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Glucosamine for Pain in Osteoarthritis

Why Do Trial Results Differ?

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Objective. **Investigators in trials of glucosamine report a range of estimates for efficacy, making conclusions difficult. We undertook this study to identify factors that explain heterogeneity in trials of glucosamine.**

Methods. **We searched for reports of trial results in Ovid Medline, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and proceedings of scientific conferences. We selected reports of randomized, double-blind, placebo-controlled trials of glucosamine for pain from osteoarthritis of the knee or hip. We extracted data regarding features of design, subjects, and markers of industry involvement, including industry funding, whether a drug was supplied by industry, industry participation, and industry-affiliated authorship. We examined which factors best accounted for differences in the effect sizes of studies grouped by these characteristics, and we examined changes in I^2, a measure of heterogeneity.**

Results. **Fifteen trials met our inclusion criteria. The summary effect size was 0.35 (95% confidence interval 0.14, 0.56). I^2 was 0.80. Except for allocation concealment, no feature of study design explained this substantial heterogeneity. Summary effect sizes ranged from 0.05 to 0.16 in trials without industry involvement, but the range was 0.47–0.55 in trials with industry involvement. The effect size was 0.06 for trials using glucosamine hydrochloride and 0.44 for trials using glucosamine sulfate. Trials using Rottapharm products had an effect size of 0.55, compared with 0.11 for the rest.**

Conclusion. **Heterogeneity among trials of glucosamine is larger than would be expected by chance. Glucosamine hydrochloride is not effective. Among trials with industry involvement, effect sizes were consistently higher. Potential explanations include different glucosamine preparations, inadequate allocation concealment, and industry bias.**

Osteoarthritis (OA) is one of the most common chronic diseases affecting Americans and is a major source of disability in elderly persons (1). Pharmacologic therapy for pain relief is widely perceived to be the backbone of effective management. Unfortunately, many of the most effective pain relievers, especially nonsteroidal antiinflammatory drugs, have well-known side effects that limit their use.

Glucosamine, which is classified as a "dietary supplement" in the US and is available over the counter, appears to be safe and is widely marketed for pain relief in OA. However, its efficacy is uncertain. While several trials have suggested that glucosamine has a marginal, if any, effect compared with placebo, others report robust efficacy.

In a series of trials using similar methods and subjects, we would expect random variation in the estimate of the true effect of an intervention. If the observed variation in outcomes from trial to trial is consistent with chance variation, then the trials are said to be homogeneous (i.e., the trials are all evaluating the same effect and their conclusions are similar). If the observed variation in outcomes is greater than expected

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by chance, then the trials are said to be heterogeneous. This implies either that the trials are evaluating different treatments or that variation in the way the studies were conducted or in the patients studied influenced individual trial results, resulting in markedly different estimates of effect.

One goal of meta-analysis is to combine the results of trials to give a more precise estimate of the effect of a treatment. However, if the combined trials are markedly heterogeneous in their estimates of treatment effect, a summarized estimate may have no interpretable meaning. By investigating the sources of heterogeneity among these trials, we can try to identify sources of bias in the summary effect measure. Such inquiries may also yield insights into whether certain patients are more likely or less likely to experience the benefits of a treatment. For instance, in a meta-analysis of the efficacy of tamoxifen for women with breast cancer, the authors demonstrated significant heterogeneity in the summary effect measure (2). When the trials were subdivided into groups with similar durations of treatment, the heterogeneity in each group was substantially reduced (3), reflecting a difference in the effect of the drug dependent upon the duration of treatment.

Many factors could account for heterogeneity in glucosamine trials. For instance, at least 2 different forms of glucosamine are in general use, and differences between them could explain the variability in results. A Cochrane Review suggested that the glucosamine formulation made by Rottapharm (Monza, Italy) may be more effective than other formulations, suggesting that other differences in formulation could be important as well (4). Other factors that could contribute to the differences among trial findings include the quality of study reporting, which has been shown to correlate with the strength of effect (5), or time-dependent differences, in which early studies show effects that later studies fail to duplicate (6).

Industry sponsorship is also a potential source of differences between trial results. Industry-sponsored trials report positive effects more often than do nonsponsored trials and more often find proindustry results (7–14). However, there has been little reported evidence that industry sponsorship plays a role in the results of glucosamine trials.

The present study had 2 goals. The first was to confirm the impression that the results of glucosamine trials show significant heterogeneity. The second was to identify factors that explain this heterogeneity. We hypothesized that industry sponsorship could be an important factor in predicting glucosamine trial results. Recent publication of results of several large industry-sponsored and non–industry-sponsored trials gave us a unique opportunity to investigate both sponsorship effects and the effects of other factors.

