

Meta-analysis: Chondroitin for Osteoarthritis of the Knee or Hip

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Background: Previous meta-analyses described moderate to large benefits of chondroitin in patients with osteoarthritis. However, recent large-scale trials did not find evidence of an effect.

Purpose: To determine the effects of chondroitin on pain in patients with osteoarthritis.

Data Sources: The authors searched the Cochrane Central Register of Controlled Trials (1970 to 2006), MEDLINE (1966 to 2006), EMBASE (1980 to 2006), CINAHL (1970 to 2006), and conference proceedings; checked reference lists; and contacted authors. The last update of searches was performed on 30 November 2006.

Study Selection: Studies were included if they were randomized or quasi-randomized, controlled trials that compared chondroitin with placebo or with no treatment in patients with osteoarthritis of the knee or hip. There were no language restrictions.

Data Extraction: The authors extracted data in duplicate. Effect sizes were calculated from the differences in means of pain-related outcomes between treatment and control groups at the end of the trial, divided by the pooled SD. Trials were combined by using random-effects meta-analysis.

Data Synthesis: 20 trials (3846 patients) contributed to the meta-analysis, which revealed a high degree of heterogeneity among the

trials ($I^2 = 92\%$). Small trials, trials with unclear concealment of allocation, and trials that were not analyzed according to the intention-to-treat principle showed larger effects in favor of chondroitin than did the remaining trials. When the authors restricted the analysis to the 3 trials with large sample sizes and an intention-to-treat analysis, 40% of patients were included. This resulted in an effect size of -0.03 (95% CI, -0.13 to 0.07 ; $I^2 = 0\%$) and corresponded to a difference of 0.6 mm on a 10-cm visual analogue scale. A meta-analysis of 12 trials showed a pooled relative risk of 0.99 (CI, 0.76 to 1.31) for any adverse event.

Limitations: For 9 trials, the authors had to use approximations to calculate effect sizes. Trial quality was generally low, heterogeneity among the trials made initial interpretation of results difficult, and exploring sources of heterogeneity in meta-regression and stratified analyses may be unreliable.

Conclusions: Large-scale, methodologically sound trials indicate that the symptomatic benefit of chondroitin is minimal or non-existent. Use of chondroitin in routine clinical practice should therefore be discouraged.

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Pharmacologic therapy for osteoarthritis consists mainly of analgesics and nonsteroidal antiinflammatory drugs. Although these are the most commonly prescribed agents for this condition, they may cause serious gastrointestinal and cardiovascular adverse events and do not affect the underlying structural cartilage damage (1, 2). A disease-modifying therapy would be more beneficial. Attempts have been made to influence cartilage loss in osteoarthritis by administering such cartilage constituents as chondroitin (3–8). Chondroitin is a highly hydrophilic, gel-forming polysaccharide macromolecule. Its hydrocolloid properties convey much of the compressive resistance of cartilage. Despite its large molecular size, ingested chondroitin is partially absorbed in the intestine (9–12) and some of it may reach joints (9, 13).

Oral chondroitin for treating osteoarthritis has become widespread (14). A previous meta-analysis demonstrated moderate to large effects on symptoms (4) but questioned the quality of the included studies. Recently published large-scale trials of high methodological quality (3, 8) found conflicting results. We performed a systematic review and meta-analysis of all available randomized, controlled trials to determine the effects of chondroitin on pain and joint space width and to explore whether reported beneficial effects could be explained by biases affecting individual trials or publication bias.

METHODS

Literature Search

We searched the Cochrane Central Register of Controlled Trials (1970 to 2006), MEDLINE (1966 to 2006), EMBASE (1980 to 2006), and CINAHL (1982 to 2006) using a combination of keywords and text words related to osteoarthritis; these were combined with generic and trade names of the various preparations of chondroitin plus a validated filter for controlled clinical trials (15). **Appendix Table 1** (available at www.annals.org) shows the details of the search. We used similar strategies to identify previously published systematic reviews and meta-analyses. In addition, we manually searched conference proceedings and textbooks, screened reference lists of all papers, retrieved reports citing relevant articles through Science Citation In-

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Context

People sometimes use chondroitin preparations to prevent hip or knee damage and pain.

Contribution

This systematic review summarized data from 20 trials that compared the effects of chondroitin with either placebo or no treatment in patients with hip or knee osteoarthritis. Recent high-quality trials showed chondroitin had minimal or no effect on joint pain. Effects on joint space were inconclusive. Few adverse events were reported.

Implication

Chondroitin probably does not prevent or reduce joint pain in people with osteoarthritis.

—The Editors

dex (1981 to 2006), and contacted trialists and content experts. Finally, we searched 4 clinical trial registries (www.clinicaltrials.gov, www.controlled-trials.com, www.actr.org.au, and www.umin.ac.jp/ctr) to identify ongoing trials. The last update of searches was performed on 30 November 2006.

Trial Selection

We included randomized or quasi-randomized, controlled trials in patients with osteoarthritis of the knee or hip, which compared chondroitin with placebo or with no intervention. Trial groups given low doses (<400 mg/d administered orally) were excluded. No language restrictions were applied. Two reviewers independently evaluated reports for eligibility. Disagreements were resolved by discussion.

Quality Assessment

Two of 3 reviewers independently assessed concealment of treatment allocation, blinding, and adequacy of analyses (16). Concealment of allocation was considered adequate if the investigators responsible for patient selection were unable to suspect before allocation which treatment was next. Analyses were considered adequate if all recruited patients were analyzed in the group to which they were originally allocated, regardless of the treatment received (intention-to-treat principle). Because there is debate about how to handle missing data in the analyses of continuous outcomes (17), we did not assess whether the methods that were used were appropriate. **Appendix Table 2** (available at www.annals.org) shows additional details regarding quality assessment. Disagreements were resolved by discussion with a third reviewer and subsequent consensus.

Outcome Measures

The prespecified primary end point was pain at the end of the trial or at a maximum of 3 months after termination of chondroitin therapy (whichever came first). When an article provided data on more than 1 pain scale,

we referred to a previously described hierarchy of pain-related outcomes (18) and extracted the outcome that was highest on this list. Global pain took precedence over pain on walking and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscores. If a trial report provided data on global pain scores and WOMAC pain subscores, we only recorded data on global pain scores. Secondary end points were changes in minimum and mean radiographic joint space width and, as measures of drug safety, the number of patients experiencing any adverse event, patients who withdrew because of adverse events, and patients experiencing any serious adverse events (19).

Data Collection

Data regarding publication status, trial design, patient characteristics, treatment regimens, outcome methods, results, and funding were extracted in duplicate on a standardized form. When necessary, means and measures of dispersion were approximated from figures in the reports. For crossover trials, we extracted data from the first period only because of a possible carry-over effect of chondroitin. If effect sizes could not be calculated, we contacted the authors for additional data. Disagreements were resolved by discussion with a third reviewer and subsequent consensus.

Statistical Analysis

Whenever possible, we used results from an intention-to-treat analysis. Effect sizes were calculated by dividing the differences in mean values at the end of the trial across treatment groups by using the pooled SD (20). **Appendix Table 3** (available at www.annals.org) shows the formulas

Figure 1. Study flow diagram.

