



Comparable effects of exercise and analgesics for pain secondary to knee osteoarthritis: a meta-analysis of trials included in Cochrane systematic reviews

Aim: Evidence of comparative effectiveness of different treatment approaches is important for clinical decision-making, yet absent for most recommended treatments of knee osteoarthritis pain. The objective of this study was to estimate the comparative effectiveness of exercise versus orally administered analgesics for pain in patients with knee osteoarthritis. **Methods:** The Cochrane Database of systematic reviews was searched for meta-analyses of randomized controlled studies comparing exercise or analgesics with a control group (placebo or usual care) and with pain as an outcome. Individual study estimates were identified and effect sizes were calculated from group differences. We combined study-level effects on pain with a random effects meta-analysis and compared effect sizes between exercise trials and trials with analgesic interventions. **Results:** We included six Cochrane reviews (four pharmacology, two exercise). From these, 54 trials were eligible (20 pharmacology, 34 exercise), with 9806 participants (5627 pharmacology, 4179 exercise). The pooled effect size of pharmacological pain interventions was 0.41 (95% CI: 0.23–0.59) and for exercise 0.46 standardized mean difference (95% CI: 0.34–0.59). There was no statistically significant difference between the two types of intervention (difference: 0.06 standardized mean difference [95% CI: -0.28–0.16; $p = 0.61$]). **Conclusion:** This meta-epidemiological study provides indirect evidence that for knee osteoarthritis pain, the effects from exercise and from oral analgesics are comparable. These results may support shared decision-making where a patient for some reason is unable to exercise or who consider exercise as unviable and analgesics as a more feasible choice.

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Osteoarthritis (OA) of the knee is a chronic condition with pain as the cardinal symptom. There is currently no cure for OA; management focuses on reducing pain and restoring physical function. Recommended management strategies include nonpharmacological and/or pharmacological treatments. Among the nonpharmacological management strategies for knee OA, exercise is considered a core treatment [1–3] with

a small-to-moderate effect on pain. [4,5] Although several exercise types have been evaluated, no specific type has proven more effective at relieving pain than others [6]. Pharmacological treatments are recommended as adjunctive and in the lowest effective dose [1,3,7]. Acetaminophen is recommended for use as an analgesic in knee OA. [1,3] For symptomatic knee OA flare-ups, short periods of NSAIDs have docu-

Marius Henriksen^{*1,2}, Julie B Hansen¹, Louise Klokke¹, Henning Bliddal¹ & Robin Christensen¹

¹The Parker Institute, Copenhagen University Hospital at Bispebjerg & Frederiksberg, Copenhagen, Denmark

²Department of Physical & Occupational Therapy, Copenhagen University Hospital at Bispebjerg & Frederiksberg, Copenhagen, Denmark

*Author for correspondence: marhus.henriksen@regionh.dk

mented effects on pain but carry a risk of considerable and potentially harmful side effects. [8]

Despite the priority of exercise over pharmacological treatments in the recommended treatment algorithm [1,3], some patients may not be able to exercise or view exercise as unviable and may prefer pharmacological treatments. While a crude comparison of the pooled effect sizes of exercise and analgesics suggests similar magnitudes, [5] comparative studies are very sparse. One randomized trial in patients with knee OA compared 8 weeks of home exercise and NSAID treatment and found pain improvement in both groups but no significant group differences. [9] Further comparative effectiveness studies are needed in order to provide clinicians, patients and policy makers with relevant information about comparative effects of exercise and pharmacological treatment for knee OA pain.

To illuminate this issue, we performed a meta-epidemiological study based on published Cochrane reviews to make an indirect comparison [10] of the comparative effectiveness of exercise and pharmacological treatment of knee OA pain from existing evidence.

Methods

This study is a systematic review and meta-analysis based on an overarching systematic review titled 'Assessing bias in osteoarthritis trials included in Cochrane reviews: a meta-epidemiological study' [11]. The protocol for the parent study is registered on PROSPERO (CRD42013006924) and published [11]. This report conforms to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' statement [12].

Identification of cochrane reviews

From the original literature search of the Cochrane Database of Systematic Reviews, eligible trials were identified from published Cochrane reviews (i.e., meta-analyses). Eligible Cochrane reviews had to focus on knee OA and orally administered pharmaceutical analgesics or therapeutic exercise, and their analyses had to include pain as an outcome. Two reviewers (JB Hansen and L Klokke) independently assessed the eligibility of the individual Cochrane reviews; disagreement was resolved by discussing with a third arbiter (R Christensen).

