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Similar Effects of Exercise Therapy, Nonsteroidal Anti-inflammatory Drugs, and Opioids for Knee Osteoarthritis Pain: A Systematic Review with Network Meta-analysis

OBJECTIVE: To compare the effectiveness of opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and exercise therapy for knee osteoarthritis pain.

DESIGN: Systematic review with network meta-analysis.

LITERATURE SEARCH: We searched the databases MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials from inception to April 15, 2021. Web of Science was used for citation tracking.

STUDY SELECTION CRITERIA: Randomized controlled trials comparing exercise therapy, NSAIDs, and opioids in any combination for knee osteoarthritis pain.

DATA SYNTHESIS: Network meta-analysis comparing exercise therapy, NSAIDs, opioids, and placebo/control for knee osteoarthritis pain. Additional trials from previous reviews were included to create the external placebo/control anchor.

RESULTS: We included 13 trials (1398 patients) with direct comparisons, supplemented with data from 101 additional trials. The treatment effect of NSAIDs for knee osteoarthritis pain was similar to that of opioids (standardized mean difference [SMD], 0.02; 95% confidence interval [CI], −0.14 to 0.18; Grading of Recommendations, Assessment, Development and Evaluations [GRADE]: low certainty). Exercise therapy had a larger effect than NSAIDs (SMD, 0.54; 95% CI, 0.19 to 0.89; GRADE: very low certainty). No estimate could be made for exercise vs opioids due to the lack of studies. Exercise therapy ranked as the "best" intervention in the network meta-analysis, followed by NSAIDs, opioids, and placebo/control intervention (GRADE: low certainty).

CONCLUSION: Exercise therapy ranked as the best treatment for knee osteoarthritis pain, followed by NSAIDs and opioids. The difference between treatments was small and likely not clinically relevant, and the overall confidence in the ranking was low. The results highlight the limited evidence for comparative effectiveness between exercise therapy, NSAIDs, and opioids for knee osteoarthritis pain.
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KEY WORDS: *analgesics, knee, osteoarthritis, pain, physiotherapy*

Opioids are frequently used to treat chronic musculoskeletal pain conditions.[18] In Sweden, 1 in 4 patients with knee or hip osteoarthritis (OA) have an opioid dispensed within a 12-month period, and a substantial proportion of patients have opioids prescribed within the first year of OA diagnosis.[43,44] The appropriateness for treating musculoskeletal pain conditions, such as OA, with opioids is the subject of strident debate due to risk of adverse events (AEs) and addiction.[8,16,42] Guidelines generally do not recommend opioids for knee OA pain unless other treatment options are exhausted, ineffective, or contraindicated.[28,30] The most recent guidelines from the Osteoarthritis Research Society International made a strong recommendation against any use of opioids for knee OA.[3]

Two other common treatments for knee OA pain are exercise therapy and nonsteroidal anti-inflammatory drugs (NSAIDs). The treatment effect estimated in systematic reviews and meta-analyses of opioids compared to placebo for knee OA pain does not seem to be larger than the treatment effect of NSAIDs compared to placebo or the treatment effect of exercise therapy compared to control interventions.[10,15,45] However, comparing effects across interventions obtained from randomized trials in pairwise meta-analysis is

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limited because no direct statistical comparison can be made between all relevant interventions. We used network meta-analysis to provide more valid estimates of the comparative effectiveness of opioids, NSAIDs, and exercise therapy for knee OA pain. Such information is important for musculoskeletal rehabilitation clinicians when supporting patients to make decisions about treatment for knee OA. Important knowledge gaps may also be identified.

METHODS

We preregistered the protocol in the PROSPERO (International Prospective Register of Systematic Reviews) database (registration number CRD42018106484; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=106484) and performed the study according to the guidelines for network meta-analysis using Stata.[40] We report the findings of our study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for reporting systematic reviews incorporating network meta-analyses.[24]

Eligibility Criteria

We included randomized controlled trials comparing exercise therapy with NSAIDs, exercise therapy with opioids, or NSAIDs with opioids for knee OA pain. We excluded trials where patients had a knee replacement surgery and trials where patients suffered from conditions other than OA, unless separate data were available for patients with knee OA. Trials including mixed populations of both knee and hip OA were included, as the majority of these patients typically have knee OA (this was a deviation from the protocol registered at PROSPERO). We defined exercise therapy as a regimen or plan of physical activities designed and prescribed for a specific therapeutic goal (ie, to reduce knee OA pain or improve muscle function), as defined by the Medical Subject Headings term in PubMed. We excluded trials that involved combined interventions in which exercise therapy constituted less than 50% of the intervention. We included all trials on drugs classified as NSAIDs or opioids according to the Anatomical Therapeutic Chemical codes.

