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Review

Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: A meta-analysis of randomised placebo-controlled trials

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Abstract

Background: Pain is the most debilitating symptom in osteoarthritis of the knee (OAK).
Aim and methods: To determine the short-term pain-relieving effects of seven commonly used pharmacological agents for OAK pain by performing a systematic review of randomised placebo-controlled trials.
Results: In total, 14,060 patients in 63 trials were evaluated. Opioids and oral NSAIDs therapy in patients with moderate to severe pain (mean baseline 64.3 and 72.8 mm on VAS respectively) had maximum efficacies compared to placebo at 2–4 weeks of 10.5 mm [95% CI: 7.4–13.7] and 10.2 mm [95% CI: 8.8–11.2] respectively. The efficacy of opioids may be inflated by high withdrawal rates (24–50%) and "best-case" scenarios reported in intention-to-treat analyses. In patients with moderate pain scores on VAS (mean range from 51 to 57 mm), intra-articular steroid injections and topical NSAIDs had maximum efficacies at 1–3 weeks of 14.5 mm [95% CI: 9.7–19.2] and 11.6 mm [95% CI: 7.4–15.7], respectively. Paracetamol, glucosamin sulphate and chondroitin sulphate had maximum mean efficacies at 1–4 weeks of only 4.7 mm or lower.

Heterogeneity tests revealed that best efficacy values of topical NSAIDs may be slightly deflated, while data for oral NSAIDs may be slightly inflated due to probable patient selection bias.
Conclusion: Clinical effects from pharmacological interventions in OAK are small and limited to the first 2–3 weeks after start of treatment. The pain-relieving effects over placebo in OAK are smaller than the patient-reported thresholds for relevant improvement.

Keywords: Systematic review; Knee; Osteoarthritis; NSAID; Drug therapy

1. Introduction

Osteoarthritis of the knee (OAK) is a common condition (Andrianakos et al., 2003) with increasing prevalence (Felson et al., 2000). OAK is associated with pain and inflammation of the joint capsule (Vaatainen et al., 1998; Suenaga et al., 2001; Speldewinde et al., 2001), impaired muscular stabilisation (Radebold et al., 2001; Cowan et al., 2001), reduced range of motion (Steultjens et al., 2000), and functional disability (Altman et al., 1986). European League Against Rheumatism (EULAR) guidelines state that both pharmacological and non-pharmacologial interventions are

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needed for optimal treatment of OAK. Among pharmacological agents, first-line recommended treatment is oral paracetamol, followed by non-steroidal antiinflammatory drugs (NSAIDs). Selective cyclooxygenase 2 inhibitor NSAIDs (coxibs) are recommended for patients at risk of developing adverse gastrointestinal effects. Other recommended pharmacotherapies include glucosamine or chondroitin sulphate and intra-articular steroid injections (Jordan et al., 2003).

A recent UK patient survey showed that pharmacological strategies dominate pain management of OA, with 50% of patients using NSAIDs (1/3 of which use coxibs) and 15% using paracetamol (OA Nation survey UK, 2003). Paracetamol, NSAIDs and steroid injections have symptomatic effects and do not affect disease progression in any beneficial way (Scott et al., 2000). In contrast, glucosamine sulphate and chondroitin sulphate have been claimed to exert their effect by modifying cartilage structure and thereby slowing disease progression (Bruyere et al., 2004). The various agents may also differ in terms of time to onset and maximum analgesic efficacy (Godwin and Dawes, 2004; Richy et al., 2003).

Based on empirical data, clinically relevant thresholds or treatment targets have recently been established for OAK (Bijlsma, 2005). For pain, the average minimal perceptible clinical improvement and the minimal clinically important improvement have been reported to correspond to mean changes of 9.7 and 19.9 mm on WOMAC or a 100 mm visual analogue scale (VAS), respectively (Ehrich et al., 2000; Bijlsma, 2005), and 12.3 mm on VAS has been reported to correspond to a pain reduction which defines a categorical shift from "unchanged" to "slight improvement" (Angst et al., 2002). This has been termed the minimal clinically important difference. All these changes refer to baseline pain of approximately 60 mm on VAS, as higher baseline pain scores requires higher VAS-values of change (Farrar et al., 2001).

In a survey of 447 general practitioners in the UK, 99% reported that pain management advice was an integral part of patient care in OAK (Bedson et al., 2003). For clinicians, important questions are not only whether an intervention is effective over placebo or not, but also the time of onset and duration compared to other interventions. Meta-analyses can be used for reliable comparison of the efficacy of different interventions (Song et al., 2003). Although several meta-analyses on OAK have been published, different review protocols and heterogenous selections of outcomes hamper comparisons between interventions. Meta-analyses based on end-of-treatment results vary in time from 2 to 13 weeks for oral NSAIDs (Jordan et al., 2003; Bjordal et al., 2004) and from 4 to 156 weeks for glucosamine sulphate (Richy et al., 2003; Towheed et al., 2005). For topical NSAIDs, efficacy estimates have been based on five OAK trials with categorical data (Mason et al., 2004), while other meta-analyses for topical NSAIDs (Lin et al., 2004) and paracetamol (Zhang et al., 2004) have included other OA locations too. For steroid injections, meta-analyses have demonstrated variable efficacy at different time-points (Godwin and Dawes, 2004; Arroll and Goodyear-Smith, 2004; Bellamy et al., 2005). The aims of the current study were threefold. We wanted (1) to identify the timepoint of maximum effect, (2) to determine the effect size over placebo, and (3) to relate the pain-relieving efficacy over placebo to patient-centered outcome thresholds. For these purposes, we decided to evaluate efficacy under the same protocol criteria for seven widely used pharmacological interventions in OAK (Mazieres et al., 2005).

2. Materials and methods

2.1. Review protocol specification

A detailed review protocol was specified prior to analysis. This included a sequential three-step reviewing procedure of (1) harvesting randomised placebo-controlled trials where patients were treated with specified interventions for knee ostoarthritis, (2) evaluating their methodological quality according to predefined criteria, and (3) calculating their pooled effect as the weighted mean difference (WMD) in change between active drug and placebo groups in mm on VAS.

2.2. Literature search

A specified literature search was performed from 1966 through November 2005 on Medline, EMBASE, PedRo and the Cochrane Controlled Trials Register for randomised controlled trials (RCTs). In addition, cross-checking of reference lists in systematic reviews, search of conference abstracts and discussions with clinical experts were undertaken. Papers in English, German and Scandinavian languages were eligible for inclusion.

Key words were knee, osteoarthritis, randomised, controlled, placebo, NSAID, coxib, COX-2 inhibitor.