Individual study identification, eligibility & data extraction

From the included reviews, individual studies were identified, assessed for eligibility and their data extracted. Individual studies were excluded if they were not randomized controlled trials (RCTs), if they did not include patients with knee OA, if they did not include pain as an outcome or if the control condition

was not considered inert (i.e., sham, placebo or no intervention control). Two reviewers (JB Hansen and L Klokke) independently assessed the eligibility of the individual studies, and disagreement was resolved by discussing with a third arbiter (M Henriksen). From the eligible studies, the following data were extracted: author, year of publication, journal, intervention (drug name or exercise type), comparator type, number of participants, pain outcome measure, study duration and effect estimates on pain (either by groups or as differences among groups), with uncertainty stated typically as standard deviations or confidence limits. If more than one analysis on pain was included in a study, we extracted estimates from the first available analysis, which was assumed to be the main analysis on pain. Two reviewers (JB Hansen and L Klokke) independently extracted data from each included study and resolved their disagreements by discussion. The risk of bias within each full-text trial was assessed using the risk of bias tool as recommended by the Cochrane Collaboration [13]. The risk of bias tool comprises assessment of reported methods for generating allocation sequence, managing incomplete outcome data and maintaining allocation concealment and blinding, as well as an assessment of risk of reporting bias. Each bias item was rated as adequate, inadequate or unclear.

Evidence synthesis

Effect sizes on pain were expressed as standardized mean differences (SMDs) estimated from each trial's mean and standard deviations abstracted from the Cochrane reviews. Assuming that there is no relevant difference in the SMD's based on follow-up and change data we decided to combine these estimates [14].

Using generic inverse variance analysis, we calculated pooled effect sizes for exercise and analgesics using a random effects model (restricted maximum likelihood), allowing for anticipated differences in treatment effects from study to study [15]. We stratified the analysis by treatment (pharmacology and exercise, respectively) comparing the pooled effect sizes. For sensitivity purposes we repeated the analysis using a fixed effects model to test the robustness of our findings.

Results

The literature search in the parent study was carried out on 31 January 2014 [11]. From the Cochrane reviews included in the original search, we identified six eligible Cochrane reviews, of which four were related to oral analgesics and two to exercise (Figure 1 & Supplementary data). From the included Cochrane reviews, we identified 54 trials that fulfilled the inclusion criteria (34 exercise, 20 analgesics), including 9806 patients with OA (4179 exercise, 5627