Literature Search and Study Selection

We carried out systematic searches in MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. Citation tracking was performed in Web of Science. The final search was performed on April 15, 2021. We developed the search strategies in MEDLINE and adjusted to the other databases using a combination of key words (ie, Medical Subject Headings) and text words (**SUPPLEMENTAL FILE 1**). We had no restrictions for publication year and language. Two members of the study team (K.P. and D.B.B.) independently assessed all titles and abstracts of the identified reports for eligibility. If at least 1 of the reviewers judged a trial eligible, we obtained the full text and had 2 members independently evaluate for study inclusion eligibility. To identify additional trials, we reviewed reference lists of included trials and reviews published within the last 5 years. We resolved disagreements on inclusion by consensus.

Because we identified a low number of trials with direct comparison between treatments and no trials investigating exercise therapy vs opioids, we created an external anchor for the comparison in the network meta-analysis from trials comparing NSAIDs to placebo, opioids to placebo, and exercise therapy to control interventions. We used the same search (filtered for systematic reviews) to identify the most recent and relevant meta-analyses in Cochrane reviews. When no suitable Cochrane review was found, we extracted data from the most recent/relevant systematic review and meta-analysis we could identify (this approach was a deviation from the protocol registered with PROSPERO).

Data Extraction

The prespecified outcome of interest was pain. When a report provided data on more than 1 pain scale, a published hierarchy for the selection of patient-reported outcomes was used.[26] We extracted data on outcomes for each of the intervention groups for the longest follow-up assessment reported in the included trials. As recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*, we extracted the standard deviation (SD) of the outcome measurements, and when the SD was not described, it was estimated from standard errors, confidence intervals (CIs), *P* values, or interquartile ranges.[21] If data were reported in graphical form only, mean values and measures of dispersion were extrapolated using the WebPlotDigitizer software. In crossover trials, both phases of the trial were included, as the crossover effect of opioids and NSAIDs are minimal. For each intervention group, we also extracted the number of participants who were randomized, distribution of sex, mean age at baseline, body mass index at baseline, pain (intensity) at baseline, details about the interventions, number of AEs, type of AEs, and number of withdrawals due to AEs. Furthermore, we extracted definition criteria of OA for each trial. A customized data extraction form was used to independently extract all data by 2 of the study authors (M.S. and J.B.T.).

Similarity of Study Populations

A qualitative assessment of the clinical similarity of the treatment populations was performed based on mean age, sex distribution, OA severity (eg, Kellgren-Lawrence score), and baseline pain.

Data Synthesis

The effects from individual trials were expressed as the standardized mean difference (SMD) with a 95% CI. The SMD was estimated as the mean difference at the end of follow-up between treatment groups divided by the pooled SD. This estimate of the treatment effect size has a slight bias especially in smaller studies

overestimating the effect, and a correction factor was applied to convert the effect size to Hedges's *g*.[19] In trials reporting the effect as the number of participants reaching a predefined level of pain, the effect was estimated as an odds ratio (with a 95% CI) and transformed into an SMD using the formula proposed by Chinn.[9] First, we pooled the results from the individual trials with direct comparisons between the 3 interventions (ie, opioids, NSAIDs, and exercise). Then, we performed frequentist network meta-analysis based on the direct comparison of interventions (ie, opioids, NSAIDs, and exercise) to estimate the effect of pairwise comparisons (ie, based on direct and indirect comparisons).

We identified few trials with direct comparison between treatments and no trials investigating exercise therapy vs opioids. Therefore, we created an external anchor for the comparison in the network meta-analysis by extracting data from trials included in previous systematic reviews comparing NSAIDs to placebo, opioids to placebo, and exercise therapy to control interventions. The final network meta-analysis was performed including the extracted trials comparing the 3 interventions to placebo/control interventions.

Assessing Inconsistency

The heterogeneity in the analyses including direct comparisons between treatments was estimated using the I^2 statistic,[22] which measures the proportion of variation in the combined estimates attributable to between-study heterogeneity.[23] We checked the overall model for consistency using the command "network meta inconsistency" in Stata applying an F test for evaluating consistency. Side-split tables were produced to identify the source of inconsistency. The relative rank of the interventions along with the surface under the cumulative ranking curve was estimated.

Interpreting the Results

The SMD is often poorly understood.[25] To facilitate interpretation of the results, we also converted the estimated SMD in the final network meta-analysis into pain scores on a visual analog scale (VAS) using previously published methods. The converted VAS pain score (from 0 to 100 mm) was calculated by multiplying the SMD with an SD equal to 16.9 mm for pain.[6] The SDs used to convert the SMD into millimeters were based on a cohort of 914 patients with knee OA.[47] We considered that a difference in change in VAS pain between interventions had to be at least 15 mm to be clinically important. Finally, the network meta-analysis was repeated, stratified by OA classification (only patients with knee OA or patients with mixed knee and hip OA), age (over or under the median age), and the percentage of female participants in the study (over or under the median percentage of female participants). Risk of publication bias was investigated using funnel plots. All analyses were performed with Stata (Version 17.0; StataCorp LLC, College Station, TX), using a restricted maximum likelihood method to estimate the combined effect size and the between-study variance.

