JAMA | Original Investigation

Association of Pharmacological Treatments With Long-term Pain Control in Patients With Knee Osteoarthritis
A Systematic Review and Meta-analysis

Dario Gregori, PhD; Giampaolo Giacovelli, PhD; Clara Minto, MA; Beatrice Barbetta, MS; Francesca Gualtieri, MA; Danila Azzolina, MS; Paola Vaghi, MS; Lucio C. Rovati, MD

IMPORTANCE Even though osteoarthritis is a chronic and progressive disease, pharmacological agents are mainly studied over short-term periods, resulting in unclear recommendations for long-term disease management.

OBJECTIVE To search, review, and analyze long-term (≥12 months) outcomes (symptoms, joint structure) from randomized clinical trials (RCTs) of medications for knee osteoarthritis.

DATA SOURCES AND STUDY SELECTION The databases of MEDLINE, Scopus, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials were searched until June 30, 2018 (MEDLINE alerts through August 31, 2018) for RCTs of patients with knee osteoarthritis that had treatment and follow-up lasting 1 year or longer.

DATA EXTRACTION AND SYNTHESIS Data at baseline and at the longest available treatment and follow-up of 12 months' duration or longer (or the change from baseline) were extracted. A Bayesian random-effects network meta-analysis was performed.

MAIN OUTCOMES AND MEASURES The primary outcome was the mean change from baseline in knee pain. Secondary outcomes were physical function and joint structure (the latter was measured radiologically as joint space narrowing). Standardized mean differences (SMDs) and mean differences with 95% credibility intervals (95% CrIs) were calculated. Findings were interpreted as associations when the 95% CrIs excluded the null value.

RESULTS Forty-seven RCTs (22 037 patients; mean age range, mostly 55-70 years; and a higher mean proportion of women than men, around 70%) included the following medication categories: analgesics; antioxidants; bone-acting agents such as bisphosphonates and strontium ranelate; nonsteroidal anti-inflammatory drugs; intra-articular injection medications such as hyaluronic acid and corticosteroids; symptomatic slow-acting drugs in osteoarthritis such as glucosamine and chondroitin sulfate; and putative disease-modifying agents such as cindunistat and sprifermin. Thirty-one interventions were studied for pain, 13 for physical function, and 16 for joint structure. Trial duration ranged from 1 to 4 years. Associations with decreases in pain were found for the nonsteroidal anti-inflammatory drug celecoxib (SMD, −0.18 [95% CrI, −0.35 to −0.01]) and the symptomatic slow-acting drug in osteoarthritis glucosamine sulfate (SMD, −0.29 [95% CrI, −0.49 to −0.09]), but there was large uncertainty for all estimates vs placebo. The association with pain improvement remained significant only for glucosamine sulfate when data were analyzed using the mean difference on a scale from 0 to 100 and when trials at high risk of bias were excluded. Associations with improvement in joint space narrowing were found for glucosamine sulfate (SMD, −0.42 [95% CrI, −0.65 to −0.19]), chondroitin sulfate (SMD, −0.20 [95% CrI, −0.31 to −0.07]), and strontium ranelate (SMD, −0.20 [95% CrI, −0.36 to −0.05]).

CONCLUSIONS AND RELEVANCE In this systematic review and network meta-analysis of studies of patients with knee osteoarthritis and at least 12 months of follow-up, there was uncertainty around the estimates of effect size for change in pain for all comparisons with placebo. Larger RCTs are needed to resolve the uncertainty around efficacy of medications for knee osteoarthritis.

JAMA. 2018;320(24):2564-2579. doi:10.1001/jama.2018.19319

Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 2595

Author Affiliations: Unit of Biostatistics, Epidemiology, and Public Health, Department of Cardiac, Thoracic, and Vascular Sciences, University of Padova, Padova, Italy (Gregori, Minto, Azzolina); Department of Biostatistics, Rottapharm Biotech, Monza, Italy (Giacovelli, Barbetta, Vaghi); Scientific Information and Library Services, Rottapharm Biotech, Monza, Italy (Gualtieri); Department of Clinical Research, Rottapharm Biotech, Monza, Italy (Rovati); School of Medicine and Surgery, University of Milano – Bicocca, Monza, Italy (Rovati).