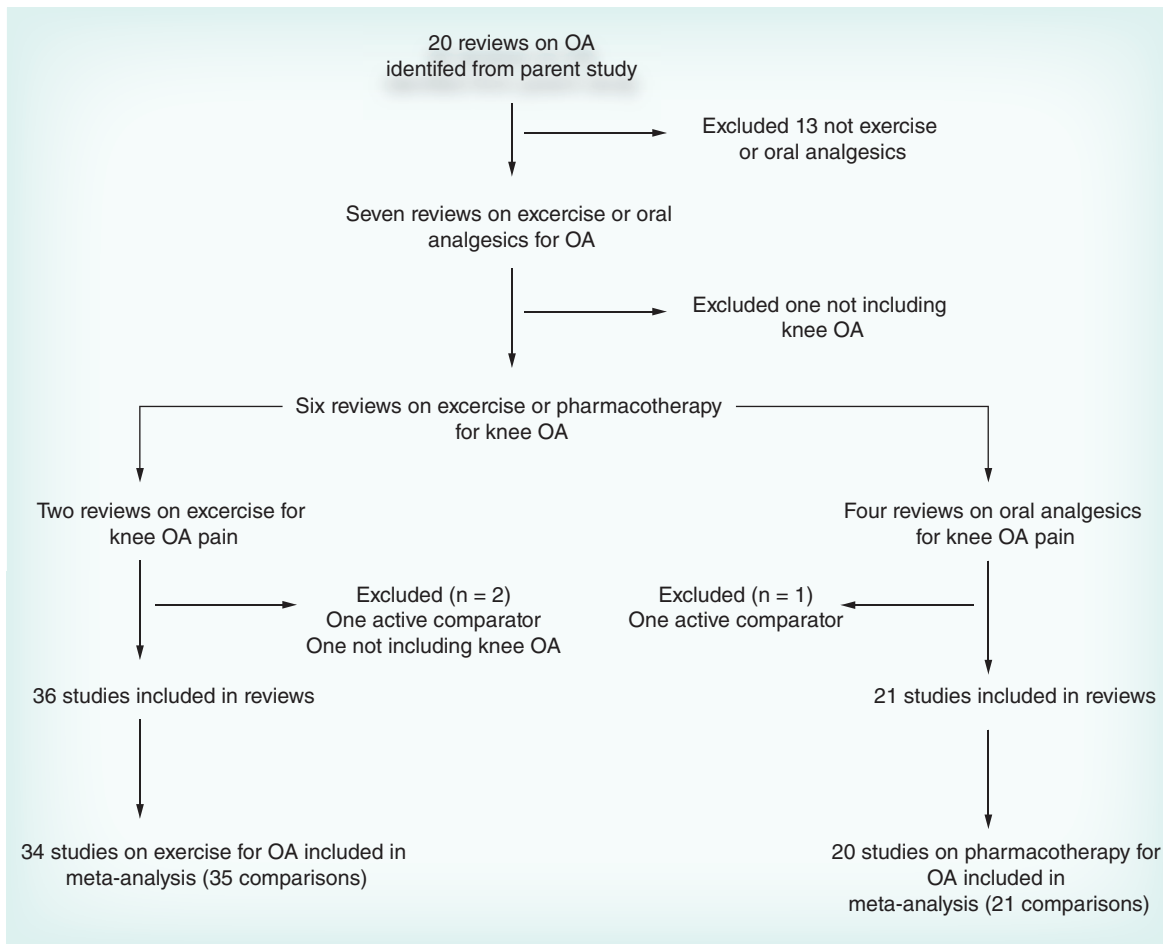


Figure 1. Flow diagram of study selection.
OA: Osteoarthritis.

analgesics) in 56 comparisons (35 exercise and 21 analgesics). Of the included trials, 34 included knee OA patients exclusively and 20 studied a mixed population of hip and knee OA. An overview of included studies is presented in [Table 1](#). The individual study SMDs are illustrated in [Figure 2](#).

The 35 comparisons of exercise with no intervention, sham or standard care were associated with an overall statistically significant benefit on pain, with an effect size of 0.46 (95% CI: 0.34–0.59) for pain ([Table 2](#)). Similarly, oral analgesics were associated with a statistically significant benefit on pain when compared with placebo or standard care, with an effect size of 0.41 (95% CI: 0.23–0.59). The comparison of the estimates allowed us to infer that for pain, exercise and orally administered analgesics demonstrated comparable effect sizes (judged by the width of the 95% CI), with a statistically nonsignificant difference in the SMDs of 0.06 (95% CI: -0.16 to -0.28).

The fixed effects analysis gave similar results but with lower SMDs for both exercise and pharmacological analgesics and with a statistically significant differ-

ence of 0.10 (95% CI: 0.01–0.19) in favor of exercise ([Table 2](#)).

Across all studies, the overall between-study heterogeneity was high, with an inconsistency index (I^2) of 54% (48% in the exercise trials and 63% in the pharmacology trials). In an attempt to explain between-study heterogeneity, we performed an additional stratification of the exercise and analgesics trials into more specified intervention types. Exercise trials were stratified by land and aquatic exercise, and the analgesics trials were stratified as acetaminophen, NSAID and opioids. No statistically significant differential responses on pain were observed ([Table 2](#)) and the additional stratified analysis did not result in lower between-study heterogeneity ($I^2 = 54\%$). We further stratified for population (knee OA vs mixed knee and hip OA patients) and found similar estimates for these populations; knee OA: SMD = 0.47 (95% CI: 0.34–0.60); mixed knee and hip OA: SMD = 0.40 (95% CI: 0.23–0.57), with no statistically significant difference in the SMDs (difference: 0.07 [95% CI: -0.14–0.29] in potential favor of the knee OA only population).

Table 1. Overview of the included studies.

Source cochrane review (year)	Study (year)	Population	Intervention	ITT population (n)	Intervention group (n)	Control group (n)	Study duration (weeks)	Control intervention	Outcome
Garner (2008) [16]	Day (2000) [17]	Mixed knee and hip	NSAID	316	242	74	6	Sham/ placebo	WOMAC pain
	Ehrich (1999) [18]	Mixed knee and hip	NSAID	145	73	72	6	Sham/ placebo	WOMAC pain
	Gibofsky (2003) [19]	Mixed knee and hip	NSAID	286	190	96	6	Sham/ placebo	VAS global
	Truitt (2001) [20]	Mixed knee and hip	NSAID	108	56	52	6	Sham/ placebo	VAS global
Nüesch (2009) [21]	Peloso (2000) [22]	Mixed knee and hip	Opioids	66	31	35	4	Sham/ placebo	VAS global
	Langford (2006) [23]	Mixed knee and hip	Opioids	399	202	197	8	Sham/ placebo	VAS global
	Caldwell (2002) [24]	Mixed knee and hip	Opioids	295	222	73	4	Sham/ placebo	WOMAC pain
	Markenson (2005) [25]	Mixed knee and hip	Opioids	107	56	51	13	Standard care	WOMAC pain
	Chindalore (2005) [26]	Mixed knee and hip	Opioids	360	309	51	4	Sham/ placebo	WOMAC pain
	Matsumoto (2005) (a) [27]	Mixed knee and hip	Opioids	179	120	59	4	Sham/ placebo	WOMAC pain
	Zutra (2005) [28]	Mixed knee and hip	Opioids	104	55	49	13	Sham/ placebo	VAS global
	Matsumoto (2005) (b) [27]	Mixed knee and hip	Opioids	288	228	60	4	Sham/ placebo	WOMAC pain
	Kivitz (2006) [29]	Mixed knee and hip	Opioids	357	270	87	2	Sham/ placebo	VAS global
Towheed (2009) [30]	Case (2003) [31]	Knee	Acetaminophen	57	29	28	12	Sham/ placebo	WOMAC pain
	Pincus (2004) (a) [32]	Mixed knee and hip	Acetaminophen	343	171	172	6	Sham/ placebo	WOMAC pain
	Pincus (2004) (b) [32]	Mixed knee and hip	Acetaminophen	367	185	182	6	Sham/ placebo	WOMAC pain
	Golden (2004) [33]	Knee	Acetaminophen	294	145	149	1	Sham/ placebo	0–4 Scale