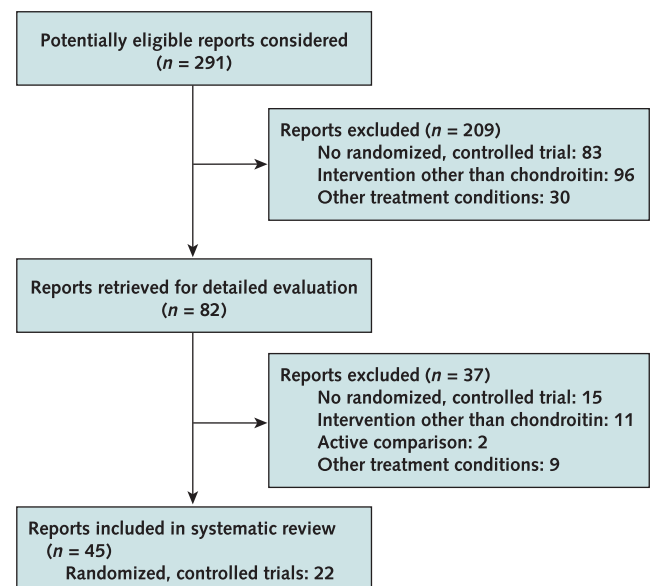


Table 1. Characteristics of Identified Trials*

Study, Year (Reference)	Daily Dose of Chondroitin	Treatment Schedule, wk	Time of Pain Assessment, wk	Patients, n†	Mean Age, y	Women, %	Mean Duration of Symptoms, y
Kerzberg et al., 1987 (36)	150 biological units intramuscular§	1 to 6	6	17	50	65	6.2
Rovetta, 1991 (42)	Intramuscular¶	1 to 13 and 27 to 40	51	40	56	55	NA
Conrozier and Vignon, 1992 (38)	1200 mg by mouth	1 to 24	24	56	61	43	5.5
L'Hirondel, 1992 (48)	1200 mg by mouth	1 to 25	25	129	63	33	NA
Mazières et al., 1992 (39)	2000 mg by mouth	1 to 13	21	120	64	66	6.3
Morreale et al., 1996 (43)	1200 mg by mouth	1 to 13**	25	146	56	59	NA
Fleisch et al., 1997 (30)	800 mg by mouth	1 to 52	52	56	NA	NA	NA
Bourgeois et al., 1998 (40)	1200 mg by mouth	1 to 13	13	127	63	76	5.3
Bucsi and Poór, 1998 (44)	800 mg by mouth	1 to 26	26	85	60	60	NA
Conrozier, 1998 (34)	800 mg by mouth	1 to 13 and 27 to 40	52	104	NA	NA	NA
Uebelhart et al., 1998 (41)	800 mg by mouth	1 to 52	52	46	59	52	NA
Alekseeva et al., 1999 (46)	1000 mg by mouth	1 to 26	39	100	60	94	NA
Malaise et al., 1999 (35)	800 mg by mouth	1 to 13 and 27 to 52	52	120	63	74	4.3
Pavelka et al., 1999 (37)	800/1200 mg by mouth††	1 to 13	13	105	65	74	4.1
Uebelhart et al., 1999 (31)	1000 mg by mouth	1 to 26	26	154	NA	NA	NA
Mazières et al., 2001 (33)	1000 mg by mouth	1 to 13	27	132	67	73	NA
Nasonova et al., 2001 (32)	1000 mg by mouth‡‡	1 to 26	26	555	57	80	NA
Soroka and Chyzh, 2002 (29)	1000 mg by mouth‡‡	1 to 12 and 27 to 31	52	100	NA	NA	NA
Michel et al., 2005 (8)	800 mg by mouth	1 to 103	103	300	63	52	NA
Clegg et al., 2006 (3)	1200 mg by mouth	1 to 24	24	631	58	27	9.6
Kahan, 2006 (45)	800 mg by mouth	1 to 132	132	622	NA	68	NA
Mazières et al., 2006 (47)	1000 mg by mouth	1 to 26	34	311	61	62	NA

* NA = not available; NSAIDs = nonsteroidal anti-inflammatory drugs; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

† Number of patients randomly assigned and relevant for the meta-analysis.

‡ The less-than sign denotes less analgesic use in the experimental group than in the control group.

§ Patients received injections 3 times per week in weeks 1 to 3 and 2 times per week in weeks 4 to 6. One biological unit corresponds to the equivalent activity of 1 mg of the standard preparation.

|| This was a cross-over trial, but only the first 6 weeks were included in the meta-analysis.

¶ No dosage reported. Patients received 2 intramuscular injections per week.

** Patients in the control group received diclofenac and placebo in the first 4 weeks and placebo only in weeks 5 to 13; patients in the experimental group received chondroitin and placebo in the first 4 weeks and chondroitin only in weeks 5 to 13.

†† Two different chondroitin treatment groups were used in the trial.

‡‡ 1500 mg of chondroitin in weeks 1 to 3.

§§ Patients were required to discontinue co-intervention 24 hours before pain assessment.

that were used. If some required data were unavailable, we used the approximations described in **Appendix Table 4** (available at www.annals.org) (21, 22). An effect size of -0.30 may be considered minimally clinically relevant. On the basis of a median pooled SD in trials that assessed

pain by using a visual analogue scale (VAS) (2.1 cm on a 10-cm VAS), this effect size corresponds to a difference in pain scores of 0.6 cm (on a 10-cm VAS) between chondroitin and placebo groups.

We used standard random-effects meta-analysis (23)