Corresponding Author: Lucio C. Rovati, MD, School of Medicine and Surgery, University of Milano – Bicocca, Via Cadore 48, 20900 Monza, Italy (lucio.rovati@unimib.it).

Osteoarthritis is among the most prevalent chronic diseases,[1] and is a leading cause of disability worldwide.[1-3] Effective management of osteoarthritis requires long-term treatment strategies for symptoms (pain and limitations in physical function) and joint structure changes that lead to disability.[4] Efficacy reviews of treatments for osteoarthritis typically emphasize short-term pain control and often do not consider long-term outcomes.[5,6] Thus, the aim of the present study was to systematically search, review, and quantitatively analyze long-term outcomes from randomized clinical trials (RCTs) of medications for knee osteoarthritis.

Knee osteoarthritis was chosen because it is the most prevalent osteoarthritis location in the lower limbs[1] and it is the location most frequently leading to disability. The evidence was assessed in a network meta-analysis. Network meta-analyses synthesize direct and indirect evidence in a network of trials that compare multiple interventions.[7] This method allows comparison of all available knee osteoarthritis medications against placebo and between pharmacological agents despite the paucity of head-to-head comparisons of therapies in RCTs.

Key Points

Question What is the association of available medications with long-term pain control in knee osteoarthritis?

Findings In this systematic review and network meta-analysis of 33 pharmacological interventions that included 22 037 patients with knee osteoarthritis in 47 randomized clinical trials lasting at least 12 months, there was uncertainty around the estimates of effect size for change in pain for all comparisons with placebo, including the 2 medications that were associated with improved pain (celecoxib and glucosamine sulfate).

Meaning Larger randomized clinical trials are needed to resolve the uncertainty around the long-term efficacy of medications for knee osteoarthritis.

Methods

This is a systematic review and network meta-analysis of long-term pharmacological intervention trials in knee osteoarthritis. Reporting was organized according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for RCTs.[8] The study protocol appears in Supplement 1.

Data Sources

An online systematic search was performed for eligible trials using the electronic databases of MEDLINE (PubMed), Scopus, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials. The search was performed from database inception until June 30, 2018 (details regarding the search procedure, strategy, and adjustment to the syntax for the different databases appear in eTables 1-1E in Supplement 2). A National Library of Medicine weekly alert was set up for the main search query until August 31, 2018, but it did not yield any relevant results.

Trial Selection Criteria

Eligible trials included placebo-controlled RCTs and those comparing any active pharmacological intervention for knee osteoarthritis alone or in combination with another intervention. Trials were eligible if the treatment or follow-up period was at least 1 year. A 1-year duration or longer was considered long term, which is consistent with scientific and regulatory criteria.[9]

Trial Identification

Two investigators (C.M. and D.A.) independently screened articles by title, abstract, and full text. Inclusion of a study was decided by consensus between the 2 investigators; however, if consensus was not reached, an independent expert was available to provide advice. Consultation with an independent expert was never necessary.

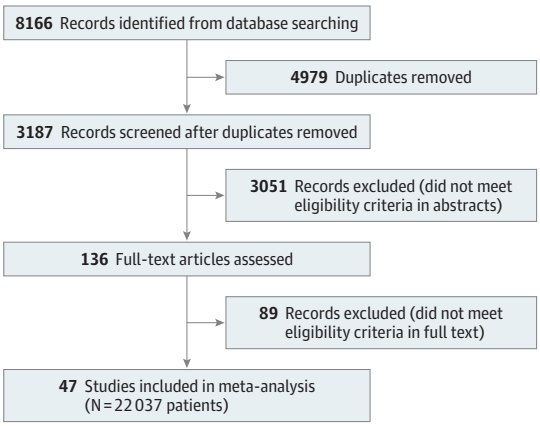
Outcomes and Data Extraction

Trials were included (**Figure 1**) if they reported data for at least 1 of the following outcomes: knee pain, physical function, or joint structure defined as radiological joint space narrowing (JSN).[10] The primary outcome was mean change from baseline to the end point (≥12 months) in knee pain because pain is likely to be the outcome that matters most to patients, physicians, and caregivers. Secondary outcomes were changes in physical function and joint structure.