(a) and (b) denotes that a study had two intervention groups that are being treated as two trials.

AIMS: Arthritis Impact Measurement Scale; ITT: Inten-to-treat; KOOS: Knee Injury and Osteoarthritis Outcome Score; OAS: Osteoarthritis Screening Index; VAS: Visual Analog Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Table 1. Overview of the included studies (cont.).

Source cochrane review (year)	Study (year)	Population	Intervention	ITT population (n)	Intervention group (n)	Control group (n)	Study duration (weeks)	Control intervention	Outcome
Towheed (2009) [30] (cont.)	Miceli-Richard (2004) [34]	Mixed knee and hip	Acetaminophen	774	401	373	6	Sham/ placebo	VAS
Cepeda (2009) [35]	Babul (2004) [36]	Knee	Acetaminophen	246	124	122	12	Sham/ placebo	VAS
	Emkey (2004) [37]	Knee	Acetaminophen	306	153	153	13	Sham/ placebo	VAS
	Malonne (2004) [38]	Mixed knee and hip	Acetaminophen	230	111	119	2	Sham/ placebo	VAS
Bartels (2007) [39]	Cochrane (2005) [40]	Mixed knee and hip	Exercise aquatic	310	152	158	12	Standard care	WOMAC pain
	Foley (2003) (a) [41]	Mixed knee and hip	Exercise aquatic	47	35	12	6	No intervention	WOMAC pain
	Wang (2004) [42]	Mixed knee and hip	Exercise aquatic	43	21	22	12	Standard care	VAS
	Patrick (2001) [43]	Mixed knee and hip	Exercise aquatic	215	98	117	20	Standard care	HAQ pain
Fransen (2009) [4]	Baker (2001) [44]	Knee	Exercise land based	44	22	22	16	Standard care	WOMAC pain
	Bautch (1997) [45]	Knee	Exercise land based	30	15	15	12	Standard care	VAS
	Bennell (2005) [46]	Knee	Exercise land based	140	73	67	12	Sham/ placebo	VAS
	Deyle (2000) [47]	Knee	Exercise land based	69	33	36	8	Standard care	WOMAC pain
	Ettinger (1997) (a) [48]	Knee	Exercise land based	218	144	74	12	Standard care	FASTx6
	Ettinger (1997) (b) [48]	Knee	Exercise land based	221	146	75	12	Standard care	FASTx6
	Foley (2003) (b) [41]	Knee	Exercise land based	35	21	14	6	No intervention	WOMAC pain
	Fransen (2001) [49]	Knee	Exercise land based	126	83	43	8	No intervention	WOMAC pain

(a) and (b) denotes that a study had two intervention groups that are being treated as two trials.
 AIMS: Arthritis Impact Measurement Scale; ITT: Inten-to-treat; KOOS: Knee Injury and Osteoarthritis Outcome Score; OASI: Osteoarthritis Screening Index; VAS: Visual Analog Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Table 1. Overview of the included studies (cont.).