Table 1—Continued

Kellgren–Lawrence Grade 0 to 2, %	Type of Analgesic Rescue Drugs in Chondroitin Group	Type of Analgesic Rescue Drugs in Control Group	Use of Analgesic Rescue Drugs Reported to Be Similar‡	Outcome Extracted for Pain	Effect Size (95% CI)
0	NA	NA	NA	Global pain (VAS)	−1.01 (−1.94 to −0.08)
100	NSAIDs	NSAIDs	No (experimental < control)	Global pain (VAS)	−2.14 (−2.80 to −1.49)
NA	NA	NA	No (experimental < control)	Global pain (VAS)	−1.93 (−2.46 to −1.41)
NA	Acetaminophen and NSAIDs	Acetaminophen and NSAIDs	No (experimental < control)	Global pain (VAS)	−0.53 (−0.88 to −0.18)
75	NSAIDs	NSAIDs	No (experimental < control)	Global pain (VAS)	−0.64 (−1.02 to −0.27)
100	Acetaminophen	Acetaminophen	No (experimental < control)	Global pain (VAS)	−1.81 (−2.16 to −1.46)
NA	Acetaminophen	Acetaminophen	No (experimental < control)	None	NA
NA	NSAIDs	NSAIDs	No (experimental < control)	Global pain (VAS)	−0.87 (−1.23 to −0.50)
92	Acetaminophen	Acetaminophen	No (experimental < control)	Global pain (VAS)	−0.94 (−1.37 to −0.51)
NA	Acetaminophen	Acetaminophen	NA	Global pain (VAS)	−0.57 (−0.96 to −0.19)
91	Acetaminophen	Acetaminophen	NA	Global pain (VAS)	−1.17 (−1.75 to −0.59)
NA	NA	NA	No (experimental < control)	Pain on activity (VAS)	−0.57 (−0.97 to −0.18)
71	Acetaminophen (maximum, 4 g/d)	Acetaminophen (maximum, 4 g/d)	No (experimental < control)	Global pain (VAS)	−0.42 (−0.79 to −0.04)
NA	Acetaminophen (maximum, 4 g/d)	Acetaminophen (maximum, 4 g/d)	No (experimental < control)	Global pain (VAS)	−1.23 (−1.63 to −0.83)
NA	Acetaminophen and NSAIDs	Acetaminophen and NSAIDs	No (experimental < control)	None	NA
56	Acetaminophen (maximum, 3 g/d) and NSAIDs	Acetaminophen (maximum, 3 g/d) and NSAIDs	Yes	Pain on activity (VAS)	−0.23 (−0.58 to 0.11)
NA	NSAIDs	NSAIDs	Yes	Pain on activity (VAS)	−0.86 (−1.07 to −0.64)
NA	NSAIDs	NSAIDs	No (experimental < control)	WOMAC pain subscale	−0.34 (−0.73 to 0.06)
40	Acetaminophen (maximum, 3 g/d) and NSAIDs	Acetaminophen (maximum, 3 g/d) and NSAIDs	Yes	WOMAC pain subscale	−0.14 (−0.36 to 0.09)
58	Acetaminophen (maximum, 4 g/d)	Acetaminophen (maximum, 4 g/d)	Yes§§	WOMAC pain subscale	0.01 (−0.15 to 0.16)
43	Acetaminophen (maximum, 4 g/d) and NSAIDs	Acetaminophen (maximum, 4 g/d) and NSAIDs	No (experimental < control)§§	WOMAC pain subscale	−0.02 (−0.18 to 0.13)
NA	Acetaminophen	Acetaminophen	Yes	WOMAC pain subscale	−0.30 (−0.52 to −0.08)

and calculated the I^2 statistic, which describes the percentage of total variation across trials that is attributable to heterogeneity rather than to chance (24). I^2 values of 25%, 50%, and 75% correspond to low, moderate, and high between-trial heterogeneity. We investigated the association between trial size and treatment effects in funnel plots by plotting effect sizes on the vertical axis against their SES on the horizontal axis (25). We assessed asymmetry by the asymmetry coefficient—the difference in effect size per unit increase in SE (26).

We then performed analyses stratified by the following trial characteristics: concealment of allocation, use of a placebo control, patient blinding, adequacy of analyses in accordance with the intention-to-treat principle, trial size,

funding, route of administration, length of follow-up, and differences in the use of cointerventions in the trial groups. We used a prespecified cutoff of 200 randomly assigned patients to distinguish between small-scale and large-scale trials and a cutoff of 26 weeks to distinguish between short-term and long-term trials. Univariable random effects meta-regression models (27) were used to examine whether effect sizes were affected by these factors. In addition, the following 3 continuous variables at trial level were included in univariable meta-regression: chondroitin dosage (in trials with oral administration), treatment duration, and length of follow-up. To explore whether small effect sizes might be explained by unusually high effects in the placebo group, we used an approach analogous to plots

used by L'Abbé and colleagues (28) and plotted changes in pain scores in the control group against changes in pain scores in the chondroitin group, which were standardized by the pooled SD (20). Finally, we restricted the analysis to large-scale placebo-controlled trials (≥ 200 randomly assigned patients) with an intention-to-treat analysis.

Differences in changes in minimal and mean joint space width were pooled by using original units in millimeters. To explore the magnitude of effects on the width of the joint space, we expressed these differences as effect sizes, dividing the pooled estimates in millimeters by the median pooled SD of 1.3 mm found for minimal and mean joint space width. We performed analyses by using Stata, version 9.2 (Stata Corp., College Station, Texas).

Role of the Funding Sources

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RESULTS

We identified 1453 references in our literature search and considered 291 to be potentially eligible (Figure 1). Forty-five reports describing 22 trials met our inclusion criteria and were included in the meta-analysis. Seventeen trials were published as full-text journal articles, and 5 trials (29–31) were published as conference abstracts only. The median year of publication was 1999 (range, 1987 to 2006). A search of trial registries yielded no ongoing trials.

Study Characteristics

Overall, the trials had allocated 4056 patients (median, 120 [range, 17 to 631]) to chondroitin, placebo, or a nonintervention control group (Table 1 [3, 8, 29–48]). Most trials included patients with osteoarthritis of the knee only, 2 trials (32, 33) included patients with osteoarthritis of the knee or the hip, and 1 trial (34) included patients with osteoarthritis of the hip only. The average age of the patients ranged between 50 years and 67 years (median, 61 years), and the percentage of women ranged from 27% to 94% (median, 62%). The average duration of symptoms was reported in 7 trials (3, 35–40) and ranged from 4 years to 10 years (median, 5 years), whereas the proportion of

patients with low-grade osteoarthritis (corresponding to Kellgren–Lawrence grades between 0 and 2) was reported in 10 trials (3, 8, 33, 35, 36, 39, 41–44) and ranged from 0% to 100% (median, 73%). Recently performed trials tended to be larger and of higher quality and included a lower proportion of patients with low-grade osteoarthritis than did earlier trials (Table 1; Appendix Table 2, available at www.annals.org).

Among the 20 trials that reported oral administration of chondroitin, the dosage ranged from 800 mg/d to 2000 mg/d (median, 1000 mg/d). Chondroitin was administered on consecutive days in 17 trials; treatment durations ranged from 6 to 103 weeks (median, 25 weeks). Three trials (29, 34, 35) administered treatments intermittently; the cumulative treatment duration was a total of 26 weeks in each of the 3 trials. Concomitant pain medication was allowed in all trials. The duration of follow-up ranged from 13 to 132 weeks (median, 31 weeks). All trials used patient-administered scales to quantify pain.