3. Methods

3.1. Inclusion criteria

The trials were subjected to 5 inclusion criteria:

Diagnosis: Knee osteoarthritis verified by clinical examination according to the American College of Rheumatology criteria and/or by X-ray. If less than 4 trials were available for an intervention, trials also including hip OA were considered, if more than 2/3 of their patients had OAK.

Symptom duration: More than 3 months.

Trial design: Randomised blinded placebo-controlled parallel groups design.

Outcome measures:

Primary outcome measure: Pain intensity within 4 weeks of treatment start scored on the Western Ontario and McMaster Universities osteoarthritis index (WOMAC) subscale of pain, or on a 100 mm VAS for global or walking pain.

Secondary outcome measure: Pain intensity, as measured for the primary outcome measure, at 8–12 weeks follow-up.

Intervention groups:

Identical placebo drug and adequate daily defined drug dosage equal to or exceeding:

Paracetamol: 4 g

Oral NSAIDs: Diclofenac 100 mg, etodolac 400 mg, ibuprofen 2,400 mg, nabumetone 1,500 mg, naproxen 1,000 mg, oxaprozin 1,200 mg, tiaprofenic acid 600 mg valdecoxib 10 mg, celecoxib 200 mg, meloxicam 7.5 mg, etoricoxib 30 mg, lumiracoxib 200 mg, rofecoxib 12.5 mg.

Topical NSAIDs: Diclofenac, piroxicam or meloxicam 1% and ibuprofen gel 3%

Steroid injection: Triamcinolone 20 mg, methylprednisolone 40 mg, cortivazol 3.75 mg

Glucosamine sulphate 1500 mg

Chondroitin sulphate 800 mg

Opioids: 50 mg codeine, 20 mg oxymorphone, 20 mg oxycodone, 30 mg morphine sulphate, 100 mg tramadol

3.2. Outcome measure extraction

The change in overall pain intensity between the active intervention group and placebo was used. If more than one attainable outcome measure was obtained in the first 4 weeks after treatment started, the time point corresponding to the largest effect values was selected. If data on overall pain intensity were missing, data were obtained as a mean of the 5 items on the WOMAC pain subscale. If WOMAC data were registered on non-continuous (categorical, Likert) scales, they were converted to 100 mm VAS and checked against other subscales and overall WOMAC score, as this has been found to have good internal consistency (Roos et al., 1999). If overall pain or WOMAC pain subscale data were unavailable, pain on movement was used as registered on a 100 mm VAS.

3.3. Heterogeneity testing

In order to give as precise effect estimates as possible, care was taken to investigate discrepancies in trial samples. Heterogeneity was tested using Q-values, and statistical significance was defined at the 0.05 level for each intervention. If statistical heterogeneity was detected, data were reassessed and plausible reasons for heterogeneity sought. The material was then subgrouped by drug types within the same class, differences in patient selection criteria or differences in handling of missing data in intention-to-treat analyses. Statistical differences were tested between subgroups and the remaining sample. If this testing provided statistically significant differences, and heterogeneity disappeared in the remaining sample and the subgroups, the identified subgroups were excluded from subsequent analysis.

3.4. Statistical analysis of pain-relieving effect

Mean differences of change for intervention groups and placebo groups and their respective standard deviations (SD) were included in a statistical pooling. If variance data were not reported as SDs, they were calculated from the trial data of sample size and other variance data such as p-values, t-values, standard error of mean, or 95% confidence intervals [CI]. Results were presented as weighted mean difference (WMD) between test drug and placebo with 95% CI in mm on VAS, i.e., as a pooled estimate of the mean difference in change between the treatment and the placebo groups, weighted by the inverse of the variance for each study (Fleiss, 1993). For heterogeneous trial samples a random effects model was used for calculation, and for confirmed absence of heterogeneity ($p < 0.05$), a fixed effects model was applied.

3.5. Appraisal of trial quality

The quality of the trials was assessed according to a predefined list of 5 criteria (Jadad scale) (Jadad and McQuay, 1996). To assess the potential for bias we evaluated the method of randomisation, concealment of allocation, blinding of trial investigators and patients, handling of dropouts and withdrawals, and analysis according to intention to treat. In addition, patient selection criteria were counted and evaluated for possible bias or dissimilarity to an average OAK population. Cut-off limits for method scores were not considered valid (Juni et al., 1999) and thereby not predefined.

4. Results

4.1. Included studies

The literature search identified 1033 potentially eligible studies, where 689 were RCTs with the specified interventions for OAK. Of these, 382 did not have a placebo control group, 227 presented combined data for OA and not OAK data separately, 8 trials did not

include outcome measurements within 4–12 weeks, and 9 did not provide continuous pain scale data. This provided a final sample of 63 RCTs that satisfied the inclusion criteria. Direct or indirect indications of sponsorship by commercial interests were found in all but 10 (15.9%) of these trials (Williams et al., 1989; Dreiser and Tisne-Camus, 1993; Gaffney et al., 1995; Jones and Doherty, 1996; Ravaud et al., 1999; Rindone et al., 2000; Scott et al., 2000; Mazieres et al., 2001; Case et al., 2003; Smith et al., 2003). The final sample included 14,060 patients who received the active intervention and provided data at ⩽4 weeks after randomisation.

The included patients had a median age of 63.2 years, and median symptom duration was 7.2 years. Females dominated at 63.2%. Mean baseline pain intensities were 72.8 mm on VAS for opioid therapy, 64.3 mm for oral NSAIDs, 57.4 mm for steroid injections, 54.9 for paracetamol, 54.7 mm for topical NSAIDs, 53.8 for glucosamine sulphate and 50.7 mm for chondroitin sulphate. All trials had a minimum limit for pain intensity (typically 40 mm on VAS) or disease activity for inclusion, and they all had a pretreatment wash-out period of 3–14 days for previous pharmacotherapy. Thirteen trials of oral NSAIDs (Weaver et al., 1995; Makarowski et al., 1996; Simon et al., 1998; Bensen et al., 1999; Zhao et al., 1999a; Ehrich et al., 2001; McKenna et al., 2001a,b; Williams et al., 2001; Gottesdiener et al., 2002; Case et al., 2003; Gibofsky et al., 2003; Kivitz et al., 2004) and one trial of topical NSAID gel (Grace et al., 1999) employed an additional criterion by requiring a predefined minimum flare of symptoms when oral paracetamol or NSAID treatment was discontinued for pretreatment wash-out. Five of these reported on shares of regular oral NSAID users ranging from 66% to 100% (median 90.5%) (McKenna et al., 2001a,b; Gottesdiener et al., 2002; Case et al., 2003; Kivitz et al., 2004). The sample characteristics for each intervention are presented in Table 1.