PATIENTS AND METHODS

Search for relevant trials. Ovid Medline, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews were searched from 1966 through February 2006 for reports of relevant trials. For reports of trials in yearly scientific conferences, we also searched the Web sites of the American College of Rheumatology for the period 1999–2005, the European League Against Rheumatism for the period 2001–2004, and the Osteoarthritis Research Society International for the period 1999–2005. Articles and abstracts identified from previous meta-analyses (4,15–17), review articles (18–21), and the references of all retrieved articles were searched. No restriction was placed on language.

Selection. We used the same search criteria as a previous meta-analysis (15). Trials were included if they were randomized, double-blind, placebo-controlled trials of parenteral or oral glucosamine for pain from OA of the knee or hip, and if subjects were followed up for >4 weeks. Trials that studied glucosamine in conjunction with another agent were included if a group of subjects treated with glucosamine alone was compared with a group receiving only placebo. Search terms included *osteoarthritis*, *osteoarthrosis*, *degenerative arthritis*, *glucosamine*, *chondroitin*, and *glycosaminoglycans*. We then excluded trials that studied only chondroitin or only chondroitin/glucosamine combinations.

Data abstraction. We abstracted data according to a predefined form. Where possible, we identified outcomes as defined by the trial investigators, with associated standard deviations for the placebo group at the end of the trial. We used the standard deviation in the placebo arm to avoid any effect of treatment on variability (22). In some trials, a number of outcomes were evaluated, and a primary outcome was not clearly identified. We therefore used the outcome presented first in the results section of the trial report. In cases where studies investigated multiple agents (e.g., glucosamine and chondroitin) and/or multiple sites (e.g., OA of the back and knee), the data given in the report were used to derive outcomes as they pertained to glucosamine use in hip and knee OA, whenever possible.

Data synthesis. Using the identified primary outcome, an effect size for each trial comparing the intervention with placebo was calculated. The effect size is a unitless measure that incorporates both the size of the effect and its variability into a single measure. Effect sizes of 0.2 are considered small, those of 0.5 are moderate, and those of 0.8 are large (23). In trials for which the standard deviation was not reported, it was imputed using similar trials with related outcome measures (15). Dichotomous outcomes from trials were converted using the method of Chinn (24). Random-effects meta-analysis methods were used to pool the effect sizes and derive a summary measure. To investigate possible publication bias, we used both the Egger test and a funnel plot (25,26).

Exploration of heterogeneity. The focus of our study was on how best to explain heterogeneity across studies. We used 2 different methods to identify the factor(s) that best accounted for heterogeneity in studies of glucosamine. First, univariate random-effects meta-regression was used to study the changes in effect size when groups of trials were stratified by various trial characteristics (26). We anticipated that successful predictors of trial outcome would produce a large difference in the effect sizes of trials with the characteristic compared with those without. Multivariate models were not used because of the small number of trials.

Second, we looked at changes to heterogeneity when studies were grouped by each characteristic. Heterogeneity was measured using the method of Higgins et al (3), which produces I^2 as a measure. I^2 can be viewed as the percentage of the variation in outcome that results from differences between studies rather than chance. When trials are divided into groups with and without a given characteristic, a reduced I^2 in both groups should indicate a feature that can explain differences in outcomes between the 2 groups (3).

We hypothesized that trial characteristics that could explain heterogeneity would include the following: the duration of the trial in weeks, the trial size as given by the number of randomly assigned patients, the mean body mass index (BMI) of all included subjects (or the mean weight in kilograms where BMI was not given), mean baseline pain measured as a percentage of the maximum measured by the scale used in the trial, the presence or absence of rescue medications, the preparation of glucosamine used (sulfate or hydrochloride), and the total daily dose used (multiple daily dosing was converted to a single daily dose equivalent [e.g., 500 mg 3 times a day = 1,500 mg daily]). We included measures of trial quality, including the Jadad score (27), the percentage of subjects withdrawing from the trial (28), the presence of an intent-to-treat analysis (28), and the presence of adequate allocation concealment. Allocation concealment was measured as adequate, intermediate, or inadequate according to Rochon et al (28). If an article described a process by which the next treatment assigned to a patient was impossible to predict, it was labeled "adequate." If there was a small chance that the next treatment could be predicted, it was labeled "intermediate." The latter included use of sealed envelopes, random numbers, and coin flips according to the protocol of Rochon et al. If the process did not meet these criteria or was not described, it was labeled "inadequate."