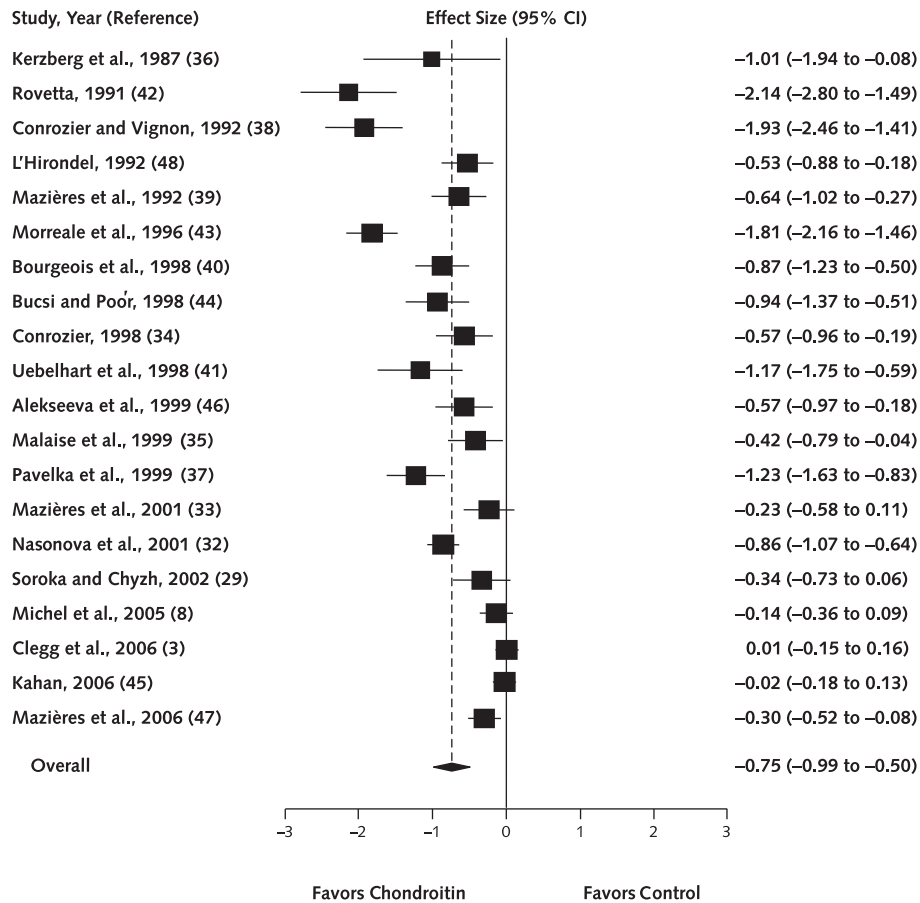
All trials except 1 (29) were reported as being randomized. However, the allocation sequence was reported to be adequately generated for 1 trial (8) and reported to be adequately concealed for only 2 other trials (3, 45). For all other trials, generation and concealment of allocation remained unclear. All but 3 trials (29, 32, 46) used a placebo control (Table 1). Only 3 trials (3, 8, 45), which had analyzed all randomly assigned patients, were considered to have an intention-to-treat analysis. Most trials did not describe approaches for handling missing data, and the remaining 8 trials (3, 8, 33, 35, 39, 40, 45, 47) used last observation carried forward (17) for imputations. Appendix Table 2 (available at www.annals.org) provides further details of methodological characteristics of included trials.

Effects on Joint Pain

Twenty trials (3846 patients) contributed to the meta-analysis of pain-related outcomes (Figure 2 [3, 8, 29, 32–48]). Two (30, 31) of the 22 identified trials were available as conference abstracts only, and we could not extract sufficient data to calculate effect sizes. Both trials had found only small, statistically nonsignificant trends in favor of chondroitin compared with placebo.

The meta-analysis identified a large effect size of -0.75 (95% CI, -0.99 to -0.50). Based on a median pooled SD of trials assessing pain with a VAS (2.1 cm on a 10-cm VAS), this effect size corresponds to a difference in pain scores of 1.6 cm (on a 10-cm VAS) between chondroitin and placebo groups (18). An I^2 of 92% indicated a high degree of between-trial heterogeneity ($P < 0.001$). The funnel plot appeared asymmetrical (Figure 3) and had an asymmetry coefficient of -4.68 (CI, -7.58 to -1.77). This coefficient indicates that the benefit of chondroitin increases by an effect size of 4.68 with each unit increase in the SE, which is a surrogate for sample size ($P = 0.003$). Figure 4 shows an exploratory analysis of effect sizes according to year of publication. On average, the benefit of

Figure 2. Forest plot of 20 trials comparing chondroitin with control.



$I^2 = 92\%$ ($P < 0.001$). The size of the boxes is proportional to the random-effects weights used in the meta-analysis.

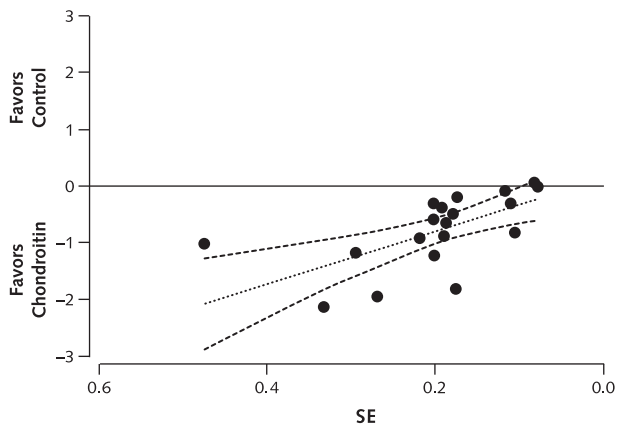
chondroitin decreased by an effect size of 0.08 per year (CI, 0.04 to 0.12; $P = 0.001$), that is, newer publications showed smaller effects than did older publications.

Table 2 presents results from stratified analyses. Estimates of effect sizes varied to some degree depending on use of placebo controls, patient blinding, length of follow-up, source of funding, and route of administration, but CIs were wide and tests of interaction were not statistically significant. However, benefits of chondroitin were smaller in trials with adequate concealment of allocation (3, 45) compared with trials with unclear concealment (P for interaction = 0.050), in trials with an intention-to-treat analysis (3, 8, 45) compared with those that had excluded patients from the analysis (P for interaction = 0.017), and in large trials (3, 8, 32, 45, 47) compared with small trials (P for interaction = 0.022). Trials with adequate concealment and trials with an intention-to-treat analysis all were large. Finally, trials that reported a similar use of analgesic cointerventions in experimental and control groups (3, 8, 32, 33, 47) showed smaller benefits of chondroitin than did the remaining trials that reported a higher use of analgesics in controls or provided no information (P for inter-

action = 0.043). I^2 estimates indicated substantial between-trial heterogeneity in all strata, with the exception of the strata that included the 2 trials with adequate concealment and the 3 trials with an intention-to-treat analysis. Additional univariable meta-regression analyses indicated no association between effect sizes and follow-up duration, maximum treatment duration, or dosage of chondroitin ($P > 0.15$). When the 2 large trials with adequate concealment of allocation were pooled, 33% of patients were included, which resulted in an effect size of -0.01 (CI, -0.12 to 0.10). When the 3 large trials with an intention-to-treat analysis were pooled, 40% of patients were included, which resulted in an effect size of -0.03 (CI, -0.13 to 0.07). This corresponds to differences of 0.2 and 0.6 mm on a 10-cm VAS, respectively.

For 18 trials, changes in pain scores between baseline and end of follow-up were available separately for experimental and control groups. Figure 5 plots standardized changes in pain scores observed in the control group against those observed in the chondroitin group. In control groups, the standardized changes ranged from -1.44 to 0.14 (median, -0.68). Only 2 trials found a mean increase

Figure 3. Funnel plot of 20 trials comparing chondroitin with control.