Assessing the Risk of Bias

Two reviewers (M.S. and J.B.T.) independently assessed risk of bias for trials with direct comparisons using the Cochrane Collaboration's risk-of-bias tool,[21] including the following domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. Other bias addressed the source of funding. We rated each domain as "low," "high," or "unclear" risk of bias. Disagreements between the 2 reviewers were resolved by consensus.

For the trials identified to create the external anchor for the network meta-analysis, we extracted the results of the risk-of-bias assessments performed in those trials (reported in the supplemental files). We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) adjusted for the network meta-analysis framework to assess the overall quality of the evidence, evaluating the certainty of the estimates on (1) study limitations, (2) indirectness and intransitivity, (3) statistical heterogeneity and statistical inconsistency, (4) imprecision, and (5) publication bias (using the GRADE approach was not registered in the PROSPERO protocol) (**SUPPLEMENTAL TABLE 1**).[39]

RESULTS

Our literature search identified 7719 independent references after excluding duplicates. Of these, 58 were considered for full-text review, and 13 trials including 1398 patients met the inclusion criteria.[1,5,7,11,13,14,27,29,34-36,48] Reasons for exclusion after the full-text review are reported in the flowchart (**FIGURE 1**) and in **SUPPLEMENTAL FILE 2**.

Study Characteristics

Of the included trials, 11 compared NSAIDs to opioids[1,5,7,11,13,27,29,33-36] and 2 compared NSAIDs to exercise therapy.[14,48] We did not identify any trials comparing opioids to exercise therapy. Five of the trials comparing NSAIDs to opioids were crossover trials, meaning that 181 of the 1398 patients were exposed to both treatments and acted as their own control.[7,13,27,35,36] The most common pain outcome was Western Ontario and McMaster Universities Osteoarthritis Index pain (n = 5), followed by VAS pain (n = 4) and numeric rating scale pain (n = 2); the remaining 2 trials used other pain outcomes. In 2 trials, pain data were extrapolated from figures.[33,36] Mean patient age ranged from 53 to 69 years, and mean baseline pain ranged from 34 to 74 mm on a 0- to 100-mm VAS. Follow-up for the primary endpoint in the trials ranged from 2 days to 52 weeks; most trials (n = 8) had their primary endpoint within 4 to 14 weeks (**SUPPLEMENTAL TABLE 2**).

The NSAIDs provided (n = 13 trials) were diclofenac (n = 3),[5,35,48] naproxen (n = 3),[27,33,36] ibuprofen (n = 1),[13] celecoxib (n = 2),[7,11] etoricoxib (n = 1),[1] and a mix of