Because of our interest in the influence of industry, we investigated 4 related areas of industry involvement (modified from Yaphe et al [14]). These included 1) industry funding, defined as whether an industry source provided the funds to conduct the trial; 2) industry-supplied drug, defined as whether the study medication was provided free of charge by the manufacturer; 3) industry participation, defined as the utilization of a drug manufacturer for any of the following: data storage, data collection, data management, or data analysis; and 4) industry-affiliated author, defined as an author who was employed by a drug manufacturer or as an author who received fees for any services (speaking fees, consultation, etc.). These categories are likely to be highly correlated. Because many published reports did not provide this information, we sent a questionnaire to at least 1 author from each trial asking for this information. If there was disagreement between the published report and the questionnaire, the data in the questionnaire were used.

RESULTS

Trial flow. The flow of the study is shown in Figure 1. The initial search yielded 128 articles of potential interest, of which 96 were excluded based on the title or abstract. The remaining 32 articles were obtained and read in their entirety. We excluded 9 more after detailed review (29–37), since they did not meet entry criteria. Of the 23 remaining articles, 8 more were excluded for the following reasons: 5 were abstracts that were subsequently published as articles that are included in this review (38–42), 1 used a combined data set derived from 2 other previously published articles (43), and 2 did not contain sufficient data to derive an effect estimate (44,45). The remaining 15 articles were included in the analysis (refs. 46–59 and unpublished results of 1 trial [see below]). All trials were of glucosamine in knee OA.

Study characteristics. The characteristics of the 15 trials are shown in Table 1. Results of 13 trials were published in articles, results of 1 trial were published in an abstract (47), and results of 1 trial were unpublished (Rovati L, Bourgeois P, Giacovelli G, Menkes C. Symptom modification by glucosamine sulfate in knee osteo-

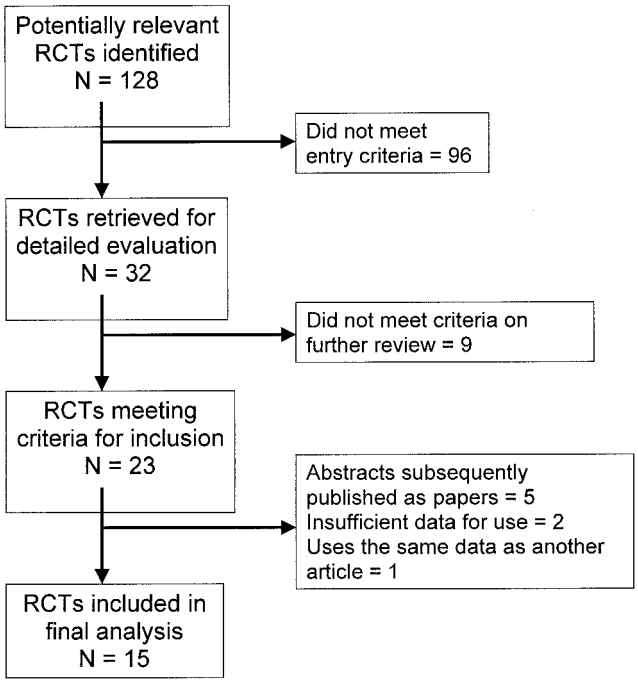

Figure 1. Flow of the study. RCTs = randomized controlled trials.