Source cochrane review (year)	Study (year)	Population	Intervention	ITT population (n)	Intervention group (n)	Control group (n)	Study duration (weeks)	Control intervention	Outcome
Fransen (2009) [4] (cont.)	Fransen (2007) [50]	Knee	Exercise land based	77	41	36	12	No intervention	WOMAC pain
	Gur (2002) [51]	Knee	Exercise land based	23	17	6	8	No intervention	VAS
	Hay (2006) [52]	Knee	Exercise land based	182	93	89	12	No intervention	WOMAC pain
	Hopman-Rock (2000) [53]	Knee	Exercise land based	80	45	35	6	No intervention	VAS
	Huang (2003) [54]	Knee	Exercise land based	132	99	33	8	No intervention	VAS
	Hughes (2004) [55]	Knee	Exercise land based	111	68	43	8	No intervention	WOMAC pain
	Huang (2005) [56]	Knee	Exercise land based	65	30	35	8	No intervention	VAS
	Keefe (2004) [57]	Knee	Exercise land based	25	16	9	12	No intervention	AIMS pain
	Kovar (1992) [58]	Knee	Exercise land based	92	47	45	8	Standard care	AIMS pain
	Maurer (1999) [59]	Knee	Exercise land based	98	49	49	8	Standard care	WOMAC pain
	Messier (2004) [60]	Knee	Exercise land based	158	80	78	24	Standard care	WOMAC pain
	Minor (1989) [61]	Knee	Exercise land based	68	49	19	12	Standard care	AIMS pain
	O'Reilly (1999) [62]	Knee	Exercise land based	180	108	72	24	No intervention	WOMAC pain
	Peloquin (1999) [63]	Knee	Exercise land based	124	59	65	12	No intervention	AIMS pain
	Quilty (2003) [64]	Knee	Exercise land based	87	43	44	20	No intervention	VAS
	Rogind (1998) [65]	Knee	Exercise land based	23	11	12	12	No intervention	VAS

(a) and (b) denotes that a study had two intervention groups that are being treated as two trials.

AIMS: Arthritis Impact Measurement Scale; ITT: Inten-to-treat; KOOS: Knee Injury and Osteoarthritis Outcome Score; OASI: Osteoarthritis Screening Index; VAS: Visual Analog Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Source cochrane review (year)	Study (year)	Population	Intervention	ITT population (n)	Intervention group (n)	Control group (n)	Study duration (weeks)	Control intervention	Outcome
Fransen (2009) [4] (cont.)	Schilke (1996) [66]	Knee	Exercise land based	20	10	10	8	No intervention	OASI pain
	Song (2003) [67]	Knee	Exercise land based	43	22	21	12	Standard care	WOMAC pain
	Talbot (2003) [68]	Knee	Exercise land based	34	17	17	12	Standard care	McGill
	Thomas (2002) [69]	Knee	Exercise land based	783	467	316	104	No intervention	WOMAC pain
	Thorstensson (2005) [70]	Knee	Exercise land based	61	30	31	6	No intervention	KOOS pain
	Topp (2002) [71]	Knee	Exercise land based	102	67	35	16	No intervention	WOMAC pain
	van Baar (1998) [72]	Knee	Exercise land based	113	54	59	12	Standard care	VAS
(a) and (b) denotes that a study had two intervention groups that are being treated as two trials. AIMS: Arthritis Impact Measurement Scale; ITT: Inten-to-treat; KOOS: Knee Injury and Osteoarthritis Outcome Score; OASI: Osteoarthritis Screening Index; VAS: Visual Analog Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.									