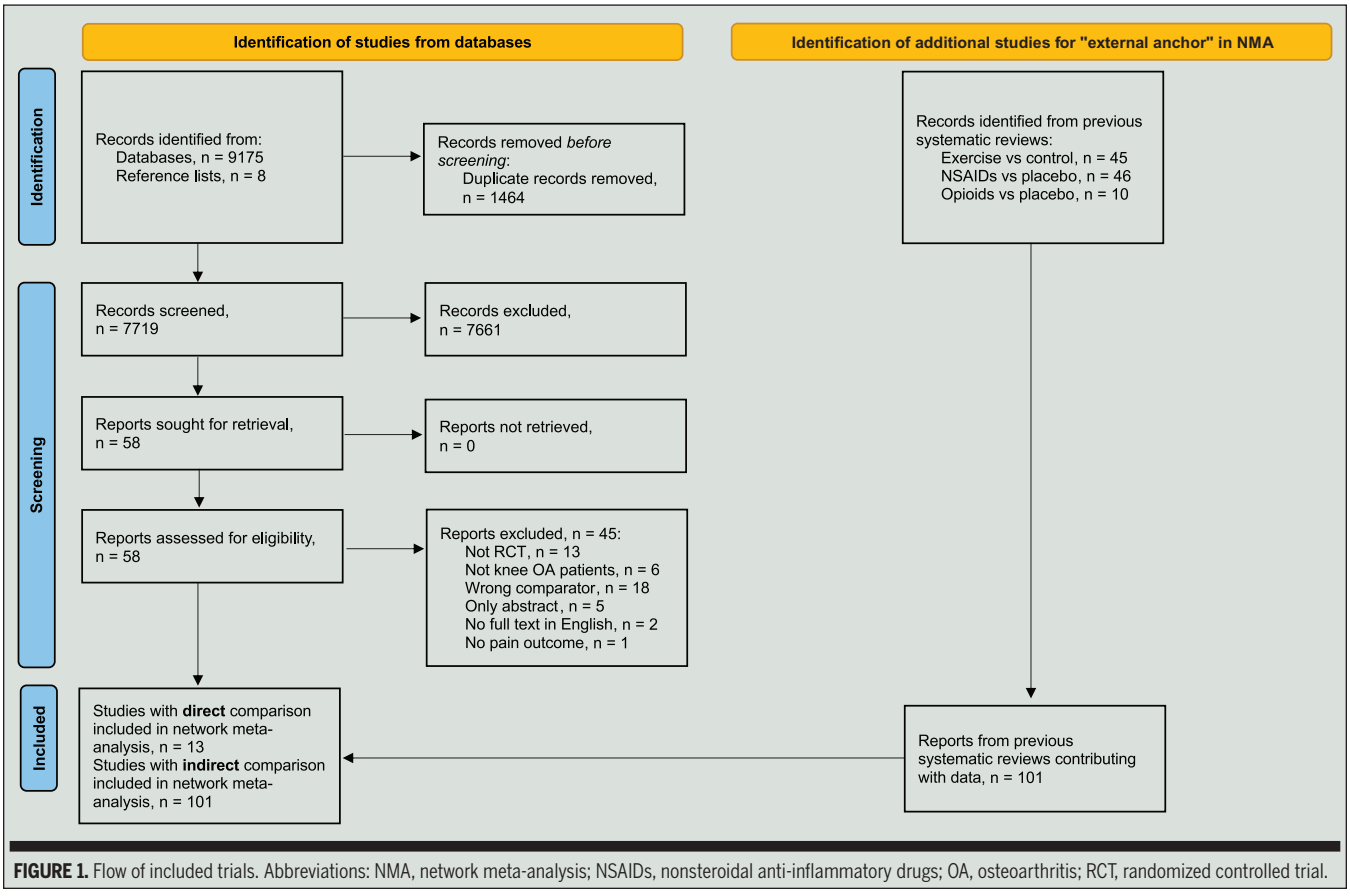

FIGURE 1. Flow of included trials. Abbreviations: NMA, network meta-analysis; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; RCT, randomized controlled trial.

NSAIDs (n = 3),[14,29,34] which were delivered orally (n = 11),[1,5,7,11,13,14,27,33-36] topically (n = 1),[48] or both orally and topically (n = 1).[29] The opioids provided (n = 11 trials) were tramadol (n = 7),[5,11,27,33-36] codeine (n = 1),[13] oxycodone (n = 1),[7] tapentadol (n = 1),[1] and a mix of opioids (n = 1),[29] which were delivered orally in all trials except for 1 trial[29] that used both oral and transdermal delivery. In the trials including exercise therapy (n = 2), 1 trial delivered a quadriceps home exercise program,[14] and the other delivered quadriceps and hamstrings isokinetic exercises using a seated dynamometer[48] (**SUPPLEMENTAL TABLE 2**).

To increase precision in the network meta-analysis, we established an external anchor for the 3 interventions by including trials identified from systematic reviews and meta-analyses comparing NSAIDs and opioids (ie, tramadol) to a placebo comparator and exercise therapy to control interventions (such as no intervention, wait-list control, patient education, ultrasound, etc).[15,41,45] From these sources, 45 trials compared exercise therapy to control interventions, 46 compared NSAIDs to placebo, and 10 compared opioids (ie, tramadol) to placebo (**SUPPLEMENTAL TABLE 3**).

Similarity of Study Populations

The populations in trials across treatments were similar with respect to mean age, sex distribution, knee OA severity, and baseline pain. However, knee OA severity and baseline pain were only reported in a limited number of trials.

Results of the Network Meta-analysis

All active treatments (ie, exercise therapy, NSAIDs, and opioids) showed small-to-moderate treatment effects (SMD, 0.27-0.45) compared with placebo/control treatment (**FIGURE 2** and **TABLE 1**). The treatment effect of NSAIDs on knee OA pain was similar to that of opioids (SMD, 0.02; 95% CI, −0.14 to 0.18; corresponding to 0.3 mm on a 0- to 100-mm VAS pain scale), with low confidence in the estimate. Exercise showed a larger effect compared with NSAIDs (SMD, 0.54; 95% CI, 0.19 to 0.89; corresponding to 9.1-mm VAS pain), with very low confidence in the estimates due to study limitations, inconsistency, and indirectness. All estimated SMDs were mixed estimates (ie, a combination of direct and indirect comparisons). Exercise had the highest probability of ranking as the "best" intervention in the network meta-analysis, followed by NSAIDs and opioids, and control intervention ranked "worst," with low confidence in the ranking (**TABLE 2**).

Pairwise Comparisons

In the 11 trials with a direct comparison between opioids and NSAIDs, we found

no difference in the treatment effect on knee OA pain (SMD, 0.03; 95% CI, −0.13 to 0.18; I^2 = 31.8%) (**FIGURE 3**). In the 2 trials investigating a direct comparison between NSAIDs and exercise therapy, we found a large SMD in favor of exercise, but with wide CIs crossing the line of no effect and considerable heterogeneity (SMD, 0.80; 95% CI, −0.19 to 1.79; I^2 = 90.7%) (**FIGURE 4**).