Table 1. Characteristics of the 15 studies analyzed*

Author, year (ref)	Trial duration, weeks	No. of subjects randomized	Jadad score, range 1–5†	Allocation concealment	Withdrawals, % of total randomized	Type of analysis	Mean baseline BMI, kg/m^2‡	Mean baseline pain, % of maximum for scale	Glucosamine preparation	Manufacturer	Industry funding	Industry participation	Industry-affiliated author
Clegg et al, 2006 (46)	24	630	5	Adequate	20	ITT	31.7	47.0	Hydrochloride	Ferro Pfanstiehl	No	No	No
Herrero-Beaumont et al, 2005 (47)	26	210	3	Inadequate	19.5	ITT	27	45	Sulfate	Rottapharm	Yes	Yes	Yes
Usha and Naidu, 2004 (48)	12	58	4	Inadequate	12	ITT	26	55.3	Sulfate	Healer	Yes	No	No
McAlindon et al, 2004 (49)	12	205	4	Adequate	9.3	ITT	32.6	30	Hydrochloride and sulfate§	Physiologics/ Rottapharm	No	No	No
Cibere et al, 2004 (50)	26	137	5	Adequate	2.2	ITT	27.5	12.5	Sulfate	Vitahealth	No	No	No
Pavelka et al, 2002 (51)	156	202	5	Intermediate	40.1	ITT	25.7	37.3	Sulfate	Rottapharm	Yes	Yes	Yes
Hughes and Carr, 2002 (52)	24	80	5	Intermediate	6.3	ITT	–	53.4	Sulfate	Health Perception	Yes	No	No
Reginster et al, 2001 (53)	156	212	4	Intermediate	34.4	ITT	27.4	41	Sulfate	Rottapharm	Yes	Yes	Yes
Rindone et al, 2000 (54)	8	114	3	Intermediate	14	Comp	91 kg	37.5	Sulfate	Applehart	No	No	No
Houpt et al, 1999 (55)	8	118	3	Adequate	16.9	ITT	80 kg	71	Hydrochloride	Ferro Pfanstiehl	Yes	No	No
Reichelt et al, 1994 (56)	6	155	4	Inadequate	8.4	Comp¶	25.7	42.3	Sulfate	Rottapharm	Yes	Yes	Yes
Noack et al, 1994 (57)	4	252	4	Adequate	4.4	Comp¶	26.4	44.2	Sulfate	Rottapharm	Yes	Yes	Yes
Vajaradul, 1981 (58)	9	60	1	Inadequate	10	Comp	99 kg	78	Sulfate	Rottapharm	Yes	Yes	No
Pujalte et al, 1980 (59)	6	24	4	Intermediate	16.7	Comp	–	61.3	Sulfate	Rottapharm	Yes	Yes	Yes
Rovati et al, 1999#	12	156	5	Intermediate	12.8	ITT	27.9	42.9	Sulfate	Rottapharm	Yes	Yes	Yes

* BMI = body mass index; ITT = intent-to-treat; Comp = completers analysis.
† According to Jadad et al (27); a score of 1 indicates high potential for bias, and a score of 5 indicates low potential for bias.
‡ Mean weight in kilograms is given if the mean BMI was not provided and there was insufficient information to calculate it.
§ The preparation was changed while the study was in progress. In our analysis, the study is treated as a "hydrochloride" study, since this formulation was used in the majority of subjects.
¶ These trials also presented ITT results. The outcomes used in the analysis were those presented first in the results sections, which were completers analyses.
# Unpublished (see Results).

Table 2. Pooled estimates of heterogeneity and pooled effect estimates*

	No. of studies in each group	Estimate of effect (95% CI)†	*P* for difference	Heterogeneity, I^2
All studies	15	0.35 (0.14, 0.56)		0.80
Glucosamine hydrochloride	3	0.06 (−0.08, 0.20)	–	0.00
Glucosamine sulfate	12	0.44 (0.18, 0.70)		0.80
Industry funding				
Absent	4	0.05 (−0.32, 0.41)	0.05	0.00
Present	11	0.47 (0.24, 0.70)		0.81
Industry participation				
Absent	7	0.11 (−0.16, 0.38)	0.02	0.00
Present	8	0.55 (0.29, 0.81)		0.84
Industry-affiliated author				
Absent	8	0.16 (−0.11, 0.42)	0.04	0.19
Present	7	0.55 (0.27, 0.84)		0.87
Use of a Rottapharm product				
Absent	7	0.11 (−0.16, 0.38)	0.01	0.00
Present	8	0.55 (0.29, 0.82)		0.84
Allocation concealment				
Adequate	5	0.09 (−0.24, 0.42)		0.00
Intermediate	6	0.47 (0.14, 0.80)	0.09	0.90
Inadequate	4	0.54 (0.14, 0.94)		0.00
ITT analysis				
No	5	0.44 (0.03, 0.84)	0.62	0.48
Yes	10	0.31 (0.05, 0.58)		0.86
Jadad score, range 1–5‡				
1–3	4	0.30 (−0.14, 0.73)	0.77	0.37
4 and 5	11	0.37 (0.11, 0.63)		0.85
Rescue medication use				
No	3	0.55 (0.01, 1.10)	0.42	0.63
Yes	12	0.31 (0.07, 0.55)		0.83

* ITT = intent-to-treat.
† Estimates and 95% confidence intervals (95% CIs) were obtained by random-effects meta-analysis methods.
‡ According to Jadad et al (27); a score of 1 indicates high potential for bias, and a score of 5 indicates low potential for bias.

arthritis: a randomized placebo- and reference-controlled double blind trial. Unpublished manuscript; 1999). The unpublished manuscript was sent to us by Lucio Rovati of Rottapharm, a manufacturer of a glucosamine sulfate product, when we requested information about other trials supported by Rottapharm.