4.2. Trial quality

The methodological quality was generally satisfactory (Table 1). Adequate randomisation, allocation and blinding procedures were comprehensively described in 10 studies (Bensen et al., 1999; Grace et al., 1999; Zhao et al., 1999a; Ehrich et al., 2001; Williams et al., 2001; Gottesdiener et al., 2002; Kivitz et al., 2002; Gibofsky et al., 2003; Smith et al., 2003; Kivitz et al., 2004). Five trials did not present intention-to-treat analyses (Williams et al., 1989; Gaffney et al., 1995; Jones and Doherty, 1996; Morreale et al., 1996; Rindone et al., 2000). Intention-to-treat analyses in opioid trials were inadequate as they presented only "last value carried forward" – scenarios, in spite of high withdrawal rates from adverse events which increased over time from 24% at 2 weeks to 50% at 12 weeks (Peloso et al., 2000; Caldwell et al., 2002; Babul et al., 2004).

4.3. Exclusion from analysis for groups with inadequate dose

A total of 5 active treatment groups with 725 patients were excluded from meta-analyses because patients received therapy below the recommended dose specified a priori in our protocol. Two groups received therapy by topical NSAIDs (Ottillinger et al., 2001), while the remaining 3 groups received oral NSAIDs (Bensen et al., 1999; Zhao et al., 1999a; Kivitz et al., 2002).

4.4. Primary outcome

Data from 14,060 patients on active therapy were available for meta-analysis. Only trials with oral and topical NSAID were significantly heterogeneous (Q-value 58.9, $p = 0.001$, and Q-value 23.9, $p = 0.002$ respectively) and their analyses were performed with random effects models, while the other interventions were analysed in fixed effects models.

For oral NSAIDs, the maximum pain-relieving effect appeared at 2.3 weeks corresponding to 10.2 mm [95% CI 8.8–11.6] on 100 mm VAS. The values dropped slightly to 9.0 mm [95% CI 4.9–13.1] at 4 weeks. The characteristics of included oral NSAIDs trials are summarised in Table 2.

For topical NSAIDs, maximum pain relief was found after a mean of 1.6 weeks corresponding to 11.6 mm

Table 1
Study characteristics and the distribution of trials for each intervention providing data within 4 weeks, included patients on active treatment, Q-values from heterogeneity tests, mean methodological scores, mean age of patients and baseline pain on a 100 mm visual analogue scale (VAS)

Type of intervention	Number of trials (comparisons)	Number of patients	Mean methodological quality [range] (max score 5)	Mean age (years)	Mean baseline pain on 100 mm VAS
Oral NSAIDs including coxibs	25 (27)	9964	3.8 [3–5]	62.6	64.3
Topical NSAIDs	9	749	4.6 [3–5]	64.2	54.7
Intra-articular glucocorticosteroid injections	6	221	3.5 [1–5]	66.1	57.4
Paracetamol	4	1306	4.0 [4–5]	67.5	54.9
Glucosamine sulphate	7	401	3.6 [3–5]	58.6	57.8
Chondroitin sulphate	6	362	3.5 [3–5]	63.0	50.7
Opioid therapy	6	1057	3.8 [3–4]	61.5	72.8

[95% CI 7.4–15.7] on VAS, while pain relief dropped to 7.0 mm [95% CI 5.5–8.6] at 4 weeks. The characteristics of included topical NSAIDs trials are summarised in Table 3.

For steroid injection trials, the time-point for maximum efficacy was at typically the first post injection evaluation at 1.5 weeks and corresponding to 14.5 mm [95% CI 9.7–19.2] on VAS, decreasing to 6.7 mm [95% CI 0.4–13.0] at week 4. The characteristics for included steroid injections trials are summarised in Table 4.

For paracetamol, we calculated a pain-relieving efficacy corresponding to 3.0 mm [95% CI 1.4–4.7] on VAS, but there were not enough data to identify a time point for maximum effect within the 4 week time frame. The characteristics of included paracetamol trials are summarised in Table 5.

Table 2
Characteristics of trials of oral NSAIDs for pain relief in patients with knee osteoarthritis

First author	Drug	No of patients on active drug ($n = 9964$)	Method quality	Mean baseline pain (mm VAS)	Best mean difference (95% CI) of change over placebo (mm VAS)	Outcome time-points (in weeks, max. effect in bold)
Bensen -99	Celecoxib-naproxen	597	5	54.1	8.0 (2.3 to 13.7)	**2**, 6, 12
Case -03	Diclofenac	25	4	39.6	11.7 (6.2 to 17.2	**2**, 12
Detrembleur -05	Celecoxib	8	3	NA	11.5 (−12.7 to 35.7)	**2**
Dore -95	Naproxen-etodolac	168	3	NA	16.3 (4.8 to 27.7)	2, **4**
Ehrich -01	Rofecoxib	147	5	61.9	21.9 (15 to 28.7)	1, **2**, 4,6
Fleischmann -97	Nabumetone-naprelan	185	3	59.9	9.3 (0.7 to 17.6)	**2**, 4
Gibofsky -03	Celecoxib-rofecoxib	379	5	67.7	11.6 (3.4 to 19.8)	**3**, 6
Gottesdiener -02	Etoricoxib-diclofenac	326	5	68.4	18.4 (16.6 to 20.2)	1, **2**, 4, 6
Kivitz -02	Valdecoxib-naproxen	408	5	71.9	5.5 (2.3 to 8.8)	**2**, 6, 12
Kivitz -04	Rofecoxib-nabumetone	834	5	74.5	15.1 (4.9 to 25.3)	**1**, 6
Lee -85	Diflunisal	279	3	57	8.5 (−2.9 to 19.5	**3**, 6
Lehmann -05	Lumiracoxib	1160	4	64.3	6.4 (4.2 to 8.6)	**2**, 4, 8, 13
Lund -98	Meloxicam	134	3	48.2	6.6 (1.4 to 11.8)	1, 2, **3**
McKenna -01a	Celecoxib-diclofenac	400	3	69.1	8.8 (5.2 to 12.3)	**2**, 6
McKenna -01b	Celecoxib-rofecoxib	122	3	73.3	14.5 (2.7 to 26.3)	**3**, 6
Schnitzer -95	Nabumetone-etodolac	180	3	57.5	13.2 (5.4 to 21)	2, **4**
Scott -00	Tiaprofenic acid	307	4	55.1	4.1 (4.0 to 4.2)	**4**
Sheldon -05	Lumiracoxib-celecoxib	1260	4	66.1	6.3 (3.9 to 8.7)	**2**, 4, 8, 13
Simon -98	Celecoxib	222	4	67.8	6.0 (−1.1 to 12.1	**1**, 2
Tannenbaum -04	Lumiracoxib-celecoxib	1459	4	65.2	9.9 (4.6 to 15.2)	**2**, 4, 8, 13
Uzun -01	Flurbiprofen-tiaprofenic aci	26	3	61	17.0 (3.9 to 37.9)	**3**
Weaver -95	Nabumetone-oxaprozin	219	3	NA	12.5 (6.4 to 18.6)	1, **2**, 4, 6
Williams -01	Celecoxib	472	4	66.4	7.5 (2.9 to 12.1)	**2**, 6
Williams -89	Etodolac	50	3	76	7.3 (0 to 14.6)	2, **4**
Zhao -99	Celecoxib	597	5	53.9	7.5 (4.8 to 10.2)	**2**, 12
Overall		9964	3.8[a]	64.3[b]	10.2 (8.8 to 11.6	2.3[a]

NA = not available.
[a] Mean.
[b] Weighted mean.