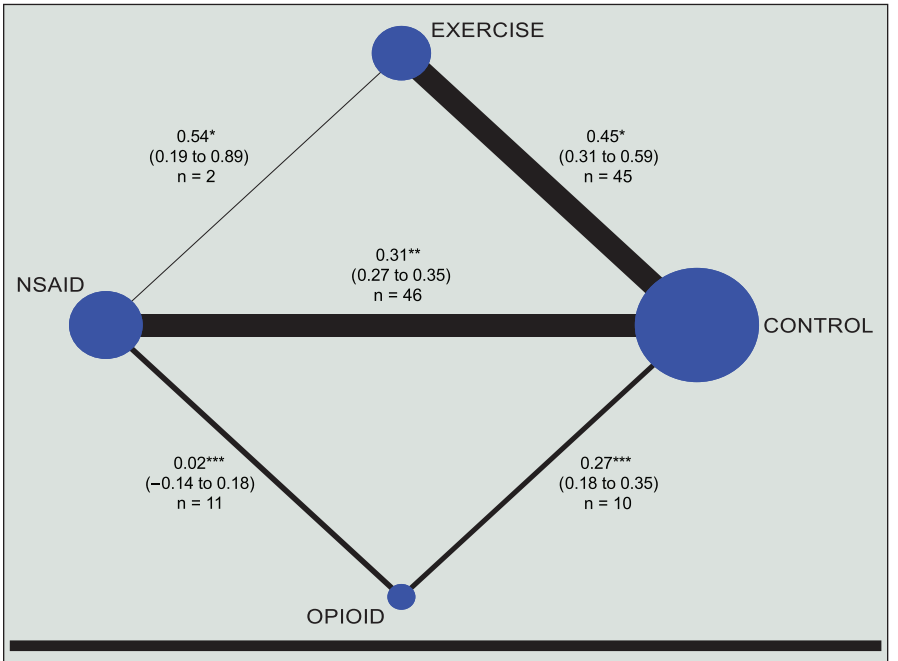

FIGURE 2. Graphic presentation of comparisons between control interventions (placebo or control), exercise therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids with standardized mean differences, 95% confidence intervals, and number of trials (n). No estimate available for exercise therapy vs opioids. *, favor exercise therapy; **, favor NSAIDs; ***, favor opioids.

Inconsistency in the Network Meta-analysis

The network meta-analysis did not provide a valid estimate for the comparison between exercise and opioids, as no trials with direct comparison were found and consistency was not reached (**FIGURE 2** and **TABLE 1**). Side-split tables revealed the largest difference between direct and indirect estimates in comparisons with exercise. The estimates in the network meta-analysis were dominated by trials comparing to placebo/control (**SUPPLEMENTAL FIGURE 1**), and the network meta-analysis showed considerable inconsistency (F[2, 109] = 4.78, P = .010). When we excluded 1 trial comparing exercise therapy with NSAIDs, which had extreme results from the network meta-analysis,[48] we observed overall model consistency (P = .709) while the estimates remained essentially the same.

Subgroup Analysis

In additional analyses, stratified by OA classification (only patients with knee

TABLE 1 Results From Network Meta-analysis Comparing Placebo/Control Interventions, Exercise Therapy, NSAIDs, and Opioids for Knee Osteoarthritis Pain[a]

Comparison	SMD (95% CI)	SMD Converted to mm VAS Pain (95% CI)	No. of Trials With Direct Comparison	SMD Favors	Nature of Evidence	Confidence	Downgrading Due to
Exercise vs control	0.45 (0.31 to 0.59)	7.6 (5.2 to 10.0)	45	Exercise	Mixed	Low	Study limitation,[b] inconsistency[c]
NSAIDs vs placebo	0.31 (0.27 to 0.35)	5.2 (4.6 to 5.9)	46	NSAIDs	Mixed	Moderate	Inconsistency[c]
Opioids vs placebo	0.27 (0.18 to 0.35)	4.6 (3.0 to 5.9)	10	Opioids	Mixed	Low	Study limitation,[b] inconsistency[c]
Exercise vs NSAIDs	0.54 (0.19 to 0.89)	9.1 (3.2 to 15.0)	2	Exercise	Mixed	Very low	Study limitation,[b] inconsistency,[c] imprecision[d]
Exercise vs opioids	NA	NA	NA	NA	None	NA	NA
NSAIDs vs opioids	0.02 (−0.14 to 0.18)	0.3 (−2.4 to 3.0)	11	Opioids	Mixed	Low	Study limitation,[b] imprecision[d]
Ranking of the treatment						*Low*	*Study limitation,[e] inconsistency[f]*