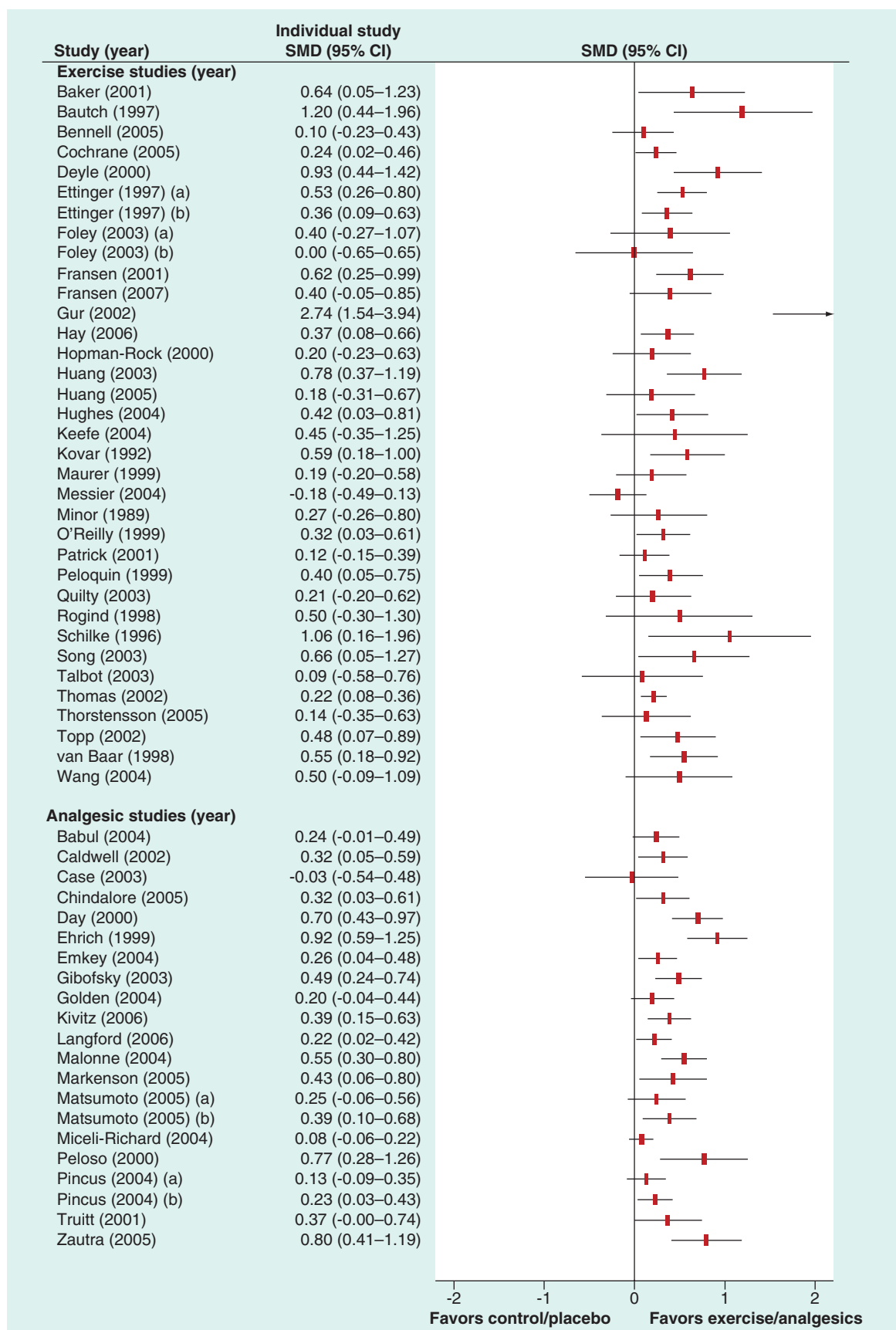


Figure 2. Forest plot of effect sizes for exercise and orally administered analgesics interventions for knee osteoarthritis pain (see facing page). Arrow indicates an estimate beyond the current x-axis scale.

SMD: Standardized mean difference.

Risk of bias assessments

Among the 21 comparisons examining analgesics for treating pain in OA, the participants' knowledge of the allocated intervention was adequately prevented in 86% (18) of the comparisons. In the 35 studies on exercise, only 6% (two studies) adequately prevented the participants' knowledge of the allocated intervention. The handling of missing data was reported adequately in 95% of the analgesics comparisons, as opposed to only 57% of the exercise comparisons. For blinding of key study personnel, 71% of the analgesics comparisons adequately prevented the knowledge of the allocated intervention versus 49% of the exercise comparisons. Concerning the reported methods to generate allocation sequences, 57% of the analgesics comparisons and 69% of the exercise group performed it adequately. Concealment of allocation was adequate in 38% of the analgesics group and 43% of the exercise group.

Discussion

This meta-epidemiological study based on trials included in Cochrane reviews, included 54 RCTs with 9806 patients, suggests comparable effects of exercise and orally administered analgesics for the conservative management of pain secondary to knee OA. Almost two-thirds of the reviewed trials pertained to exercise, which points out a trend toward testing exercise interventions for knee OA pain. This highlights the changed landscape of management and research in knee OA pain, which increasingly favors nonpharmacological interventions over drug interventions.

Our results indicate that exercise and oral analgesics are comparable in terms of their pain relieving benefits, which supports the recommendation that exercise should be considered as the first choice, possibly accompanied by analgesics for control of severe pain or pain exacerbations [1–3]. The feasibility of a standardized analgesic prescription to allow for participation in exercise therapy has recently been demonstrated, although this needs to be confirmed in a randomized trial [73]. However, for patients who are unable to exercise or prefer not to engage in an exercise program, these results indicate that oral analgesics yield similar benefits for knee OA pain.

We considered exercise interventions as a group. However, more nuanced considerations of the effectiveness of different types, intensities, frequencies and durations of exercise are warranted. A recent systematic review concluded that – based on available evidence – it is not possible to identify one particular type of exercise as superior for knee OA [6]. Thus, present recommendations are simply that 'any exercise' is beneficial for managing knee OA

pain; the optimal exercise program in terms of application and content is elusive, and comparative effectiveness studies are needed. This contrasts with pharmacological interventions, in which dosage and frequencies are established in preclinical phases of drug development.