Table 3
Characteristics of included trials of topical NSAIDs for pain relief in patients with knee osteoarthritis

First author	Drug	No of patients on active drug ($n = 749$)	Method quality	Mean baseline pain (mm VAS)	Best mean difference (95% CI) of change over placebo (mm VAS)	Outcome assessment time-points (weeks, best time-point used in bold)
Bookman -04	Diclofenac	84	5	46	7.0 (1.0 to 13.0)	**4**
Bruhlmann -03	Diclofenac	51	5	57.0	24.4 (15.3 to 33.3)	**1**, 2
Dreiser -93	Diclofenac	78	4	57.4	11.8 (5.4 to 18.2)	1, **2**
Grace -99	Diclofenac	38	4	44.7	12.1 (2.9 to 21.3)	**2**
Ottilinger -01	Eltenac (1%)	57	5	56.5	5.4 (−3.9 to 13.4)	1, **2**, 3, 4
Roth -04	Diclofenac	164	3	65	6.2 (1.5 to 10.9)	12
Rovensky -01	Ibuprofen	50	5	56.9	11.8 (2.3 to 21.3)	**1**
Sandelin -97	Eltenac (1%) ($n = 124$)	202	5	48.0	1.5 (−2.3 to 5.3)	**1**, 2, 3, 4
	Diclofenac ($n = 78$)	–		52.0	11.0 (1.6 to 20.4)	**1**, 2, 3, 4
Trnavsky -04	Diclofenac	25	5	63.1	8.0 (2.3 to 13.7)	**1**
Total		749	4.6[a]	54.7[b]	11.6[b] (7.4 to 15.7)	1.6[a]

[a] Mean.
[b] Weighted mean.

Table 4
Characteristics of included trials of steroid injections for pain relief in patients with knee osteoarthritis

First author	Drug	No of patients on active drug ($n = 221$)	Method quality	Mean baseline pain (mm VAS)	Best mean difference (95% CI) of change over placebo (mm VAS)	Outcome assessment time-points (weeks, best time-point used in bold)
Dieppe -80	Triamcinolone	12	1	52.0	30.0 (6.0 to 54.0)	**1**, 6
Friedman -80	Triamcinolone	17	4	56.0	14.0 (4. to 22.0)	**1**, 8
Gaffney -95	Triamcinolone	42	2	52.0	21.4 (10.7 to 32.1)	**1**, 6
Jones -96	Methylprednisolone	59	4	62.6	5.9 (−5.0 to 16.8)	**3**
Ravaud -99	Cortivazol	53	5	69.0	25.0 (7.4 to 42.6)	**1**, 4, 12, 24
Smith -03	Methylprednisolone	38	5	53.0	11.8 (2.3 to 21.3)	**2**, 4, 8, 12, 24
Total		221	3.5[a]	57.4[b]	14.5[b] (9.7 to 19.2)	1.5[a]

[a] Mean.
[b] Weighted mean.

Table 5
Characteristics of included trials of steroid injections for pain relief in patients with knee osteoarthritis

First author	Drug	No of patients on active drug ($n = 1306$)	Method quality	Mean baseline pain (mm VAS)	Best mean difference (95% CI) of change over placebo (mm VAS)	Outcome assessment time-points (weeks, best time-point used in bold)
Case -03	Paracetamol	25	4	39.6	0.6 (−5.6 to 6.7)	**2**, 12
Golden -04	Paracetamol	155	3	59.0	3.8 (1.9 to 5.7)	**1**
Miceli-Ricard -04	Paracetamol	405	5	66.7	1.0 (−2.7 to 4.7)	**1**, 6
Pincus -04	Paracetamol	721	4	54.2	5.9 (−5.0 to 16.8)	6
Total		1306	4.0[a]	54.9[b]	3.0[b] (1.4 to 4.7)	**1.3**[a]

Characteristics of trials of paracetamol for pain relief in patients with knee osteoarthritis.
[a] Mean.
[b] Weighted mean.

Table 6
Characteristics of included trials of glucosamine for pain relief in patients with knee osteoarthritis

First author	Drug	No of patients on active drug ($n = 401$)	Method quality	Mean baseline pain (mm VAS)	Best mean difference (95% CI) of change over placebo (mm VAS)	Outcome assessment time-points (weeks, best time-point in bold)
Houpt -99	Glucosamine	46	3	60.5	3.0 (−9.7 to 15.7)	**4**, 8
Hughes -02	Glucosamine	39	5	61.0	0.1 (−16.1 to 16.3)	12
McAlindon -04	Glucosamine	101	5	44.0	2.0 (−7.9 to 11.9)	**4**, 12
Noack -94	Glucosamine	126	5	62.3	7.0 (−0.3 to 13.7)	1, 2, 3, **4**
Pujalte -80	Glucosamine	10	4	57.5	6.2 (1.5 to 10.9)	8
Rindone -00	Glucosamine	49	3	56.9	1.5 (−9.4 to 12.4)	**4**, 8
Usha -04	Glucosamine	30	4	58.0	7.5 (−7.3 to 22.3)	2, **4**, 8, 12
		401	3.6[a]	53.8[b]	4.7[b] (0.3 to 9.1)	**4.0**[a]

[a] Mean.
[b] Weighted mean.

For glucosamine sulphate, data on pain relief corresponding to 4.7 mm [95% CI – 0.3–9.1] on VAS were only available at the 4 week time point. The characteristics of included trials are summarised in Table 6.

For chondroitin sulphate, pain relief data were only available at 4 weeks with a mean value of 3.7 mm [95% CI 0.3–7.0] on VAS. The trial characteristics are summarised in Table 7.