Abbreviations: CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs; SMD, standardized mean difference; VAS, visual analog scale.
[a]*Overall network meta-analysis heterogeneity, F test: F(2, 109) = 4.78, P = .01 and I2 = 6.6%.*
[b]*Evidence mainly from trials with high risk of bias.*
[c]*Inconsistency (ie, difference between direct and indirect evidence or difference in estimates of the included trials).*
[d]*Confidence interval includes values favoring either treatment.*
[e]*Study limitation (ie, almost 60% of the included trials were judged high risk of bias).*
[f]*Inconsistency (ie, inconsistency in the overall network meta-analysis).*

TABLE 2 Relative Ranking of Individual Treatments Estimated From the Network Meta-analysis

	Treatment			
Ranking	**Exercise**	**NSAIDs**	**Opioids**	**Control[a]**
Best	100.0	0.0	0.0	0.0
2nd	0.0	85.5	14.5	0.0
3rd	0.0	14.5	85.5	0.0
Worst	0.0	0.0	0.0	100.0
Mean rank	1.0	2.1	2.9	4.0
SUCRA	1.0	0.6	0.4	0.0

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; SUCRA, surface under the cumulative ranking curve.
[a]*Control: Placebo or control interventions.*

OA or patients with mixed knee and hip OA), age (over or under 61 years), and percentage of female participants in the study (over or under 70%), the estimates remained essentially the same (**SUPPLEMENTAL TABLE 4**).

Adverse Events

AEs were not consistently reported in the included trials, precluding meaningful summary measures. In trials comparing NSAIDs with opioids, a larger proportion of patients who received opioids reported experiencing AEs, and more patients dropped out for this reason. For an overview of the number and types of AEs, please refer to **SUPPLEMENTAL TABLE 5.**

Risk of Bias

One trial[33] had low risk of bias for all domains, and 2 trials[7,36] were considered low on all domains except "other bias," as these trials were sponsored by pharmaceutical companies or had authors who were employed by pharmaceutical companies. Many trials were scored as having high risk of bias or unclear risk of bias for "blinding of participants and personnel" (6/13 trials),[1,14,27,29,34,48] "blinding of outcome assessment" (6/13 trials),[1,14,27,29,34,48] "incomplete outcome data" (6/13 trials),[1,5,11,13,34,48] and "selective outcome reporting" (9/13 trials).[1,5,11,13,14,27,34,35,48] Between 5 and 8 trials had high risk of bias or uncertain risk on the remaining domains (**SUPPLEMENTAL TABLE 6**). Risk-of-bias assessment of the trials included to provide the external anchor is reported in **SUPPLEMENTAL TABLES 7-9.** An inspection of the funnel plot did not indicate a severe risk of publication bias for the overall network meta-analysis and pairwise comparisons (**SUPPLEMENTAL FIGURE 2**).

DISCUSSION

We were unable to identify any trials with direct comparison between exercise therapy and opioids for knee OA pain and could not provide any valid estimate for this comparison. Eleven trials investigated

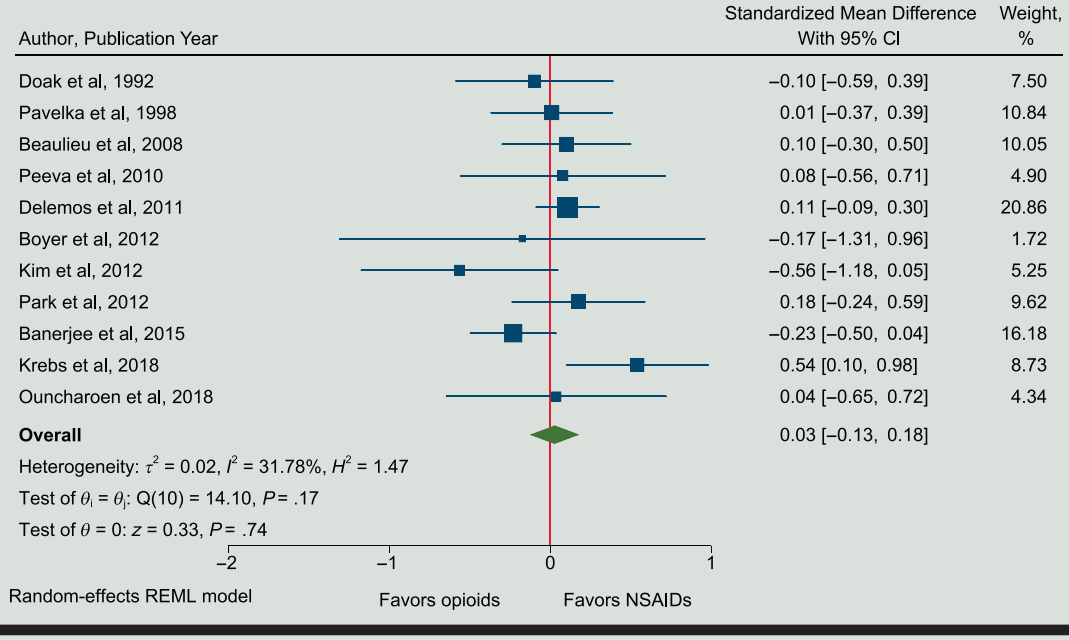

FIGURE 3. Results from the analysis of direct comparison of included trials comparing nonsteroidal anti-inflammatory drugs (NSAIDs) with opioids. Abbreviations: CI, confidence interval; REML, restricted maximum likelihood.