Effect sizes on the vertical axis are plotted against their SE on the horizontal axis. Circles indicate individual studies. The dotted line indicates the predicted treatment effect (regression line) from univariable meta-regression by using SE as the explanatory variable. Dashed lines represent the 95% CIs.

in pain in the control group: 1 small-scale trial with atypically large benefits of chondroitin (42) and 1 large-scale trial without a placebo control (32). The standardized changes in control groups in the 3 large-scale trials with an intention-to-treat analysis (-1.13 [45], -0.76 [3], and -0.07 [8]) were not systematically different from the remaining trials.

Effects on Radiologic Joint Space Width

Five trials reported changes in joint space width (8, 34, 35, 41, 45). The meta-analysis of differences in changes between chondroitin and placebo groups revealed a small effect in favor of chondroitin: 0.16 mm on minimum joint space width (CI, 0.08 to 0.24) and 0.23 mm on mean joint space width (CI, 0.09 to 0.37). This corresponds to small effect sizes (0.12 and 0.18 SD units). There was little evidence for between-trial heterogeneity with I^2 values of 8% and 21%, respectively. Funnel plots appeared asymmetrical on visual inspection, with corresponding asymmetry coefficients of 1.8 mm (CI, -1.2 to 4.7; $P = 0.150$) and 2.1 mm (CI, -2.8 to 7.1, $P = 0.20$).

Adverse Events

Twelve trials contributed to the meta-analysis of patients experiencing any adverse events (3, 30, 33, 35, 37–40, 42–44, 47), with a pooled relative risk of 0.99 (CI, 0.76 to 1.31). Nine trials (8, 33, 35, 39, 40, 43–45, 48) contributed to the analysis of patients who withdrew because of adverse events (relative risk, 0.98 [CI, 0.64 to 1.52]), and 2 trials (33, 44) contributed to the analysis of serious adverse events (relative risk, 1.52 [CI, 0.12 to 19.97]). Between-trial heterogeneity was low in all 3 analyses ($I^2 < 30\%$).

DISCUSSION

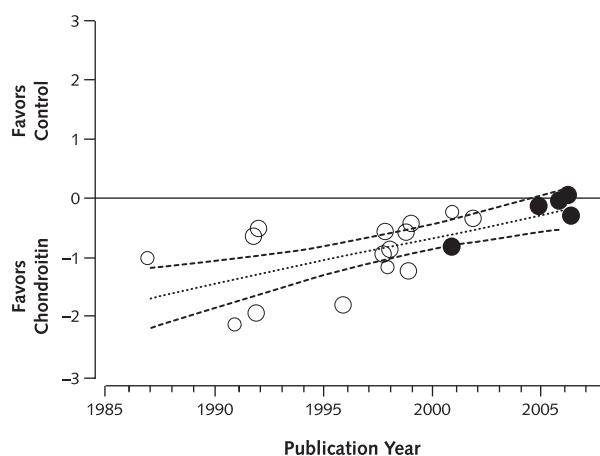
Our meta-analysis of trials comparing chondroitin with placebo or a nonintervention control revealed a high degree of heterogeneity among trials, which made the interpretation of results difficult. Meta-regression analyses indicated that heterogeneity could be explained by 3 methodological characteristics: concealment of allocation, intention-to-treat analysis, and sample size. When we pooled the 3 trials with large sample sizes and an intention-to-treat analysis, 40% of randomly assigned patients were included, which resulted in an effect size near 0, with CIs excluding any clinically relevant benefit of chondroitin. Only a few trials reported the effects of chondroitin on joint space narrowing, and pooled estimates were small and potentially affected by biases associated with small sample sizes. Finally, we found no evidence to suggest that chondroitin is unsafe.

Strengths and Limitations

Our review is based on a broad literature search, and it seems unlikely that we missed relevant trials (49). Trial selection and data extraction, including quality assessment, were done independently by 2 authors to minimize bias and transcription errors (50). Components used for quality assessment are validated and reported to be associated with bias (51).

As with any systematic review, our study is limited by the quality of included trials. Most trials had poor methodological quality or inadequate reporting. Only 2 trials (3, 45) described how allocation of patients was concealed (51), and only 3 trials (3, 8, 45) seemed to have been

Figure 4. Effect sizes according to time of publication.



Effect sizes on the vertical axis are plotted against the publication year on the horizontal axis. Open circles represent studies with fewer than 200 participants, and solid circles represent studies with 200 or more participants. The size of the circles is proportional to the random-effects weights that were used in the meta-regression. The dotted line indicates the predicted treatment effects (regression line) from univariable meta-regression by using publication year as the explanatory variable, and dashed lines represent the 95% CIs.

Table 2. Results of the Stratified Meta-analyses

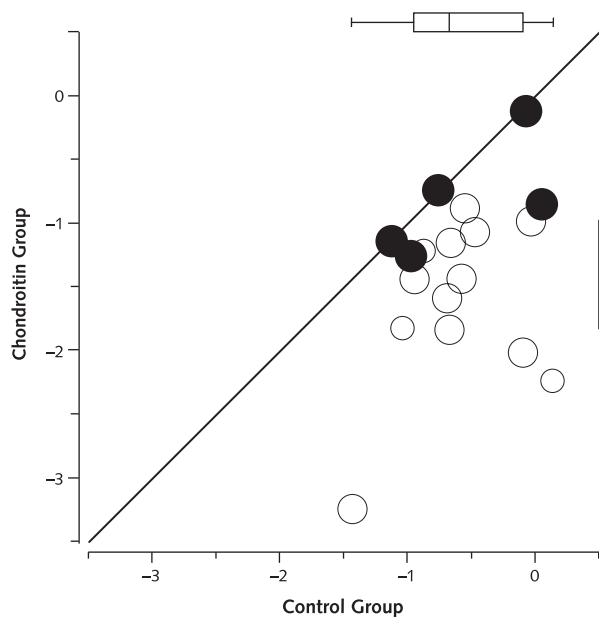
Variable	Total Trials, <i>n</i>	Patients Who Were Randomly Assigned, <i>n</i>	Effect Size (95% CI)	I ² , %	P Value for Interaction
All trials	20	3846	-0.75 (-0.99 to -0.50)	92	-
Concealment of allocation					0.050
Adequate	2	1253	-0.01 (-0.12 to 0.10)	0	
Unclear	18	2593	-0.84 (-1.08 to -0.59)	88	
Placebo control					0.63
Yes	17	3091	-0.78 (-1.06 to -0.50)	93	
No	3	755	-0.62 (-0.94 to -0.30)	65	
Patient blinding					0.22
Adequate	12	1952	-0.93 (-1.34 to -0.51)	95	
Unclear or no	8	1894	-0.53 (-0.81 to -0.24)	86	
Intention-to-treat analysis					0.017
Yes	3	1553	-0.03 (-0.13 to 0.07)	0	
No or unclear	17	2293	-0.88 (-1.13 to -0.64)	86	
Patients randomly assigned					0.022
>200 patients	5	2419	-0.26 (-0.56 to 0.04)	92	
≤200 patients	15	1427	-0.93 (-1.22 to -0.65)	86	
Duration of follow-up					0.152
>6 mo	11	2430	-0.55 (-0.81 to -0.29)	88	
≤6 mo	9	1416	-0.98 (-1.49 to -0.48)	95	
Funding by nonprofit organization					0.186
Yes	1	631	0.01 (-0.15 to 0.16)	-	
Unclear or no	19	3215	-0.79 (-1.04 to -0.54)	91	
Route of administration					0.062
Oral	18	3789	-0.67 (-0.92 to -0.43)	92	
Intramuscular	2	57	-1.63 (-2.73 to -0.53)	74	
Analgesic co-intervention					0.043
Similar	5	1929	-0.30 (-0.62 to 0.02)	91	
Less in experimental group or unclear	15	1917	-0.92 (-1.26 to -0.59)	92	