For opioids, pain relief was calculated to 12.9 mm [8.4–17.4] at 2–4 weeks, but withdrawal rates were high and intention-to-treat analyses were only presented in last value carried forward scenarios. Two trials authors were contacted for additional data, but none responded to our requests. In the only opioid trial presenting categorical data of improvement at 2 weeks, there was no significant difference in the responder rate between groups (59% vs 56%) (Malonne et al., 2004). The characteristics of included opioid trials are summarised in Table 8.

4.5. Clinical relevance for subjective outcome thresholds

None of the therapies had effect size or 95% confidence intervals exceeding the mean threshold for minimal clinical important improvement. Intra-articular steroid injections produced a mean effect size over pla-

Table 7
Characteristics of included trials of chondroitin sulphate for pain relief in patients with knee osteoarthritis

First author	Drug	No of patients ($n = 362$)	Method quality	Mean baseline pain (mm VAS)	Best mean difference (95% CI) of change over placebo (mm VAS)	Outcome assessment timepoints (weeks, best time point in bold)
Bourgeois -98	Chondroitin sulphate	83	3	56.0	6.5(−1.6 to 14.6)	**2**, 6, 12
Bucsi -98	Chondroitin sulphate	39	3	56.0	5.0 (−4.2 to 14.2)	**4**, 12
Mazieres -92	Chondroitin sulphate	58	4	48.0	−0.4 (−10.1 to 9.3)	2, **4**, 12
Mazieres -01	Chondroitin sulphate	63	3	54.4	2.1 (−3.9 to 8.1)	**4**, 8, 12
Morreale -96	Chondroitin sulphate	65	3	30.9	4.8 (−1.3 to 11.3)	**4,** 8, 12
Uebelhart -05	Chondroitin sulphate	54	5	58.8	3.9 (−7.2 to 15.3)	12
Total		362	3.5[a]	50.7[b]	3.7[b] (0.3 to 7.0)	**3.6**[a]

[a] Mean.
[b] Weighted mean.

Table 8
Characteristics of included trials of opioids for pain relief in patients with knee osteoarthritis

First author	Drug	No of patients ($n = 1057$)	Method quality	Mean baseline pain (mm VAS)	Best mean difference (95% CI) of change over placebo (mm VAS)	Outcome assessment time-points (weeks, best time-point in bold)
Babul -04	Tramadol	124	4	78.2	13.7 (4.3 to 23.1)	1, 2, **4**, 8, 12
Caldwell -02	Morphine sulphate	222	4	78.9	8.9 (−0.7 to 18.5)	**1**, 2
Chindalore -03	Oxycodone, Oxymorphone	310	4	76.0	7.0 (−1.4 to 15.4)	1, 2, **3**
Malonne -04	Tramadol	111	3	60.0	8.8 (2.1 to 15.5)	1, **2**
Matsumoto -04	Oxymorphone	242	4	NA	8.8 (−3.9 to 13.4)	**3**, 4
Peloso -00	Codeine	48	4	58.2	20.4 (2.3 to 33.1)	1, 2, 3, **4**
Total		1057	3.8	72.8[b]	10.5[b](7.4 to 13.7)	**2.8**[a]

NA – not available.
[a] Mean.
[b] Weighted mean.

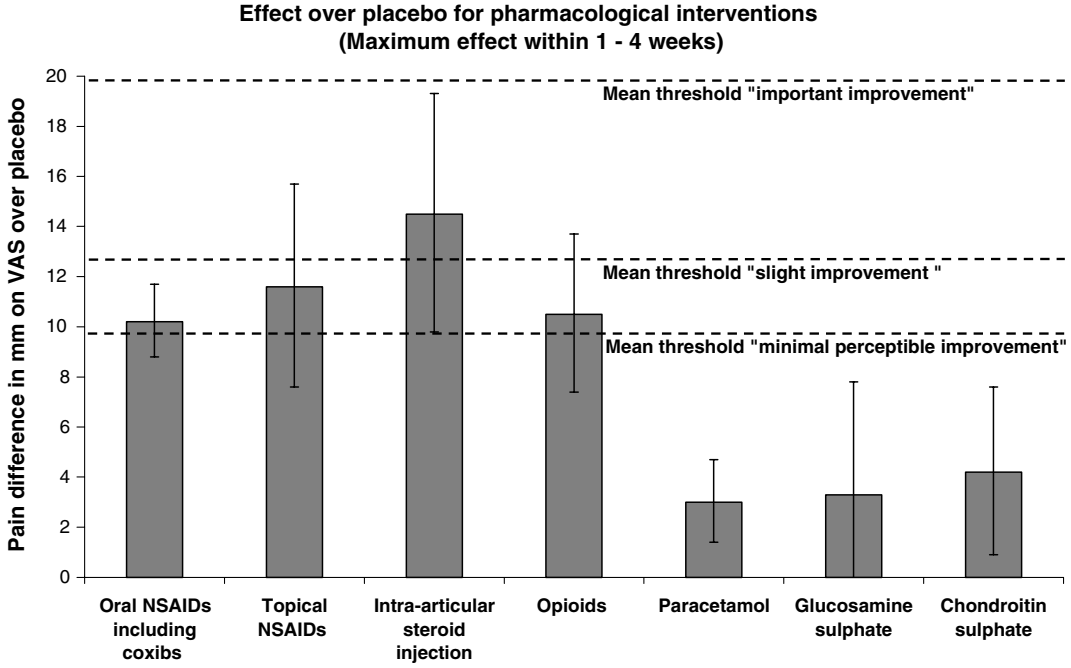

Fig. 1. The combined maximum efficacy (at any time-point within the first 4 weeks of therapy) is shown by bar graphs and their 95% confidence intervals for each of the seven pharmacological interventions are also shown. The stapled horizontal lines indicate mean thresholds for clinically important improvement (Tubach et al., 2005), for categorical shift from none to slight improvement (Angst et al., 2002), and threshold for the minimal perceptible threshold (Ehrich et al., 2000) in descending order.

cebo which was large enough to exceed the mean threshold for "slight improvement". Oral and topical NSAIDs and opioids had values slightly above the mean threshold for "minimal perceptible clinical improvement". Mean pain relief values for paracetamol, glucosamine sulphate, and chondroitin sulphate did not transcend any of the three subjective thresholds for clinical relevance within 4 weeks (Fig. 1).