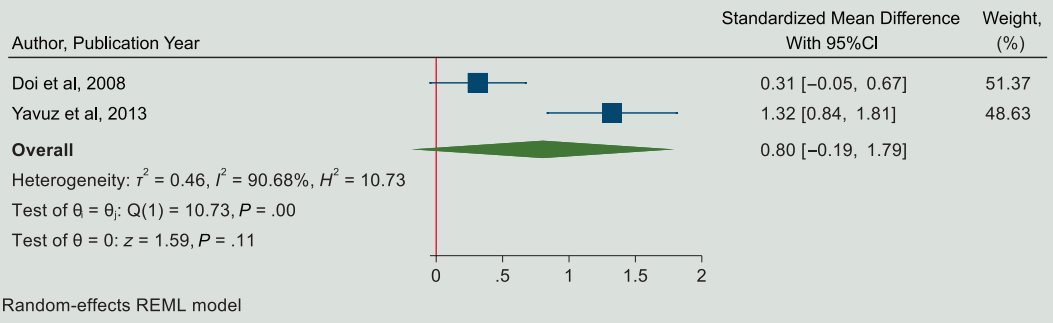

FIGURE 4. Results from the analysis of direct comparison of included trials comparing nonsteroidal anti-inflammatory drugs (NSAIDs) with exercise therapy. Abbreviations: CI, confidence interval; REML, restricted maximum likelihood.

NSAIDs vs opioids for knee OA pain, and the estimates from our network meta-analysis suggested similar pain-relieving effects, but with low confidence due to study limitations and imprecision. Exercise appeared superior for pain relief than NSAIDs, corresponding to 9.1 mm on a 0- to 100-mm VAS pain scale. However, this is unlikely to represent a clinically meaningful difference.[17,46] We have very low confidence in this estimate due to trial limitations (ie, only 2 high-risk-of-bias trials with direct comparison), inconsistency, and imprecision (ie, CIs overlapping the line of no effect). All 3 interventions showed small-to-moderate treatment effects when compared with placebo or control interventions. All estimates should be interpreted with caution, as estimates were driven by indirect comparisons, which highlights the need for trials comparing exercise therapy with NSAIDs and opioids.

A previous review attempting to compare the treatment effect of exercise therapy with analgesics for knee OA pain generally found no difference between interventions.[20] However, all estimates were based on indirect comparisons. We build on these findings by including trials with direct comparison between interventions. We initially aimed to only include trials with direct comparison between the 3 investigated interventions, but we had to adjust this strategy as we only found a limited number of trials with direct comparisons. To create an external anchor for the comparison in the network meta-analysis, we included data from relevant systematic reviews comparing opioids and NSAIDs to placebo as well as exercise therapy to control interventions (ie, active non-exercise intervention or no treatment including wait list). Thus, all estimates in this study are based on a mix of direct and indirect comparisons, and we could not provide any estimate comparing exercise therapy with opioids.

Comparison of Estimates From Network Meta-analyses With and Without External Anchor

Estimates from the analysis of NSAIDs vs opioids based on the network meta-analysis (SMD, 0.02) and the meta-analysis including direct comparisons alone (SMD, 0.03) for knee OA pain were similar. We found a considerable difference in the size of the estimates in the network meta-analysis with only direct comparisons for exercise therapy vs NSAIDs (SMD, 0.80) compared with the network meta-analysis including the external anchor (SMD, 0.54). The main reason for this discrepancy was that only 2 high-risk-of-bias trials were included in the direct comparison between exercise therapy (involving lower limb strengthening) and NSAIDs, with extreme results reported in 1 of these trials, resulting in high heterogeneity.

Risk of Harm

Use of NSAIDs for treating OA pain is associated with risk of harm. The risk of harm is greater with opioids, which also have a substantial addiction potential.[10,12,37,45] On the contrary, exercise therapy for knee OA pain has minimal or no risk of AEs[31,38] and is therefore unanimously recommended by international clinical guidelines as first-line treatment for all patients with knee OA.[30] However, quality-of-care utilization studies report that exercise therapy as treatment is greatly underprescribed.[32,4] Too many patients with OA are missing out on guideline-recommended first-line treatment, as they are directed to second-line pharmacological treatment.