When pain or physical function outcomes were measured using different scales in the RCTs, the outcomes were prioritized as recommended by Juhl et al[11] (additional details appear in eTable 2 in Supplement 2). Using this method of prioritization, the preferred pain outcome measure was the pain subscale[12] of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC); followed by the visual analog scale (VAS) for pain during any activity, pain during walking, or a global measure of knee pain; and then any other pain measures.

For physical function, the preferred outcome measure was the WOMAC physical function subscale (the other types of physical function measures and a full hierarchy for both the pain and physical function outcomes appears in eTable 2 in Supplement 2).[11] The WOMAC is a disease-specific questionnaire separately addressing the severity of pain (5 questions) and any limitation in physical function (17 questions) for the activities of daily living during the past 48 hours.[12] In the Likert scale version, each answer is scored on a scale from 0 to 4 and 0 represents "none" and 4 represents "extreme" (score range: 0-20 for pain and 0-68 for physical function). In the VAS version, each answer is scored on a 100-mm VAS and 0 mm represents "none" and 100 mm represents "extreme" (score range: 0-500 mm for pain and 0-1700 mm for physical function). When pain severity is assessed as the answer to a single question (eg, "how much is your pain during walking today?") on a 100-mm VAS, 0 mm represents "absent" and 100 mm represents "the worst imaginable" (score range: 0-100 mm). Data on JSN were derived from measuring

Figure 1. Flow Diagram of Study Identification, Screening, Eligibility Assessment, and Inclusion



change in the radiological joint space width in millimeters at the medial tibiofemoral joint.

For each outcome, the change from baseline was extracted at the longest available time point after at least 12 months, if reported; otherwise, numerical data for the outcome were extracted at baseline and at the longest available time point after at least 12 months, and the change from baseline was calculated. For graphical information, numerical data were extracted using a standard procedure.[13]

Other extracted data included characteristics of the study design to assess trial quality, baseline demographic characteristics (age, sex, and body mass index), administration route and dose of each treatment, and duration of treatment and follow-up. Only trials with extractable data were included. No additional information was requested from authors.

Quality and Risk of Bias Assessment

Quality was assessed independently by researchers in a blinded fashion. Disagreements were discussed and resolved through consensus. The quality of the included trials was assessed using the Cochrane Collaboration tool for assessing risk of bias in RCTs.[14] Large studies were those with more than 100 patients per study group.[15]

Data Synthesis and Analysis

When no variability measures were reported, imputation of the maximum standard deviation from another study using the same measurement scale was performed. In addition, the imputation of the correlation method was used when standard deviations were available for absolute baseline and follow-up values, but not for the mean change values.[16] When studies did not report mean change, these values were calculated as the arithmetic difference between baseline and follow-up. Trials considering different medication schedules or doses for the same intervention were divided into a corresponding number of pairwise comparisons of the intervention vs the reference group.

A Bayesian multiple treatment network meta-analysis[17] with random effects and uninformative priors was performed and considered both placebo- and active-controlled trials. The main analysis was performed on all eligible trials and in the subgroup excluding trials at high risk of bias.[14] The Glass Δ was used as the standardized mean difference (SMD) measure with a 95% credibility interval (CrI).[18] An SMD of 0.20 is considered a small difference between the experimental and the control group; 0.50, a moderate difference; and 0.80, a large difference.[19]

Pain data also were analyzed and are presented as the mean difference. The WOMAC knee pain subscale scores were normalized to a scale from 0 to 100 to provide a measure comparable with a single-question VAS pain assessment.[12] The minimum clinically important difference relative to placebo ranges from 5 to 10 on the normalized scale from 0 to 100, depending on the drug class and length of treatment.[20] Data on JSN were analyzed and are presented as the mean difference on the natural scale in millimeters.

The between-study standard deviation was modeled using a uniform distribution of the 0 to 5 interval.[21] A random-effects model was computed using Markov chain Monte Carlo methods with Gibbs sampling based on simulations of 200 000 iterations in each of 4 chains.