4.6. Secondary outcome – time-effect profiles

For efficacy analysis at weeks 6–12 after start of therapy, follow-up data were available from 3 trials of paracetamol (Case et al., 2003; Miceli-Richard et al., 2004; Pincus and Koch, 2004), 14 trials of oral NSAIDs (Lee et al., 1985; Weaver et al., 1995; Bensen et al., 1999; Zhao et al., 1999b; Ehrich et al., 2001; McKenna et al., 2001a,b; Gottesdiener et al., 2002; Kivitz et al., 2002; Gibofsky et al., 2003; Kivitz et al., 2004; Tannenbaum et al., 2004; Lehmann et al., 2005; Sheldon et al., 2005), 5 trials of steroid injections (Friedman and Moore, 1980; Gaffney et al., 1995; Jones et al., 1995; Ravaud et al., 1999; Smith et al., 2003), and from a single trial of topical NSAIDs (Bookman et al., 2004). For paracetamol, efficacy did not change during the follow-up period, and corresponded to 4.0 mm [95% CI 1.1–6.9] on VAS at week 12. For oral and topical NSAIDs and intra-articular steroid injections, efficacy gradually declined during follow-up to values equal to 9.8 mm [95% CI 6.9–12.8], 7.0 mm [95% CI 1.0–13.0] and 5.7 mm [95% CI 1.4–10.1] on VAS at week 12, respectively. For topical NSAIDs, follow-up for efficacy were only available from one trial (Bookman et al., 2004) after 4 weeks at 7.0 mm [95% CI 1.0–13.0] and from another trial(Roth and Shainhouse, 2004) at 12 weeks at 6.2 mm [95% CI 1.0–10.9]. Results from 2 trials (Dieppe et al., 1980; Gaffney et al., 1995) for intra-articular steroid injections were 5.6 mm [95%CI −4.4–15.6] on VAS after 6 weeks, and 5.5 mm [95% CI 0.8–10.2] on VAS from 4 trials (Friedman and Moore, 1980; Jones and Doherty, 1996; Ravaud et al., 1999; Smith et al., 2003) after 8–12 weeks. For the glucosamine sulphate trials, efficacy was 3.8 mm [95% CI −1.4–9.0] at week 8 (Pujalte et al., 1980; Houpt et al., 1999; Rindone et al., 2000; McAlindon et al., 2004; Usha and Naidu, 2004), and 5.6. mm [95% CI −1.1–12.2] at week 12 (Hughes and Carr, 2002; McAlindon et al., 2004; Usha and Naidu, 2004). Analysis of 6 trials (Mazieres et al., 1992; Morreale et al., 1996; Bourgeois et al., 1998; Bucsi and Poor, 1998; Uebelhart et al., 1998; Mazieres et al., 2001) with chondroitin sulphate demonstrated a slightly larger increase of treatment efficacy corresponding to a maximum of 7.1 mm [95% CI 3.3–10.8] at week 8 and 10.6 mm [95% CI 6 to 15.2] at week 12. For opioids, only one trial was available for analysis. Efficacy was calculated to 10.2 mm [95% CI 4.1–16.3] at 12 weeks with 49.4% of the randomised patients completing the trial. The results are summarised in Fig. 2.

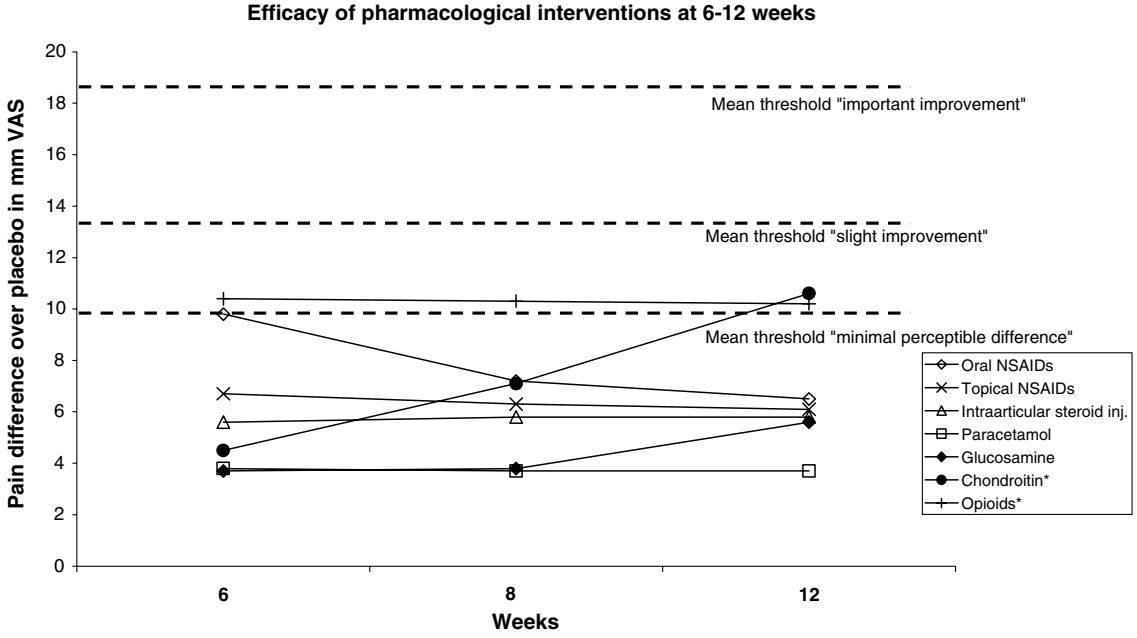

Fig. 2. The secondary outcome results by graph lines for efficacy at 6, 8 and 12 weeks for seven pharmacological interventions are shown. The stapled horizontal lines indicate mean thresholds for clinically important improvement (Tubach et al., 2005), for categorical shift from none to slight improvement (Angst et al., 2002), and threshold for the minimal perceptible threshold (Ehrich et al., 2000) in descending order. Asterisks for opioid therapy and chondroitin sulphate indicate that categorical data for these therapies contradict the positive results shown for continuous data.

4.7. Heterogeneity and subgroup analyses

Heterogeneity in trial samples for the primary outcomes were evident for oral NSAIDs (Q-value 58.9, $p = 0.001$, and pain reduction corresponding to 10.2 mm [95% CI: 9. to 11.9] on VAS) and for topical NSAIDs (Q-value 23.2, $p = 0.002$, and pain reduction equal to 11.6 mm [95% CI: 6.1 to 16.5] on VAS). Heterogeneity in trials of oral NSAIDs was assumed to result from patient selection bias in trials which excluded patients who did not experience a flare of symptoms after being taken off their NSAID prior to treatment allocation. This hypothesis was tested by subgrouping the trials by this criterion. Subgroup analyses showed a reduction of heterogeneity to non-significance ($p \geqslant 0.3$) for pain data in both subgroups (Q-value 13.8 and 10.8 for biased and unbiased trials, respectively). Maximum efficacy for the subgroup of 14 trials (Weaver et al., 1995; Makarowski et al., 1996; Simon et al., 1998; Bensen et al., 1999; Zhao et al., 1999a; Ehrich et al., 2001; McKenna et al., 2001a,b; Williams et al., 2001; Gottesdiener et al., 2002; Case et al., 2003; Gibofsky et al., 2003; Kivitz et al., 2004; Detrembleur et al., 2005) which used this responder criterion was significantly higher ($p < 0.001$) at 11.8 mm [95% CI 10.5–13.1] on VAS, than for the 12 other trials (Lee et al., 1985; Williams et al., 1989; Dore et al., 1995; Schnitzer et al., 1995; Fleischmann et al., 1997; Lund et al., 1998; Scott et al., 2000; Uzun et al., 2001; Kivitz et al., 2002; Tannenbaum et al., 2004; Lehmann et al., 2005; Sheldon et al., 2005) where maximum efficacy was 7.9 mm [95% CI 6.9 to 8.9] on VAS. This difference persisted over time and was highly significant at secondary outcome measurements too ($p < 0.001$). The results are summarised in Fig. 3.