Trials were reported between 1980 and 2006. They ranged in size from 24 subjects to 630 subjects and lasted from 4 weeks to 156 weeks. Twelve trials used glucosamine sulfate, 2 used glucosamine hydrochloride, and 1 used both. This last trial initially used glucosamine hydrochloride but switched to the sulfate formulation when the first supplier stopped the supply of the study drug (49). Since ~85% of subjects receiving the active medication received the hydrochloride form, this trial was classified as a glucosamine hydrochloride trial. All but 2 trials used the equivalent of 1,500 mg/day glucosamine (one of the 2 trials used 400 mg twice weekly given intramuscularly [56]; the other used weekly intra-articular injections and the dose was not stated [58]).

Industry funding was reported for 11 trials. Investigators in 1 of these trials (55) received funding from a company separate from the one that provided the study drug. Thirteen studies used an industry-supplied drug. Because there were only 2 trials in which the drug was not obtained from industry, we did not undertake further analyses using this variable. Rottapharm provided glucosamine sulfate in 8 trials and contributed to a ninth trial. Ferro Pfanstiehl Laboratories (Waukegan, IL) supplied glucosamine hydrochloride for 2 trials. Investigators in 2 trials (46,49) purchased part of the medication and received the rest for free. Investigators in 8 trials reported industry participation. Investigators in 7 trials reported an industry-affiliated author. There was considerable overlap between trials with industry funding, those with industry participation, and those with an industry-affiliated author.

Data synthesis findings. There was marked heterogeneity between trials. The summary I^2 was 0.80, suggesting that 80% of the variation in outcome was due to

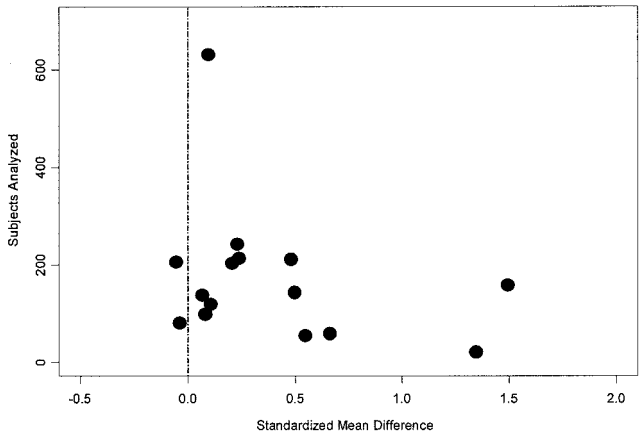

Figure 2. Funnel plot for publication bias. Each symbol represents 1 trial. Effect size is shown on the x-axis as the standardized mean difference. Study size is shown on the y-axis. In the absence of publication bias, the plot should be roughly symmetric.

heterogeneity rather than chance (see Table 2). The pooled effect size was 0.35 (95% confidence interval [95% CI] 0.14, 0.56) for glucosamine compared with placebo; however, due to the marked heterogeneity, pooling of the results is not recommended since the pooled effect size may not accurately reflect the true effect of glucosamine.

Publication bias was not detected using the Egger test ($P = 0.14$), but visual examination of the funnel plot suggested that bias might be present (Figure 2). In the absence of publication bias, points should be symmetrically distributed about a central line in the shape of an inverted funnel.

When examined using differences in effect sizes or reduction in I^2, there were marked differences between subgroups of trials when grouped by various trial characteristics (Tables 2 and 3 and Figure 3). Both effect size and heterogeneity were greatly reduced among trials using glucosamine hydrochloride; the pooled effect size was 0.06 (95% CI −0.08, 0.20), and I^2 was 0.00. Glucosamine sulfate trials had an effect size of 0.44 (95% CI 0.18, 0.70) and retained marked heterogeneity, with an I^2 of 0.80. Again, the marked heterogeneity of the latter trials may make pooling the effects inadvisable.