analyzed according to the intention-to-treat principle (51). Two early trials evaluating intramuscular applications were small and of particularly poor methodological quality. One of these trials (42) showed an unrealistic effect size of about twice the magnitude of what would be expected for total joint replacement (18). Similarly, 1 large-scale trial (32) had methodological drawbacks, such as unclear reporting of concealment of allocation, a lack of placebo control, and no intention-to-treat analysis. The results from this trial showed a large effect size in favor of chondroitin, which was incompatible with the results from the remaining large-scale trials. Clearly, inclusion of such trials in a meta-analysis overestimates the benefits of chondroitin and inflates between-trial heterogeneity.

Several relevant variables were poorly reported. For example, we could not fully address the potential for performance bias (16) by extracting consistent data on concomitant treatment (the average dosages of acetaminophen or nonsteroidal antiinflammatory drugs taken at the time of pain assessments). Unequal cointervention is an unlikely reason for small effect sizes in the recently published, large,

methodologically sound trials. Contrary to what would be expected in the presence of performance bias, we found smaller benefits of chondroitin in trials reporting similar uses of analgesic cointerventions (3, 8, 32, 33, 47) compared with the remaining trials that reported either a higher use of analgesics in control groups or provided no information. The trials by Clegg and colleagues (3) and Michel and colleagues (8), both of which found effect sizes near 0, had carefully monitored and reported analgesic use and found no evidence for a difference in cointerventions between groups. In another large-scale trial with an effect size near 0, Kahan (45) reported a higher intake of nonsteroidal anti-inflammatory drugs in patients assigned to placebo. However, the difference between groups for the last 3 months of the trial corresponded to an average difference in the daily dosage of 67 mg of ibuprofen between patients receiving chondroitin and those receiving placebo, which is unlikely to explain the observed null results. Finally, in this trial and the trial by Clegg and colleagues (3), patients were required to discontinue analgesic cointerventions 24 hours before pain assessments, which makes performance bias

Figure 5. Plot of standardized changes in pain scores in the control group against those in the chondroitin group.



Open circles represent individual studies with fewer than 200 participants, and solid circles represent studies with 200 or more participants. The size of the circles is proportional to the random-effects weights that were used in the meta-analysis. The solid line indicates no difference in changes between the placebo and chondroitin groups. Box plots indicate the interquartile range and median (rectangle) and minimum and maximum changes (error bars).

even more unlikely. Another explanation of the observed effect sizes near 0 in large trials (3, 8, 32, 45, 47) is an atypically large response in control groups. We addressed this by plotting standardized changes in pain scores in control groups against those in experimental groups (Figure 5) and found that trials observing effect sizes near 0 did not systematically differ from the remaining trials. For 2 trials reported only in conference abstracts (16, 51), we were unable to extract sufficient information to calculate effect sizes. One of the trials recruited only 17 patients and would have contributed little to the analysis (36). In line with publication and other reporting biases, the second trial recruited more than 150 patients and found only small, clinically irrelevant benefits of chondroitin (31). Nine additional trials (8, 29, 33, 34, 38, 45–48) did not provide sufficient details to allow exact calculations of effect sizes, and we had to use approximations to derive effect sizes. Although these approximations are established for meta-analyses of continuous outcomes (22), their validity has not been evaluated systematically in osteoarthritis research.

Our analysis was limited by the heterogeneity among component trials. We therefore explored possible sources of heterogeneity by using meta-regression and stratified analyses. These analyses should be viewed as hypothesis-

generating. They are observational in nature and have the same disadvantages as do other observational studies (52, 53). In addition, the multiplicity of analyses has increased the probability of identifying spurious associations.

Relation to Other Systematic Reviews

Our search revealed 4 other meta-analyses on the effectiveness of chondroitin (4, 6, 7, 54). McAlindon and colleagues' study (4) was the most comprehensive. This analysis included 9 trials and showed a pooled effect size of -0.96 (CI, -1.30 to -0.63). As with our study, this analysis was limited by the statistical heterogeneity of trials. We were able to include 11 additional trials with 3047 additional patients. The difference in results between our study and that of McAlindon and colleagues should not be viewed as contradictory but rather as a trend over time, which resulted from the accumulation of higher-quality evidence. An exploratory analysis of time trends in our study indicated that effect sizes gradually decreased over time. In addition, we used a more conservative approach to calculate effect sizes and divided differences between groups by the pooled SD rather than the SD in the control group. As with our assessment of trial quality, McAlindon and colleagues (4) identified methodological problems of component trials, which limited their conclusions. Smaller trials are, on average, conducted and analyzed with less methodological rigor than are larger studies (55), and the asymmetrical funnel plot in our study suggests that methodological problems combined with publication bias may have led to an overestimation of effect sizes in small trials. Attrition bias (16) may have contributed in particular: Trials that excluded participants from the analysis showed systematically larger treatment benefits than those that included all randomly assigned participants in an intention-to-treat analysis.

In contrast to the study by McAlindon and colleagues (4) and our study, Richy and colleagues (6) identified no methodological weaknesses of component trials. This may be related to the scale used for quality assessment (56). The use of another quality assessment scale may have resulted in a different judgment (57). In addition, Richy and colleagues' assessments of quality items (6) conflict with our assessments. For example, the report by Pavelka and colleagues (37) was judged to properly describe the random allocation of patients. However, the concealment of allocation remains unclear because the authors only report that patients were assigned "according to a randomization key" and provide no further information.

Implications for Research

Overall, the quality of reporting in the component trials was low. Future trials should adhere to methodological standards that reduce possible biases, including concealed allocation, blinding of patients and outcome assessors, measures to reduce withdrawals, and an analysis based on all patients recruited regardless of the intervention (intention-to-treat analysis). Moreover, reports of trials should

adhere to generally accepted standards of reporting clinical trials (for example, the Consolidated Standards of Reporting Trials [CONSORT] statement [58]).

Recently performed, methodologically sound, large-scale trials with effect sizes near 0 tended to include a lower proportion of patients with low-grade osteoarthritis than did earlier, smaller trials of lower methodological quality, which showed moderate to large effect sizes. Therefore, confounding could exist between methodological characteristics of trials and the proportion of patients with low-grade osteoarthritis: The larger benefit of chondroitin in earlier trials could not only be related to lower methodological quality but also to a high proportion of patients with low-grade osteoarthritis. Although we deem it unlikely that patients with advanced osteoarthritis will benefit, we cannot exclude a clinically relevant effect of chondroitin in patients with low-grade osteoarthritis. A rigorously designed, adequately powered, randomized placebo-controlled trial restricted to patients with low-grade osteoarthritis would be required to address this. A search of clinical trial registries revealed no ongoing trials, and it seems unlikely that suitable evidence will become available in the near future.