Homogeneity and consistency assumptions were verified using node splitting and the method of Bland Altman.[22-25] For each iteration, treatments were ranked by their effect relative to an arbitrary baseline. The findings were interpreted as associations when the 95% CrI excluded the null value. A frequency table was constructed from these rankings and normalized by the number of iterations giving the rank probabilities. Convergence was assessed using standard diagnostics.[26]

Probability values were summarized and are reported as the surface under the cumulative ranking (SUCRA) curve and with a rankogram plot to provide a hierarchy of treatments with consideration of both the location and the variance of all relative treatment effects.[27] The SUCRA value would be 0 when a treatment is certain to be the worst and 1 when it is certain to be the best. All analyses were conducted using the R-evolution[28] version 3.3.1 and the gemtc package[29] version 0.8 that interfaces with OpenBUGS[30] version 3.2.3 for computing a Markov chain Monte Carlo simulation.

The planned sensitivity analyses were conducted to evaluate the robustness of the model. All analyses were repeated in the sensitivity analyses to take into consideration networks derived from inclusion of only (1) studies with oral comparators, (2) studies with intra-articular injection comparators, or (3) blinded studies (irrespective of comparators). In additional statistical sensitivity analyses, all analyses were repeated and the imputation methods previously applied were excluded. Additional post hoc sensitivity analyses were performed using alternative methods to those described herein. Further details on the statistical analyses appear in Supplement 3.

Results

A total of 8166 records were retrieved, of which 47 RCTs (N = 22 037 patients) met eligibility criteria and were included

in the meta-analysis (Figure 1). A total of 33 pharmacological interventions were studied in these RCTs, representing the following classes of therapies: analgesics, antioxidants, bone-acting agents, nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular injection medications such as hyaluronic acid and corticosteroids, symptomatic slow-acting drugs in osteoarthritis, and putative disease-modifying agents (**Box**). Thirty-one interventions were studied for pain, 13 for physical function, and 16 for joint structure. Trial duration ranged from 1 to 4 years.

Acetaminophen (paracetamol) was included in the analgesics class and vitamin E was included in antioxidants class and each was studied in 1 included trial only. Conversely, NSAIDs were represented by different molecular classes, including cyclooxygenase-2 selective agents and nonselective agents. These agents were studied in 14 trials that had mostly single head-to-head NSAID comparisons or less often comparisons with placebo or other agents. Diclofenac was the most frequently studied NSAID (5 trials), followed by naproxen and celecoxib in 4 trials, rofecoxib in 2 trials, etoricoxib in 2 trials, and the remaining NSAIDs were studied in 1 trial each. Intra-articular injections of corticosteroids were used alone in 4 trials (triamcinolone in 2, betamethasone in 1, and methylprednisolone in 1) and in combination with intra-articular injections of hyaluronic acid in 3 trials (1 trial for each agent combination). Hyaluronic acid was studied alone in 12 trials and was the most tested intervention.

Bone-acting agents consisted of either antiresorptive drugs (such as bisphosphonates in 4 trials [risedronate in 3 and zoledronic acid in 1], calcitonin in 1 trial, and vitamin D in 2 trials) or bone-forming agents (such as strontium ranelate in 1 trial). Symptomatic slow-acting drugs in osteoarthritis[31] were represented by diacerein (1 trial), chondroitin sulfate (8 trials), glucosamine sulfate (2 trials accounting only for the prescription product approved as a drug in Europe and Asia[32]), and glucosamine hydrochloride (4 trials formulated with or without sodium sulfate and identified as glucosamines).

The distinction between glucosamine sulfate and other glucosamines was necessary because of their molecular differences[33] and because previous meta-analyses found differences in efficacy between prescription-grade glucosamine sulfate and other glucosamines.[34,35] Similar to glucosamine sulfate, chondroitin is available as a prescription drug in Europe and as lower-quality dietary supplements elsewhere. Prescription-grade chondroitin was used in 7 of the 8 studies considered in this meta-analysis. The combination of nonprescription glucosamines with chondroitin sulfate was used in 3 trials. Putative disease-modifying agents included 1 trial each for doxycycline, cindunistat, sprifermin, and the matrix metalloproteinase inhibitor PG-116800.

