in hand osteoarthritis and psoriatic arthritis: a randomized, double-blind placebo-controlled trial. *Pain* 2022;163:1206–14.
30 Deveza LA, Robbins SR, Duong V, *et al*. Efficacy of a combination of conservative therapies vs an education comparator on clinical outcomes in thumb base osteoarthritis: a randomized clinical trial. *JAMA Intern Med* 2021;181:429.
31 Metin Ökmen B, Ökmen K, Altan L. Effectiveness of superficial radial nerve block on pain, function and quality of life in patients with hand osteoarthritis: a prospective, randomized and controlled single-blind study. *Arch Rheumatol* 2018;33:464–72.
32 Muratore M, Quarta L, Grimaldi A, *et al*. Efficacy of ketoprofen lysine salt in reducing inflammation and pain in primary osteoarthritis of the hand: preliminary results of a retrospective and prospective clinical trial.: 2239. *Arthritis Rheumatol* 2014;66.
33 Riley N, Vella-Baldacchino M, Thurley N, *et al*. Injection therapy for base of thumb osteoarthritis: a systematic review and meta-analysis. *BMJ Open* 2019;9:e027507.
34 Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods* 2012;3:80–97.
35 Nielsen SM, Storgaard H, Ellingsen T, *et al*. Population characteristics as important contextual factors in rheumatological trials: an exploratory meta-epidemiological study from an OMERACT working group. *Ann Rheum Dis* 2020;79:1269–76.
36 Thompson SG, Higgins JP. Can meta-analysis help target interventions at individuals most likely to benefit *Lancet* 2005;365:341–6.
37 Leung YY, Li JCH, Thumboo J. Domains rated as important by patients with hand osteoarthritis. *Int J Rheum Dis* 2019;22:2045–51.
38 Nikolakopoulou A, Higgins JPT, Papakonstantinou T, *et al*. Cinema: an approach for assessing confidence in the results of a network meta-analysis. *PLoS Med* 2020;17:e1003082.