Trials were divided into industry-funded and

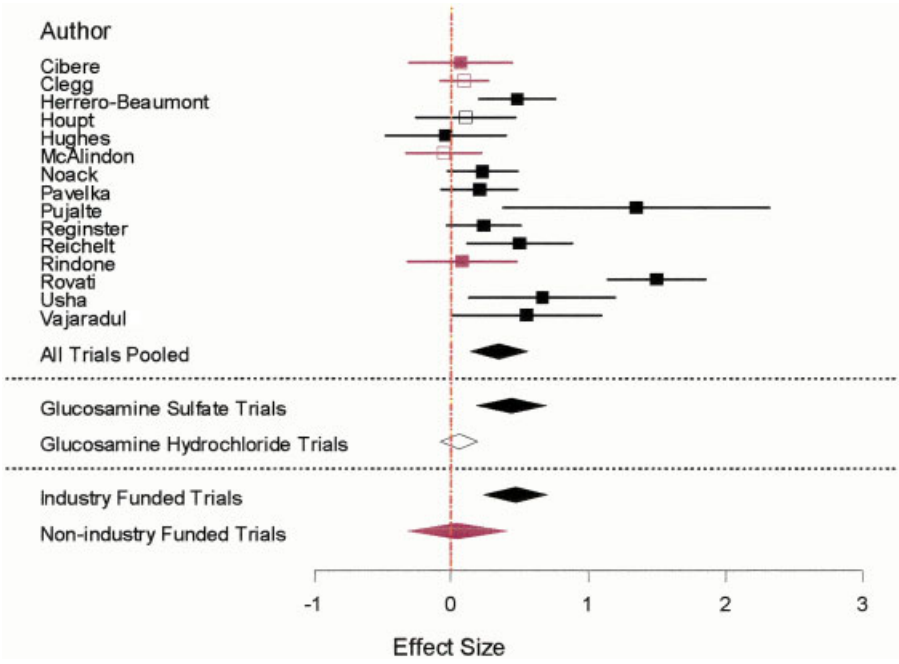

Figure 3. Summary effect sizes with 95% confidence intervals. Trials represented in black are industry funded. Trials represented in red are non–industry funded. Solid squares represent trials of glucosamine sulfate. Open squares represent trials of glucosamine hydrochloride. Studies correspond to the following references: Cibere et al (50), Clegg et al (46), Herrero-Beaumont et al (47), Houpt et al (55), Hughes and Carr (52), McAlindon et al (49), Noack et al (57), Pavelka et al (51), Pujalte et al (59), Reginster et al (53), Reichelt et al (56), Rindone et al (54), Rovati et al (unpublished; see Results), Usha and Naidu (48), and Vajaradul (58).

non–industry-funded trials. The 11 industry-funded trials had a pooled effect size of 0.47 (95% CI 0.24, 0.70) compared with a pooled effect size of only 0.05 (95% CI −0.32, 0.41) for the 4 non–industry-funded trials. Heterogeneity remained high in the industry-funded trials ($I^2 = 0.81$) but was absent in the non–industry-funded trials ($I^2 = 0.00$).

A similar trend was evident for trials with an industry-affiliated author; the effect size was 0.55 (95% CI 0.27, 0.84), with an I^2 of 0.87, compared with trials without an industry-affiliated author, where the effect size was 0.16 (95% CI −0.11, 0.42) and the I^2 was 0.19. For trials with industry participation, the effect size was 0.55 (95% CI 0.29, 0.81) and the I^2 was 0.84, compared with those without industry participation, where the effect size was 0.11 (95% CI −0.16, 0.38) and the I^2 was 0.00. There was a statistically significant difference in effect size for each comparison of industry involvement (see Table 2).

Grouping by other trial characteristics showed less marked changes in effect size or heterogeneity (see Tables 2 and 3). There were 2 exceptions. The first exception was allocation concealment, which showed a difference in effect size for trials with adequate (0.09) versus those with intermediate (0.47) or inadequate (0.54) concealment. However, the overall *P* value for the comparison among the 3 groups was not statistically significant ($P = 0.09$). Heterogeneity was absent in the adequately concealed trials ($I^2 = 0.00$), high in the intermediate trials ($I^2 = 0.90$), and absent in the inadequately concealed trials ($I^2 = 0.00$).

The second exception was year of publication of the study findings. For each decade in which studies were reported (1980s, 1990s, and 2000s), the effect size dropped by an average of 0.26 (i.e., the effect size was, on average, 0.26 lower for studies reported in the 1990s compared with those reported in the 1980s, and 0.52 [0.26 × 2] lower for studies reported in the 2000s compared with those reported in the 1980s) (Table 3). This trend did not reach statistical significance (zero was included in the 95% CI).

Post hoc analyses. Since almost all trials used 1,500 mg/day glucosamine, we looked for differences due to the dosing schedule (3 times a day versus daily dosing). Among the 13 trials using oral formulations, 9 used 3-times-a-day dosing. The effect size in these 9 trials was 0.12 (95% CI 0.02, 0.23), with an I^2 of 0.39. In the 4 trials using daily dosing, the effect size was 0.59 (95% CI 0.01, 1.18), with an I^2 of 0.92. These 4 trials all used Rottapharm products.