Of the 47 RCTs included, 32 were placebo-controlled trials. The characteristics of the included trials appear in the **Table**.[36-82] The demographic and clinical characteristics of the included patients reflect typical knee osteoarthritis populations (mostly between 55 and 70 years for mean age and a higher proportion [around 70%] of women than men). Body mass index (calculated as weight in kilograms divided by height in meters squared) ranged from overweight to obese (mostly between 27 and 30 for mean body mass index). Mean disease duration was between 2 and 11 years.

Disease severity based on Kellgren and Lawrence[83] radiological grading was primarily between grades 2 and 3 (grade range, 0-4). For oral medications, the timing of follow-up testing was coincident with treatment duration. In contrast, in all RCTs of intra-articular injection medications (hyaluronic acid, corticosteroids, or sprifermin in 15 studies), the interventions were administered at intervals of variable length and the final injection occurred before the duration of follow-up (Table).

Twenty-five of the 47 trials (53%) included more than 100 participants per group. Thirty-three studies (70%) were high-quality studies according to the Cochrane Collaboration tool

Box. Pharmacological Interventions Eligible for Inclusion in the Network Meta-analysis by Therapeutic Class

Analgesics
- Acetaminophen (paracetamol)

Antioxidants
- Vitamin E

Bone-Acting Agents
- Calcitonin
- Risedronate
- Strontium ranelate
- Vitamin D
- Zoledronic acid

Intra-Articular Injection Medications
- Hyaluronic acid
- Betamethasone
- Methylprednisolone
- Triamcinolone
- Hyaluronic acid plus betamethasone
- Hyaluronic acid plus methylprednisolone
- Hyaluronic acid plus triamcinolone

Nonsteroidal Anti-Inflammatory Drugs
- Celecoxib
- Diclofenac
- Etofenamate
- Etoricoxib
- Indomethacin
- Licofelone
- Naproxen
- Nimesulide
- Rofecoxib
- Tiaprofenic acid

Symptomatic Slow-Acting Drugs in Osteoarthritis
- Chondroitin sulfate
- Diacerein
- Glucosamine sulfate (prescription product only)
- Glucosamines (glucosamine hydrochloride with or without sodium sulfate)
- Glucosamines plus chondroitin sulfate

Putative Disease-Modifying Agents
- Cindunistat
- Doxycycline
- Matrix metalloproteinase inhibitors
- Sprifermin

Table. Characteristics of Trials Included in the Analysis and Summary Trial Quality Assessment