Ranking Treatments

Our analyses ranked exercise first (low confidence) and suggested that exercise therapy may yield superior treatment effects to NSAIDs (compared head-to-head) and better treatment effects than NSAIDs and opioids when compared with placebo/control interventions for knee OA pain. This ranking suggests that a potential to reverse from second-line pharmacological care to first-line treatment with exercise therapy may exist for patients using NSAIDs and opioids, particularly those who initially missed out on proper first-line care. This is important for clinicians when considering treatment options for patients with knee OA pain who are using analgesics.

Limitations

We identified only a limited number of trials reporting direct comparisons between the investigated interventions.

Thus, we supplemented the network meta-analysis with data from trials comparing the interventions to placebo/control interventions. The majority of trials contributing to the network meta-analysis therefore provided data from indirect comparisons. We identified no trials comparing exercise therapy to opioids for knee OA pain, and as a result, we could not provide a valid estimate of this comparison despite addition of the external anchor. Similar to previous attempts to compare different analgesic interventions with exercise,[20] our review also suffers from the limitation that patients in the included trials comparing treatments (exercise, NSAIDs, and opioids) to placebo/control may have varying disease severity, and to a large extent, we rely on data from indirect comparisons.

Trials involving pharmacological interventions included a variety of NSAIDs and opioids. As the majority of trials with direct comparison of opioids used tramadol (7 out of 11), we extracted data from a recent Cochrane review on tramadol for OA.[45] For NSAIDs, a broader range of drugs was used in the included trials; thus, we opted to include data from the most recent systematic review that best matched this variation.[2]

We observed considerable inconsistency in the network meta-analysis. This was mainly due to an extreme effect size in 1 trial that compared exercise therapy with NSAIDs.[48] When we excluded the trial, the overall model reached consistency (P = .709), and estimates remained essentially the same. However, the heterogeneity in the comparison between NSAIDs and exercise remained high.

Ten of the 13 trials with direct comparisons between the 3 investigated interventions had unclear or high risk of bias on 2 or more domains. Some trials included both patients with knee and hip OA. To increase the number of included trials with direct comparisons, we decided to include these trials as most patients had knee OA, and in the analysis stratified by OA classification, results remained similar (**SUPPLEMENTAL TABLE 4**). Participants in crossover trials contributed with data to both the NSAID and opioid arms of these trials. This may result in the overestimation of the precision of the reported estimates.

Reporting of AEs varied in definition and reporting, and it was therefore not possible to pool these data in a meaningful way. We did not include disability as an outcome, as we considered pain was the main and most comparable domain targeted by the 3 interventions investigated.

There were some deviations from the registered protocol, as follows: (1) We decided to include trials with mixed populations as the majority of these patients typically have knee OA, (2) we created an external anchor in the network meta-analysis including trials comparing the 3 investigated interventions with placebo/control interventions, (3) we used the GRADE approach to assess the overall quality of evidence, and (4) a number of preplanned subgroup analyses could not be performed due to limited data availability.

CONCLUSION

Our network meta-analysis suggested exercise therapy as the best treatment for knee OA pain, followed by NSAIDs and opioids. Differences between treatments were likely not clinically relevant (<10-mm VAS pain), and the overall confidence in the ranking of treatments was low, with few trials reporting direct comparisons of exercise therapy, NSAIDs, and opioids. ◉

KEY POINTS

FINDINGS: Our network meta-analysis ranked exercise therapy as the best treatment for knee OA pain, followed by NSAIDs and opioids, although differences between treatments are likely not clinically relevant.

IMPLICATIONS: More high-quality studies with direct comparison are needed to better ascertain the comparative effectiveness of exercise therapy, NSAIDs, and opioids for knee OA pain. A potential to reverse from second-line pharmacological care to first-line treatment with exercise therapy may exist for patients using NSAIDs and opioids, particularly those who initially missed out on proper first-line care.

CAUTION: Only a small number of trials had direct comparison between exercise therapy and NSAIDs and between NSAIDs and opioids. No trials directly compared exercise therapy with opioids. The confidence in the estimates from the network meta-analysis was generally low.

STUDY DETAILS

AUTHOR CONTRIBUTIONS: Drs Thorlund, Simic, Day, Koes, and Juhl participated in the conception and design of the study. Drs Thorlund, Simic, Pihl, and Juhl and Dorthe Bang Berthelsen were responsible for the acquisition of data. Dr Juhl performed the analysis, and Drs Juhl and Thorlund interpreted the data. Dr Thorlund drafted the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version of the manuscript.

DATA SHARING: Data are available upon request. Extracted data from trials included in the network meta-analysis can be shared upon request to the corresponding author. There are no restrictions on reuse of data.

PATIENT AND PUBLIC INVOLVEMENT: No patients were involved in setting the research question or the conduct of this study.

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