In another post hoc analysis, we examined the effect size of trials using Rottapharm products compared with the effect size of the rest of the trials. The effect size for trials with Rottapharm products (a sulfate compound) was 0.55 (95% CI 0.29, 0.82) compared with an effect size of 0.11 (95% CI −0.16, 0.38) for trials with other products ($P = 0.01$). Since the summary effect size was essentially null within non–industry-funded trials (0.05, with $I^2 = 0.00$), we therefore examined the difference in effect size between trials with and those without Rottapharm products only within the industry-funded group. We found that the effect size for the 3 trials funded by companies other than Rottapharm was 0.22 (95% CI −0.30, 0.74), as compared with an effect size of 0.57 (95% CI 0.25, 0.88) for the 8 trials funded by Rottapharm. This difference was not statistically significant ($P = 0.27$). For trials funded by Rottapharm, the I^2 was 0.84; for trials funded by other companies, the I^2 was 0.55. No similar comparisons were possible between studies with industry participation or with an industry-affiliated author, since there were no trials with these characteristics that were not also funded by Rottapharm.

Since markers of industry involvement and allocation concealment gave the most impressive differences in effect sizes, we looked for an association between these features; that is, we examined whether studies with industry involvement more often had inadequate or intermediate allocation concealment, explaining their apparent better efficacy. We regrouped studies into 2 new groups of allocation concealment: those in which it was adequate, and those in which it was intermediate or inadequate. We then used Fisher's exact test to compare actual with expected frequencies. Three of 4 non–industry-funded trials had adequate allocation concealment (75%), while only 2 of 11 industry-funded trials had adequate allocation concealment (18%) ($P = 0.08$). The associations between allocation concealment and

Table 3. Changes in effect sizes by other trial parameters*

	No. of studies in each group	Change in effect size per unit (95% CI)†
Year, decades‡	15	−0.26 (−0.57, 0.06)
Withdrawals, %	15	0.00 (−0.02, 0.02)
Trial duration, weeks	15	0.00 (−0.006, 0.003)
Baseline pain, % of maximum possible	15	0.01 (−0.01, 0.02)
Baseline BMI	10	−0.06 (−0.17, 0.06)
Arthritis duration, years	7	−0.04 (−0.10, 0.01)

* BMI = body mass index.
† Estimates and 95% confidence intervals (95% CIs) were obtained by random-effects meta-analysis methods.
‡ Studies were grouped by decade of publication (1980–1989, 1990–1999, 2000–2006).

trials with industry participation or an industry-affiliated author were similar, although they were somewhat weaker ($P = 0.12$ and $P = 0.28$, respectively).

DISCUSSION

We confirm that heterogeneity among trials of glucosamine is larger than would be expected by chance alone. In attempting to explain this heterogeneity, we draw 3 major conclusions. First, among non–industry-funded trials, mostly of the glucosamine hydrochloride preparation, there was no heterogeneity, and the effect size of glucosamine was not statistically different from zero. Second, among trials with industry involvement, effect sizes were higher, but heterogeneity remained substantial. Unfortunately, the small number of studies does not allow fuller multivariate statistical exploration of characteristics of these studies that would allow a better understanding of the causes of this heterogeneity. Third, possible explanations for the differing effects seen in trials with industry involvement versus trials without industry involvement include use of different glucosamine preparations (sulfate versus hydrochloride, and differences in sulfate formulations), inadequate allocation concealment in trials with positive results, and inherent bias due to industry involvement. We address each of these explanations in further detail below.

Trials using glucosamine hydrochloride had a very small summary effect size that was statistically indistinguishable from the null. The finding that heterogeneity among these trials was absent suggests that this summary effect is valid. Therefore, we conclude that glucosamine hydrochloride has no effect on pain and that future studies of this preparation are unlikely to yield useful results.

It is more difficult to understand the effect of glucosamine sulfate on knee pain from OA. Trials using this drug had a moderate summary effect size of 0.44, but heterogeneity was marked, suggesting that differences between these studies are large and that pooling the results is inadvisable.

We attempted to further examine sulfate study heterogeneity by rerunning our analyses on the effects of industry involvement and excluding the 3 trials using glucosamine hydrochloride. Although we saw similar effect size changes as we did when using all formulations, the differences between trials with and those without industry involvement were not statistically significant, likely reflecting reduced power (results not shown).

However, we note that among the 12 glucosamine sulfate trials, the only trials not funded by industry (n = 2) had essentially null results (effect sizes of 0.07 and 0.08) (50,54). The only industry-funded glucosamine sulfate trial with a null result (effect size of −0.04) (52) was investigator initiated, and the funding source was not involved in any aspect of the trial aside from funding and drug supply. The remaining sulfate studies were all industry supported and had positive results to varying degrees. This suggests that independent studies of glucosamine sulfate find that it has no effect, although there are not enough trials to confirm this impression statistically.