Heterogeneity in the outcome in trials of topical NSAIDs was assumed to be caused by inefficacy of one of the three different gels (eltenac) and use beyond 2 weeks. This hypothesis was tested by subgrouping 7 trials with diclofenac and ibuprofen, and comparing them with a subgroup of 2 trials with eltenac gel and one with 4 weeks duration. The subgroup results for 1–2 weeks treatment by diclofenac/ibuprofen increased to 14.2 mm [95% CI 11.3–17.2], and heterogeneity was not present in any of the two subgroups with Q-values of 10.7 and 2.6, respectively. Outcome measures during the first 4 weeks of treatment for glucosamine sulphate, chondroitin sulphate and paracetamol were not heterogeneous with Q-values of 1.3, 1.8 and 2.3 respectively.

The time-effect profile from 4 to 12 weeks showed a gradually decreasing efficacy for oral and topical NSAIDs, and little or no change for paracetamol intra-articular steroid injections, glucosamine sulphate, and opioids. For chondroitin sulphate, there was a slight increase in efficacy equivalent to a categorical shift from none to perceptible improvement over this time period (see Fig. 2).

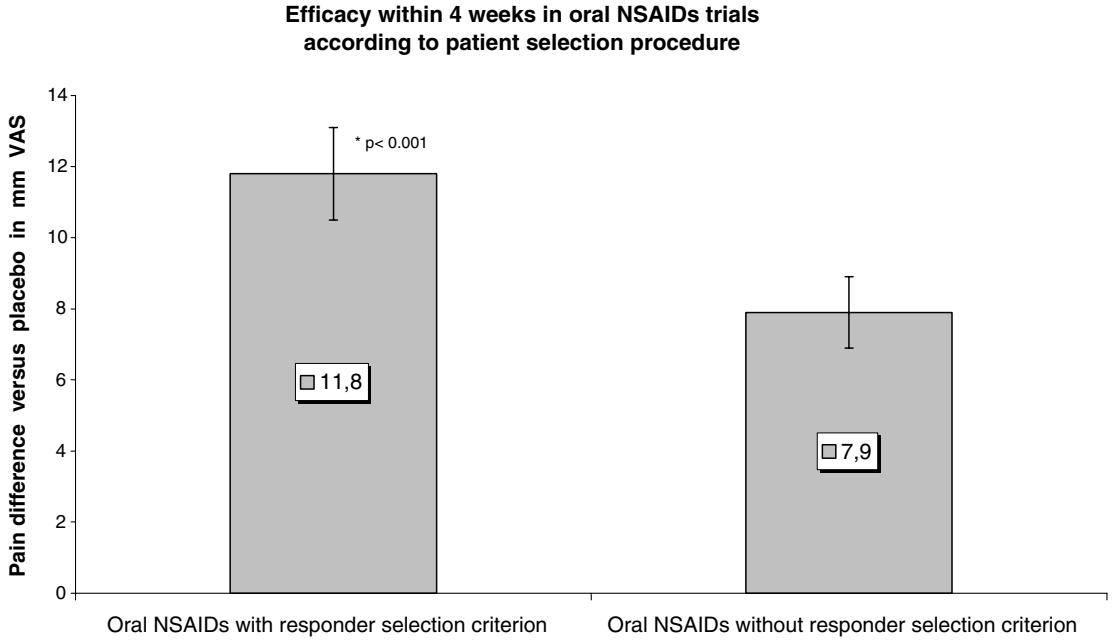

Fig. 3. The result of the sub-group analysis for oral NSAIDs is shown. Trials were sub-grouped in one subgroup which recruited patients from regular NSAID-users and only included those who experienced an increase in pain intensity of at least 15 mm on VAS after discontinuing medication in the pre-trial wash-out period and had baseline pain over 40 mm on VAS. We call this the responder selection criterion, as this patient selection procedure ensures that only known NSAID-responders are allowed to participate. The second subgroup only used the inclusion criterion of a minimum baseline pain intensity of 40 mm on VAS.

5. Discussion

According to a recent European pain survey (Breivik et al., 2005), arthritis is the most commonly reported cause for chronic pain. Pharmacological interventions were used by the majority of patients, but 40% of chronic pain sufferers reported that their pain was inadequately controlled. In this perspective, the disappointing efficacy results for pharmacological interventions provided by our study should not be surprising. Our results do not differ much from results commented upon in previous meta-analyses of pharmacological OA (Lin et al., 2004; Zhang et al., 2004; Bellamy et al., 2005). The most profound difference is that we perhaps present our results in a way that can be more easily related to patient-centred outcomes. Although most included interventions provided statistically significant efficacy, none had efficacies over time above the subjectively reported thresholds for benefit in OAK patients. In view of the widespread use of pharmacological agents in OAK management, a discussion is needed to clarify if the limited benefits and considerable costs can justify current recommendations (Jordan et al., 2003) and practice (Mazieres et al., 2005).

Only steroid injections and topical diclofenac/ibuprofen gel provided efficacies over 1–3 weeks that would make most patients report a categorical shift from no improvement to slight improvement. The result for oral NSAIDs is disappointing, even though we excluded groups with low and ineffective doses from the meta-analyses.

The comparison of interventions by assessing separate meta-analyses of each intervention, may be less robust than head-to-head comparisons within trials. However, this question has been addressed in an analysis in which results from head-to-head comparisons of different interventions in trials and the results of separate meta-analyses of each intervention showed no significant difference for 93.2% of the comparisons (Song et al., 2003). Comparisons between separate meta-analyses may be jeopardised by differences in baseline data and prognostic factors. Because of this, we carefully assessed baseline demographics and clinical characteristics in the trials comprising the current meta-analysis. Except for baseline pain, which was higher in the opioid and oral NSAID (72.8 mm and 64.2 mm, respectively) trials, the baseline demographic and clinical data were surprisingly uniform across interventions. Because of the paucity of published trials which make head-to-head comparisons between drugs of different classes, our approach may be the best we have at present.