Source	Type of Intervention and Dose	No. of Patients	Women, No. (%)	Age, y[a]	BMI[a,b]	Grade[c]	Duration of Knee Osteoarthritis, y[a]	Follow-up, mo	Outcome Measure	Cochrane Collaboration Risk of Bias[d]
Arden et al,[36] 2016	Placebo	237	145 (61)	64 (8)	29 (5)	0-4	NR	36	WOMAC pain and physical function, joint space width	All low
	Vitamin D, 800 IU/d	237	144 (61)	64 (8)	30 (5)					
Bingham et al,[37] 2006[e]	Placebo	622	NA: 757 (61) EU: 991 (79)	NA: 60.5 (8.8) EU: 63.6 (8.1)	NA: 30.3 (4.9) EU: 29.4 (4.2)	NR	NR	24	WOMAC pain and physical function	Low; unclear; low; low; high; unclear; unclear
	Risedronate, 5 mg/d	628								
	Risedronate, 15 mg/d	609								
	Risedronate, 35 mg/wk	310								
	Risedronate, 50 mg/wk	314								
Bisicchia et al,[38] 2016	Hyaluronic acid, 24 mg/3 mL (2 IA injections 7 d apart)	75	53 (71)	71.5 (10.6)	NR	2-3	NR	12	VAS global knee pain	Low; low; high; high; low; high; high
	Methylprednisolone, 40 mg/1 mL (2 IA injections 7 d apart)	75	50 (67)	68.6 (9.9)						
Brandt et al,[39] 2005	Placebo	213	213 (100)	55.0 (5.8)	36.5 (6.0)	2-3	NR	30	Joint space width	Low; unclear; low; low; low; low; unclear
	Doxycycline, 100 mg twice/d	218	218 (100)	54.8 (5.5)	36.8 (6.3)					
Buckland-Wright et al,[40] 1995	Placebo	22	24 (73)[f]	65.5 (10.2)[f]	NR	NR	2.0 (3.0)[f]	18	VAS pain at night, joint space width	Low; unclear; low; low; low; low; unclear
	Diclofenac, 100 mg/d	23								
Cannon et al,[41] 2000	Diclofenac, 50 mg 3 times/d	268	185 (69)	62.5 (10.1)	NR	NR	11.4 (9.4)	12	WOMAC pain	Low; low; low; low; low; unclear; low
	Rofecoxib, 12.5 mg/d	259	169 (65)	62.8 (10.2)			11.1 (8.9)			
	Rofecoxib, 25 mg/d	257	175 (68)	62.8 (10.3)			11.5 (8.7)			
Curtis et al,[42] 2005	Diclofenac, 150 mg 3 times/d	102	79 (77)	62.3 (10.4)	NR	NR	7.5 (7.1)	12	WOMAC pain	Low; low; low; low; high; unclear; low
	Etoricoxib, 30 mg/d	198	141 (71)	61.9 (10.4)			7.8 (7.9)			
	Etoricoxib, 60 mg/d	102	75 (73)	62.3 (10.2)			7.5 (6.6)			
	Etoricoxib, 90 mg/d	148	100 (68)	60.6 (9.6)			7.8 (7.4)			
Dahlberg et al,[43] 2009	Diclofenac, 50 mg twice/d	462	321 (69)	71.0 (7.3)	NR	1-3	NR	12	VAS pain at rest	Low; low; low; low; low; high; low
	Celecoxib, 200 mg/d	463	314 (68)	71.0 (7.0)						
Dougados et al,[44] 1993	Placebo (IA injection)	55	36 (65)	69.0 (10.6)	NR	NR	6.4 (6.3)	12	VAS pain during exercise	Unclear; high; high; unclear; high; unclear; high
	Hyaluronic acid, 20 mg/2 mL (1 IA injection/wk for 4 wk)	55	42 (76)	67.0 (9.7)			5.0 (3.5)			
Ertürk et al,[45] 2016	Hyaluronic acid, 2.5 mL (1 IA injection/wk for 5 wk)	35	26 (74)	61.4 (8.4)	30.1 (3.0)	2-4	7.1 (1.2)	12	WOMAC pain	Low; low; high; low; low; unclear; high
	Hyaluronic acid, 2.5 mL (1 IA injection/wk for 5 wk) and betamethasone, 1 mL/d (1 IA injection of 6.43 mg and 2.63 mg in 1 mL/20 mg solution of lidocaine)	35	27 (77)	62.7 (7.8)	30.6 (4.8)		7.3 (1.1)			

(continued)

Table. Characteristics of Trials Included in the Analysis and Summary Trial Quality Assessment (continued)