Supporting the above observations are our findings that markers of industry involvement appear to be the most potent predictors of trial results. Any one of the markers of industry involvement that we investigated could explain the entire effect of glucosamine. Each group of trials without the marker of industry involvement had an essentially null summary effect size and homogeneous results compared with the corresponding group of trials with the marker of industry involvement, which was heterogeneous and had a larger summary effect size. All effect size differences between groups were statistically significant (although we recognize that there may be statistical issues related to multiple comparison and high correlation of these variables). However, since heterogeneity remained high in the trials with industry markers, these factors alone may not account for the entire variability in effect.

Post hoc analyses suggested that trials using Rottapharm preparations of glucosamine sulfate had an especially large effect size compared with other studies. We therefore grouped Rottapharm trials together and compared them with non–industry-funded studies and with studies funded by companies other than Rottapharm. Trials using products made by other companies had a smaller effect size and were somewhat less heterogeneous than trials using Rottapharm products; most noteworthy, however, was the persistently large heterogeneity of trials using Rottapharm products. The heterogeneity within this group of trials may account for most of the heterogeneity of glucosamine trials in general. Some of this heterogeneity may arise from different interventions among trials of Rottapharm products. For instance, 2 studies used intramuscular (56) and intraarticular (58) forms of glucosamine, and later trials tended to utilize a once-daily dosing regimen rather than the "traditional" 3-times-a-day dose.

Allocation concealment was the only other factor that had a major impact on effect size and heterogeneity. Although adequate allocation concealment failed to

reach statistical significance as a predictor of efficacy among trials, trials with adequate allocation concealment had null results and were homogeneous. Likewise, trials with inadequate allocation concealment were efficacious and homogeneous.

When we looked for correlations between allocation concealment and markers of industry involvement, we found that trials without industry involvement more often had adequate allocation concealment than trials with industry involvement. However, we must urge caution when interpreting these results. Our interpretation of Rochon and coworkers' method for determining adequate allocation concealment was stringent, and only studies that clearly reported excellent standards were judged to be "adequate." However, it has been shown that even though investigators may not report adequate allocation concealment, they may, in fact, have used adequate methods (60).

The last explanation for our findings is that bias related to industry involvement contributed to heterogeneity, in that trials with industry involvement were substantially more likely to have positive results than those without industry involvement. The null and homogeneous results of non–industry-funded trials would support this argument, as would the large summary effect size of industry-funded trials. However, it leaves unexplained the persistent heterogeneity of industry-funded trials.

Some of the latter heterogeneity could be due to differences in glucosamine sulfate formulations or in dosing methods (i.e., in each case, one may be more effective than others). However, removing the trials that used nonoral formulations from the analysis affected neither the effect size nor the I^2 (results not shown), and among studies using similar dosing schedules (3 times a day or daily), heterogeneity continued to be large in 1 of the groups ($I^2 = 0.92$ in the daily dosing group). Even among trials using only Rottapharm products, which should be fairly similar to each other, heterogeneity was large. We cannot convincingly explain the persistent heterogeneity among industry-funded trials.

The major limitation of our study is the lack of a sufficient number of trials for more complex analyses. We were unable to explore the role of confounding and interactions between trial characteristics. The small number of trials also reduced our power to find statistically significant differences between different predictors of efficacy. It is possible that with greater numbers, some of our nonsignificant effects would have been significant. In particular, the lack of nonindustry glucosamine sulfate trials and of industry trials not funded by Rottapharm makes generalizations difficult.

However, we believe that there is sufficient information to conclude that glucosamine hydrochloride lacks efficacy for pain in OA. Among glucosamine sulfate trials, enough heterogeneity existed such that no definitive conclusion about efficacy is possible. This heterogeneity appeared to be most prominent among trials with industry involvement. Explanations for the effect of industry involvement in trials include differing efficacy of glucosamine sulfate preparations (including the possibility that the Rottapharm glucosamine sulfate product is more efficacious than others), inadequate allocation concealment in trials with positive results, unidentified factors that we did not investigate, and bias due to industry involvement.

AUTHOR CONTRIBUTIONS

Dr. Vlad had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Vlad, LaValley, McAlindon, Felson.
Acquisition of data. Vlad, LaValley.
Analysis and interpretation of data. Vlad, LaValley, Felson.
Manuscript preparation. Vlad, LaValley, McAlindon, Felson.
Statistical analysis. LaValley.

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