Our selection of only continuos data may be limiting, but there is good correlation between pain, stiffness and physical function (Roos et al., 1999). Our reasons for not using categorical data is partly the observation that this measure is less frequently reported in OAK trials, but also that the literature shows a lack of consensus on how to dichotomise responders and non-responders in OAK. A recent attempt by OA experts to developed consensus are the OMERACT-OARSI responder criteria, which allow the relative pain reduction to be as low as 20% for registering a patient as a responder (Pham et al., 2003). This is lower than what is commonly used in acute pain trials (Barden et al., 2003), and these responder criteria are yet to be implemented in the literature. In a two recent oral NSAID trials (Lehmann et al., 2005; Sheldon et al., 2005) which used the OMERACT-OARSI responder criteria, NNT values were not better than 5.2 at 2 weeks and 6.1 at 13 weeks. Considering that the responder criterion only incorporates VAS values similar to thresholds for slight or barely perceptible improvement, the results are disappointing.

The pharmacotherapies included in the current analysis are all among those awarded the highest level of recommendation in the recent EULAR guidelines for management of OAK (Jordan et al., 2003). However, results from our meta-analysis demonstrate that the recommended drugs offer limited pain relief in the average OAK patient. The analysis provides evidence suggesting a modest and transient effect of topical NSAIDs. Based on a recent 12-week comparative controlled trial (Tugwell et al., 2004), equal efficacy, but superiority in safety of topical over oral NSAID formulations, has been advocated (Moore, 2004). However, it must be added that so far, no trials have demonstrated clinically relevant mean effects above the minimally perceptible threshold of 9.7 mm after 2 weeks or more of therapy with topical NSAIDs.

In the current analysis, short-term efficacy of intra-articular glucocorticosteroid injections was of similar magnitude and slightly longer duration than that observed for topical NSAIDs. In this context, it is notable that all the included steroid injection trials were performed in specialist settings (Godwin and Dawes, 2004), thus limiting their applicability in a primary care context. In addition steroid injections cannot be repeated indefinitely. One meta-analysis of categorical data has demonstrated a long-term effect of steroids after 16–24 weeks (Arroll and Goodyear-Smith, 2004). However, the present analysis of continuous data did not show clinically relevant effects at any point from 6 to 24 weeks post injection. It may be argued that the 4 week time span for the primary outcome is too short to detect beneficial effects of glucosamine sulphate and chondroitin sulphate, as these agents are reported to have maximum efficacy after 2–3 months (Richy et al., 2003). From our analysis, it seems clear that glucosamine sulphate is largely ineffective in relieving pain also within 12 weeks. For chondroitin sulphate, the results show a hardly perceptible improvement in pain intensity by week 12. However, categorical data from the GAIT-trial, which outnumbers all included trials, have shown no signifi-

cant effect of chondroitin sulphate over placebo (Clegg et al., 2006). In addition 5 of the 6 trials in this analysis were funded by pharmaceutical companies, and the single independent trial did not report any perceptible decrease in pain intensity at week 12. As funding by for-profit organisations is associated with bias in favor of the experimental intervention (Kjaergard and Als-Nielsen, 2002), the slightly improved results of treatment with chondroitin sulphate over time must be independently verified.

For opioids, there was a paucity of data from the six trials which limits the robustness of the results. The results of the meta-analysis suggest that opioid therapy at best induce a slight improvement in the average patient at 4 weeks. However, the only opioid trial presenting categorical data of improvement found no significant difference in the responder rates between groups of tramadol patients (59%) and placebo patients (56%) (Malonne et al., 2004). As opioids have the highest drop-out/withdrawal rates from adverse events of all interventions (from 23.6 at 2 weeks to 50.6% at 12 weeks), a cautious handling of missing data is necessary. One of the trials did not perform intention-to-treat analyses (Malonne et al., 2004), while the others performed intention-to-treat analysis with the last-value-carried-forward method (Peloso et al., 2000; Babul et al., 2004). Serious flaws still prevailed as all randomised patients were not included in the intention-to-treat analysis in one of these trials (Peloso et al., 2000), and the best case scenarios used for intention-to-treat analyses limits the validity of results. To conclude, the identified methodological shortcomings and uncertainty about efficacy estimates, suggest that opioid therapy cannot be recommended in OAK.

Analysis of the oral NSAID trials divulged a problem of patient selection bias. Several trials recruited mainly regular NSAID users, and required a minimum increase in disease activity after pre-trial NSAID discontinuation before patient inclusion. This selective exclusion of non-responders would be expected to introduce bias in favour of oral NSAIDs when comparing efficiacy with other interventions. Indeed, our results show that this procedure significantly inflated results in favour of the trial drug, and subsequent analysis of unbiased data clearly demonstrates a lack of adequate analgesic effect of oral NSAIDs in OAK. This effect is less than the average OAK patient is able to perceive, and without disregarding that the occasional patient may benefit, our results suggest that less than 10% of the patients will be able to discriminate between active drug and placebo. For paracetamol, the situation is almost identical, with an analgesic efficacy which is even more modest.

These minor therapeutic benefits are in addition offset by drug-induced adverse effects. We lack information to enable a comparison of the toxicities conferred by the treatment strategies included in the analysis, but a panel of experts have ranked oral NSAIDs and opioids as the most toxic of these therapies, followed by corticosteroid injections, paracetamol, topical NSAIDs, chondroitin and glucosamine sulphate, in order of decreasing toxicity (Jordan et al., 2003). The narrow inclusion criteria and short duration of trials analysed do not allow us to compare the costs of the different treatments in terms of adverse effects, but there is ample evidence to suggest that elderly, unselected populations of OAK patients are indeed vulnerable to drug-induced toxicity. In this respect, intermittent use of topical NSAIDs seems to be the best alternative among the generally inefficient treatment options evaluated.

6. Conclusion

During the first 4 weeks after treatment initiation, topical NSAIDs and intra-articular steroid injections offer limited pain relief over placebo within 1–2 weeks, but neither intervention seem to offer meaningful pain relief beyond the first month. In best-case scenarios, where possible patient selection bias in NSAID trials and large withdrawal rates in opioid trials with last value carried forward, both therapies only offer pain-relieving effects over placebo which are near the mean minimal perceptible difference of 9.7 mm within 4 weeks. Paracetamol, glucosamine sulphate and chondroitin sulphate are largely ineffective for short-term pain relief within a month. In conclusion, common pharmacological interventions give limited, if any, short-term pain relief in OAK. These findings suggest that it is time to reconsider the place of these drug therapies in OAK management.

Acknowledgement

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