Implications for Practice

No robust evidence supports the use of chondroitin in osteoarthritis. Large-scale, methodologically sound trials indicate that the symptomatic benefit is minimal to non-existent. The effect of chondroitin on joint space narrowing was assessed in only a few trials. This effect is likely to be small, and its clinical significance is uncertain. In patients with low-grade osteoarthritis, the use of chondroitin should be restricted to randomized, controlled trials. For patients with advanced osteoarthritis, a clinically relevant benefit is unlikely and the use of chondroitin should be discouraged.

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Appendix Table 1. Search Strategy*

Step	Search Strategy
1	animal/
2	animal/ and human/
3	1 not 2
4	RANDOMIZED CONTROLLED TRIAL.pt.
5	CONTROLLED CLINICAL TRIAL.pt.
6	RANDOMIZED CONTROLLED TRIALS.sh.
7	RANDOM ALLOCATION.sh.
8	DOUBLE BLIND METHOD.sh.
9	SINGLE BLIND METHOD.sh.
10	CLINICAL TRIAL.pt.
11	exp CLINICAL TRIALS/
12	(clin\$ adj25 trial\$.ti,ab.
13	((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
14	PLACEBOS.sh.
15	placebo\$.ti,ab.
16	random\$.ti,ab.
17	RESEARCH DESIGN.sh.
18	COMPARATIVE STUDY.sh.
19	exp EVALUATION STUDIES/
20	FOLLOW UP STUDIES.sh.
21	PROSPECTIVE STUDIES.sh.
22	(control\$ or prospectiv\$ or volunteer\$.ti,ab.
23	or/4-22
24	glucosamin\$.mp.
25	glycosamin\$.mp.
26	glicosamin\$.mp.
27	chondroitin\$.mp.
28	GAG.mp.
29	NAG.mp.
30	mucopolysaccharid\$.mp.
31	proteoglycan\$.mp.
32	(cartilage adj protective).mp.
33	(anti adj osteoarthritic).mp.
34	Structum.mp.
35	Chondrosulf.mp.
36	Condrosulf.mp.
37	FCHG49.mp.
38	TRH122.mp.
39	Rumalon.mp.
40	Arteparon.mp.
41	Versican.mp.
42	Cosequin.mp.
43	Glycoflex.mp.
44	Arthri-Nu.mp.
45	J-Flex.mp.
46	Glucomotion.mp.
47	or/24-46
48	osteoarthritis\$.ti,ab,sh.
49	osteoarthro\$.ti,ab,sh.
50	gonarthritis\$.ti,ab,sh.
51	gonarthro\$.ti,ab,sh.
52	coxarthritis\$.ti,ab,sh.
53	coxarthro\$.ti,ab,sh.
54	arthros\$.ti,ab.
55	arthrot\$.ti,ab.
56	((knee\$ or hip\$ or hand\$ or finger\$ or joint\$) adj3 (pain\$ or ach\$ or discomfort\$)).ti,ab.
57	((knee\$ or hip\$ or joint\$) adj3 stiff\$).ti,ab.
58	or/48-57
59	23 and 47 and 58
60	59 not 3
61	remove duplicates from 60

* MEDLINE, EMBASE, and CINAHL were searched through the Ovid platform (www.ovid.com). The Cochrane Central Register of Controlled Trials was searched through the Wiley InterScience platform (www3.interscience.wiley.com) without the 2 methodological filters (steps 1 to 3 and steps 4 to 23). The search was last updated on 30 November 2006.

Appendix Table 2. Methodological Characteristics of Included Trials*

Study, Year (Reference)	Study Design	Concealment of Allocation†	Reported to Be Double-Blind‡	Adequate Blinding of Patients§	Adequate Blinding of Therapists	Described as Placebo-Controlled¶	Withdrawal Rate in the Chondroitin Group	Withdrawal Rate in the Control Group	Intention-to-Treat Analysis Performed**	Method to Handle Missing Data
Kerzberg et al., 1987 (36)	RCT	Unclear	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear
Rovetta, 1991 (42)	RCT	Unclear	Yes	Yes	Unclear	Yes	0.10	0.10	No	Unclear
Comrozier and Vignon, 1992 (38)	RCT	Unclear	Yes	Yes	Unclear	Yes	0.17	0.70	Unclear	Unclear
L'Hirondel, 1992 (48)	RCT	Unclear	Yes	Yes	Unclear	Yes	0.05	0.02	No	Unclear
Mazières et al., 1992 (39)	RCT	Unclear	Yes	Yes	Unclear	Yes	0.00	0.02	No	LOCF
Morreal et al., 1996 (43)	RCT	Unclear	Yes	Yes	Yes	Unclear	0.12	0.15	No	Unclear
Fleisch et al., 1997 (30)	RCT	Unclear	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear
Bourgeois et al., 1998 (40)	RCT	Unclear	Yes	Yes	Unclear	Yes	Unclear	Unclear	Unclear	LOCF
Bucsi and Poór, 1998 (44)	RCT	Unclear	Yes	Unclear	Unclear	Yes	0.08	0.04	Unclear	Unclear
Comrozier, 1998 (34)	RCT	Unclear	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear
Uebelhart et al., 1998 (41)	RCT	Unclear	No	Yes	Unclear	Yes	0.09	0.09	Unclear	Unclear
Alekseeva et al., 1999 (46)	RCT	Unclear	No	No	No	No	Unclear	Unclear	Unclear	Unclear
Malaise et al., 1999 (35)	RCT	Unclear	Yes	Yes	Unclear	Yes	0.20	0.27	No	LOCF
Pavelka et al., 1999 (37)	RCT	Unclear	Yes	Yes	Unclear	Yes	0.01	0.03	Unclear	Unclear
Uebelhart et al., 1999 (31)	RCT	Unclear	Yes	Unclear	Unclear	Yes	Unclear	Unclear	No	Unclear
Mazonova et al., 2001 (32)	RCT	Unclear	Yes	Yes	Unclear	Yes	0.11	0.10	No	LOCF
Nasonova et al., 2001 (32)	RCT	Unclear	No	No	No	No	Unclear	Unclear	No	Unclear
Soroka and Chyzh, 2002 (29)	CCT	Unclear	No	Unclear	Unclear	No	Unclear	Unclear	Unclear	Unclear
Michel et al., 2005 (8)	RCT	Unclear	Yes	Yes	Unclear	Yes	0.27	0.27	Yes	LOCF
Clegg et al., 2006 (3)	RCT	Yes	Yes	Yes	Unclear	Unclear	0.22	0.21	Yes	LOCF
Kahan, 2006 (45)	RCT	Yes	Yes	Unclear	Unclear	Yes	0.30	0.25	Yes	LOCF
Mazières et al., 2006 (47)	RCT	Unclear	Yes	Unclear	Unclear	Yes	Unclear	Unclear	No	LOCF

* CCT = controlled clinical trial; LOCF = last observation carried forward; RCT = randomized, controlled trial.