We also considered oral analgesics as a group in the main analysis (i.e., we pooled analgesics covering acetaminophen, NSAIDs and opioids). These analgesics have different mechanisms of action and are intended for different populations of people with knee OA; intermittent use of over-the-counter acetaminophen is recommended as basic pain management in people without significant comorbidities, whereas in the absence of satisfactory clinical response, a full-dose of acetaminophen (4000 mg/day) or switching to NSAIDs is recommended [1,74]. Finally, opioids are recommended for patients with severe pain and inadequate response to both first-line pharmacological and nonpharmacological modalities [1,74]. However, in our stratified analyses we could not identify differential effects of the various analgesics against the different exercise types. Importantly, the majority of the included trials on oral analgesics and all included trials on aquatic exercise studied mixed populations of knee and hip OA patients, whereas as the included land-based exercise trials focused on knee OA patients alone. Although we found no differential effects based on population, this highlights that differences in study populations among different drug and exercise trials are important to consider when comparing effect estimates.

The stratified analyses should be interpreted cautiously, mainly due to the indirectness of the comparisons, but also because the different stratified comparisons are based on relatively few studies and are associated with broad confidence intervals meaning that further research is very likely to change the estimated differences in effects between the various analgesics and exercise types.

The Osteoarthritis Research Society International guidelines for the nonsurgical management of knee OA pain emphasize exercise as a core treatment appropriate for all individuals with knee OA [3]. However, the dearth of evidence on exercise type, frequency, intensity and duration leaves substantial uncertainty about which patients would benefit more from what type of exercise, and which forms of exercise may not be effective in different settings and subpopulations. Similarly, it is also not fully established which patient populations that benefit more from specific pharmacological interventions. A further complicating matter is the limited evidence on the potential harmful effects of exercise; adverse events associated with exercise are not

Table 2. Summary of the effect sizes for exercise and pharmacological analgesics intervention for knee osteoarthritis pain and the indirect comparisons of the effects sizes.

Analysis	SMD	SE	95% CI:	p-value	I ² (%)
Random effects analysis					
Overall	0.44	0.06	-0.54 to -0.33	<0.0001	54
Exercise	0.46	0.07	0.34–0.59	<0.0001	48
Analgesics	0.41	0.09	0.23–0.59	<0.0001	63
Exercise versus pharma	0.06	0.11	-0.16–0.28	0.61	–
Stratified analysis					
Exercise aquatic	0.22	0.19	-0.16–0.60	0.259	0
Exercise land	0.49	0.07	0.36–0.63	0.000	51
Acetaminophen	0.23	0.16	-0.08–0.53	0.143	41
NSAIDs	0.60	0.19	0.22–0.98	0.002	51
Opioids	0.45	0.14	0.18–0.71	0.001	23
Ex. aqua versus acetaminophen	-0.01	0.25	-0.50–0.48	0.97	–
Ex. aqua versus NSAIDs	-0.38	0.28	-0.92–0.16	0.16	–
Ex. aqua versus opioids	-0.23	0.24	-0.69–0.24	0.34	–
Ex. land versus acetaminophen	0.27	0.17	-0.07–0.60	0.12	–
Ex. land versus NSAIDs	-0.11	0.21	-0.51–0.30	0.60	–
Ex. land versus opioids	0.05	0.15	-0.25–0.35	0.75	–

SE: Standard error; SMD: Standardized mean difference.

systematically reported in individual trials. This contrasts the studies on analgesics, in which safety considerations are mandatory. Although exercise is generally considered safe, the statement that the potential risks associated with exercise are lower than those associated with drugs is weakly supported by evidence. Such a statement highlights the need for careful considerations about potential harms associated with prescribing exercise for knee OA patients to manage pain and also recording of harms in exercise trials.

It is worth noting that the analgesic trials mainly used placebo comparators (20/21 comparisons; Table 1), whereas the exercise trials mainly used 'no-intervention control' or 'care as usual' comparators (34/35 comparisons; Table 1). Thus, the estimated effect size of analgesics represents the net effect (i.e., gross effect minus the placebo effect), whereas the effect sizes of exercise represent the gross effect, including participant nonblinding and attention biases that are difficult to avoid in exercise studies. This finding suggests that the estimated effect size of exercise may be inflated (relative to the placebo

controlled studies on analgesics), and the difference between analgesics and exercise may be underestimated. In fact, a study testing nonpharmacological interventions against placebo found a considerably reduced effect size [46]. On the other hand, in most exercise studies, concurrent use of oral analgesics is typically not prohibited – at least not in 'no-intervention control' or 'care as usual' groups. This could suggest that the estimated effect of exercise reflects the added benefit of exercise over and above the benefit conferred from habitual analgesic usage. However, very few exercise studies report on or regulate concomitant habitual analgesic usage.