† Concealment of allocation was considered adequate if the investigators responsible for patient selection were unable to suspect before allocation which treatment was next (central randomization, sequentially numbered, sealed, opaque assignment envelopes, or coded drug packs). Any procedures based on predictable generation of allocation sequences or potentially transparent procedures were considered inadequate.

‡ Terms, such as "double-blind," were explicitly mentioned in the report.

§ Explicit description that interventions were indistinguishable.

|| Blinding of therapists was explicitly mentioned in the report.

¶ Placebo was explicitly mentioned in the report.

** All recruited patients were analyzed in the group to which they were initially randomly assigned regardless of the treatment received.

Appendix Table 3. Equations*

Variable	Equation
Difference of means at follow-up	$\Delta_{\bar{x}} = \bar{x}_{Exp} - \bar{x}_{Con}$
Means at follow-up (SE)	$SE_{\bar{x}_{Exp}} = \frac{SD_{Exp}}{\sqrt{N_{Exp}}}$
	$SE_{\bar{x}_{Con}} = \frac{SD_{Con}}{\sqrt{N_{Con}}}$
Difference of means at follow-up (SE)	$SE_{\Delta_{\bar{x}}} = \sqrt{SE_{\bar{x}_{Exp}}^2 + SE_{\bar{x}_{Con}}^2}$
Means at follow-up (pooled SD)	$SD_{pooled} = \sqrt{\frac{SD_{Exp}^2 + SD_{Con}^2}{2}}$
Effect size	$ES = \frac{\Delta_{\bar{x}}}{SD_{pooled}}$
Effect size (SE)	$SE_{ES} = \frac{SE_{\Delta_{\bar{x}}}}{SD_{pooled}}$

* Δ = difference; Con = control group; ES = effect size; *Exp* = experimental group; *N* = number of participants; \bar{x} = mean at follow-up.

Appendix Table 4. Calculation of Effect Sizes*

Study, Year (Reference)	Patients, n		Scale (Range)	Mean Baseline Score (SD)		Mean Follow-up Score (SD)		P Value	Mean Change in Score from Baseline		Mean Difference in Means (±SE)	Pooled SD	Effect Size (±SE)	Approximation Used to Calculate Effect Size
	Experimental Group	Control Group		Experimental Group	Control Group	Experimental Group	Control Group		Experimental Group	Control Group				
Kerzberg et al., 1987 (36)	8	9	Pain VAS (0 to 100)	74 (46)	77 (27)	41 (23)	59 (10)		-43	-2	-18 (±8)	18	-1.01 (±47)	
Rovetta, 1991 (42)	18	18	Pain VAS (0 to 100)	89 (22)	84 (21)	42 (21)	87 (21)				-45 (±7)	21	-2.14 (±0.33)	
Conrozier and Vignon, 1992 (38)	29	27	Pain VAS (0 to 100)								-41 (±6)	21	-1.93 (±0.27)	†‡§
L'Hirondel, 1992 (48)	63	62	Pain VAS (0 to 10)	4.0	3.9	1.8	2.9				-1.1 (±0.4)	2.1	-0.53 (±0.18)	§
Mazières et al., 1992 (39)	56	55	Pain VAS (0 to 10)	4.9 (2.2)	5.2 (2.0)	2.4 (2.0)	3.8 (2.2)				-1.4 (±0.4)	2.1	-0.64 (±0.19)	
Morreale et al., 1996 (43)	65	61	Pain VAS (0 to 100)	56 (17)	57 (19)	10 (12)	36 (16)				-26 (±3)	14	-1.81 (±0.18)	
Bourgeois et al., 1998 (40)	83	44	Pain VAS (0 to 100)	56 (13)	56 (13)	29 (19)	45 (19)				-16 (±4)	19	-0.87 (±0.19)	
Bucsi and Poór, 1998 (44)	39	46	Pain VAS (0 to 100)	56 (17)	56 (20)	32 (23)	55 (26)				-23 (±5)	25	-0.94 (±0.22)	
Conrozier, 1998 (34)	52	52	Pain VAS (0 to 100)	59	61	29	41				-12 (±4)	21	-0.57 (±0.20)	§
Uebelhart et al., 1998 (41)	23	23	Pain VAS (0 to 10)	5.8 (1.6)	6.4 (1.1)	2.1 (2.1)	4.8 (2.5)				-2.7 (±0.7)	2.3	-1.17 (±0.29)	
Alekseeva et al., 1999 (46)	50	50	Pain VAS (0 to 100)	48	50			0.003			-12 (±4)	21	-0.57 (±0.20)	§¶**
Malaise et al., 1999 (35)	54	56	Pain VAS (0-100)	59 (16)	61 (19)	34 (27)	46 (28)				-11 (±5)	28	-0.42 (±0.19)	
Pavelka et al., 1999 (37)	70	35	Pain VAS (0 to 100)	69 (11)	71 (11)	32 (19)	57 (22)				-25 (±4)	21	-1.23 (±0.20)	
Mazières et al., 2001 (33)	63	67	Pain VAS (0 to 100)	54 (14)	53 (14)				-26	-20	-5 (±4)	21	-0.23 (±0.18)	§††
Nasonova et al., 2001 (32)	159	214	Lequesne (0 to 24)	10.9 (5.4)	10.6 (5.9)	5.2 (4.5)	10.9 (8.3)				-5.7 (±0.7)	6.7	-0.86 (±0.11)	
Soroka and Chyzyh, 2002 (29)	50	50	WOMAC pain (0 to 20)					0.05			-1.5 (±0.9)	4.5	-0.34 (±0.20)	§¶††**
Michel et al., 2005 (8)	150	150	WOMAC pain (0 to 10)	2.5 (1.6)	2.7 (1.8)				-0.3	-0.2	-0.3 (±0.3)	2.3	-0.14 (±0.12)	§††
Glegg et al., 2006 (3)	318	313	WOMAC pain (0 to 500)	235 (72)	237 (74)	152 (113)	151 (113)				1 (±9)	113	0.01 (±0.08)	
Kahan, 2006 (45)	309	313	Pain VAS (0 to 100)	57	57				-24	-24	0 (±2)	21	-0.02 (±0.08)	§††
Mazières et al., 2006 (47)	155	156	Pain VAS (0 to 100)						-26	-20	-6 (±2)	21	-0.3 (±0.11)	†‡§

* VAS = visual analogue scale; WOMAC = Western Ontario McMaster Universities Osteoarthritis Index.

† Difference in means at follow-up from difference in mean changes.

‡ Pooled SD from median pooled SD of trials that used the same pain scale.

§ SD of means at follow-up from median pooled SD of trials that used the same pain scale.

¶ P value assumed to be 1-sided.

** t value for difference in means calculated from SE and t value.

†† Means at follow-up from means calculated from P value.

‡‡ Boundary P value used.