Strengths & limitations of this study

A strength of our meta-review approach is our inclusion of relevant high-quality evidence only, as Cochrane reviews are considered the highest level of evidence in the hierarchy of study designs and are unlikely to conflict with other high-quality systematic reviews. Also, Cochrane reviews represent the first-line source of evidence information for many clinicians, and thus the present study

provides a clinically relevant, yet indirect, comparison that is otherwise unavailable. However, it is an important limitation that Cochrane reviews were the only source of study estimates included, and the omission of other systematic reviews or primary studies may have resulted in underrepresentation of the available evidence. Indeed, the included reviews were last updated in 2007–2009, except for the Cochrane review on land-based exercise that was recently updated [75]. The updated Cochrane review on land-based exercise was published after the current literature search and was thus not included in the present study. However, the updated review [75] came to the same conclusion as the review we included, [4] with only a slight increase in the estimated effect size on pain. Furthermore, a recent systematic review concluded that already in 2002, the cumulative evidence supporting exercise for managing knee OA pain was sufficient and that further RCTs were unlikely to change the estimated effects of exercise [76]. With regards to the lack of recent updates of the Cochrane reviews on the analgesics, the estimates related to the analgesics included here are also considered stable [5] and compares well with estimates from a recent systematic review and network meta-analysis on pharmacological interventions for knee OA. [77] Thus, although the source of our data is 5–7 years old, we believe our estimated comparative effectiveness on pain is robust.

Although our results suggest that exercise and oral analgesics seem to have comparable effectiveness, our findings should be interpreted with caution, given the indirectness of the comparison and different settings and populations involved in the underlying studies. For example, selection criteria in pharmaceutical trials are usually more restrictive (e.g., exclusion of subjects with cardiac disease) than in exercise trials, although the majority of the pharmaceutical trials included in this review targeted a mixed population of knee and hip OA patients. The between-study heterogeneity was not negligible and it is possible that potential imbalances in the distribution of unobserved or unmeasured modifiers across interventions affected the comparative estimates. It should also be noted that we compared only effects on pain. Physical function and overall well being are also considered as core outcomes in knee OA, but the comparative effectiveness of these outcomes remains unknown.

Studies on therapeutic exercise for knee OA generally lack clear descriptions of many potential factors that may explain the success or failure of the intervention, such as the setting in which the exercise was undertaken, content of the exercise program and how it was carried out. It is particularly important to characterize the so-called ‘contextual factors’ and ‘supportive information’ (e.g., extent of supervision, progression protocols, individualized vs

group exercise, facility or home based among others), which can allow clinicians to replicate successful interventions. There is an urgent need to improve the reporting on frequency, intensity, type and time factors of exercise therapy. This concerns both the exercise program as intended, as well as the exercise program as actually performed (because of nonadherence). Most exercise trials are inherently biased due to their lack of patient blinding and their inclusion of a no-intervention control group as comparator, whereas pharmacological trials are more easily designed to minimize such biases. The included exercise trials are generally smaller and with longer durations than the trials on analgesics that on the other hand typically are done in a multicenter setup. The included exercise trials are mostly supported by nonprofit funding sources, whereas pharmacological studies typically are funded by for-profit sources, which may also introduce risks of bias. Finally, an important limitation is a missing comparison of safety. However, safety is difficult to compare because adverse reactions to exercise are extremely rarely reported.

Despite these limitations we believe that this meta-epidemiological overview provides an informative summary of the comparative effectiveness of exercise-based and pharmacological pain relief in knee OA, which may guide clinical discussions and decisions. Despite comparable effects, the evidence is indirect and future studies on comparative effectiveness and safety are warranted. The present study have synthesized the useful conclusions that can be drawn from Cochrane Systematic Reviews to support evidence-based decisions for conservative management of knee OA pain and to inform future clinical research agendas.

Conclusion

This meta-epidemiological study provides indirect evidence of comparable effects of exercise and oral analgesics for treating pain secondary to knee OA. These results can inform and support clinical management of patients that for some reason are unable to exercise or who consider exercise unviable.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/cer-2016-0007

Author contributions

M Henriksen had full access to all the data in the study and takes responsibility of for the integrity of the data and the accuracy of the data analysis. The study was conceptualised and designed by M Henriksen, H Bliddal, R Christensen. Data was acquired, analyzed and interpreted by all authors. The manuscript was drafted by M Henriksen and subsequently critically revised for important

intellectual content by all authors. The statistical analyses were carried out by R Christensen. Administrative, technical, or material support: M Henriksen, H Bliddal, R Christensen. Details of the literature search, the search results and reasons for exclusion are available from the corresponding author M Henriksen.

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Executive summary

- Comparative effectiveness of different recommended treatments of knee osteoarthritis pain is lacking.
- In this study the comparative effectiveness of exercise versus orally administered analgesics for pain in patients with knee osteoarthritis was assessed.
- We made an indirect comparison of the effectiveness of exercise and oral analgesics on knee osteoarthritis pain from published Cochrane reviews.
- The results provide indirect evidence of comparable effects of exercise and oral analgesics for treating pain secondary to knee osteoarthritis.
- These results can inform and support clinical management of patients that for some reason are unable to exercise or who consider exercise unviable.

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