Source	Type of Intervention and Dose	No. of Patients	Women, No. (%)	Age, y[a]	BMI[a,b]	Grade[c]	Duration of Knee Osteoarthritis, y[a]	Follow-up, mo	Outcome Measure	Cochrane Collaboration Risk of Bias[d]
Fransen et al,[46] 2015	Placebo	151	81 (54)	60.6 (8.1)	29.1 (5.8)	NR	NR	24	VAS pain at maximum,[g] WOMAC physical function, joint space width	Low; low; low; low; low; high; low
	Glucosamine, 1500 mg/d	152	84 (55)	61.2 (7.7)	28.4 (4.7)					
	Chondroitin sulfate, 800 mg/d	151	85 (56)	59.5 (8.0)	29.6 (5.4)					
	Glucosamine, 1500 mg/d and chondroitin, 800 mg/d	151	89 (59)	60.7 (8.4)	28.8 (6.0)					
Güner et al,[47] 2016	Hyaluronic acid, 30 mg/2 mL (1 IA injection/wk for 3 wk)	31	27 (90)	62.5 (50-70)	27.5 (22-35)	2-3	NR	12	VAS global knee pain	Low; low; high; high; high; high; high
	Etofenamate, 100 mg/2 mL (1 intramuscular injection/d for 7 d)	31	24 (83)	61.3 (50-70)	28.7 (23-36)					
Hellio le Graverand et al,[48] 2013	Placebo	486	364 (75)	61.3 (9.1)	31.6 (4.1)	1-3	6.8 (7.2)	24	WOMAC pain and physical function, joint space width	All low
	Cindunistat, 50 mg/d	485	383 (79)	61.0 (8.7)	31.9 (4.1)		6.4 (6.3)			
	Cindunistat, 200 mg/d	486	367 (75)	60.8 (8.6)	32.0 (4.1)		6.7 (7.2)			
Jørgensen et al,[49] 2010	Placebo (IA injection)	170	97 (57)	61.4 (11.1)	NR	NR	6.7 (8.2)	12	VAS pain during walking	Low; low; low; unclear; high; low; unclear
	Hyaluronic acid, 20 mg/2 mL (1 IA injection/wk for 5 wk)	167	109 (66)	62.6 (11.4)			6.1 (6.6)			
Jubb et al,[50] 2003	Placebo (IA injection)	200	128 (64)	65.0 (9.1)	29.8 (5.0)	2-3	8.5 (7.5)	12	VAS pain during walking, joint space width	Low; low; unclear; low; low; low; unclear
	Hyaluronic acid, 20 mg/2 mL (1 IA injection/wk for 3 wk every 4 mo)	208	151 (73)	63.5 (9.5)	29.8 (5.2)		7.9 (7.1)			
Kahan et al,[51] 2009	Placebo	313	209 (67)	61.8 (8.8)	M: 28.3 (4.1) F: 29.3 (5.8)	1-3	Left: 6.5 (7.1) Right: 6.3 (7.1)	24	WOMAC pain, joint space width	Low; low; low; low; low; unclear; low
	Chondroitin sulfate, 800 mg/d	309	216 (70)	62.9 (8.8)	M: 28.3 (3.9) F: 28.6 (5.9)		Left: 6.1 (5.3) Right: 6.6 (7.0)			
Karlsson et al,[52] 2002	Placebo (IA injection)	66	40 (61)	71.0 (6.0)	NR	NR	NR	12	VAS pain at maximum	Low; low; low; low; high; low; low
	Hyaluronic acid, 2.5 mL in 1% solution (1 IA injection/wk for 3 wk)	92	60 (67)	72.0 (7.0)						
	Hyaluronic acid, 2 mL in 0.8% solution (1 IA injection/wk for 3 wk)	88	56 (65)	70.0 (7.0)						
Karsdal et al,[53] 2015	Placebo	1097	687 (63)	64.3 (6.6)	28.9 (4.8)	2-3	NR	24	WOMAC pain and physical function, joint space width	Low; low; low; low; low; unclear; low
	Calcitonin, 0.8 mg twice/d	1109	737 (67)	64.5 (6.9)	29.1 (5.1)					
Kawasaki et al,[54] 2008	Placebo[h]	42	42 (100)	69.5 (7.1)	24.0 (3.0)	2-3	NR	18	WOMAC pain and physical function, joint space width	Unclear; high; high; low; low; unclear; high
	Glucosamine, 1500 mg/d	49	49 (100)	68.5 (7.3)	23.9 (2.5)					
	Risedronate, 2.5 mg/d	51	51 (100)	70.2 (7.0)	25.0 (3.6)					
Kriegel et al,[55] 2001	Nimesulide, 100 mg twice/d	183	126 (69)	64.0 (42-81)	NR	2-4	NR	12	WOMAC pain	Unclear; unclear; low; low; low; low; unclear
	Naproxen, 250 mg/d and 500 mg/d	187	140 (75)	65.0 (44-80)						

(continued)

Table. Characteristics of Trials Included in the Analysis and Summary Trial Quality Assessment (continued)

Source	Type of Intervention and Dose	No. of Patients	Women, No. (%)	Age, y[a]	BMI[a,b]	Grade[c]	Duration of Knee Osteoarthritis, y[a]	Follow-up, mo	Outcome Measure	Cochrane Collaboration Risk of Bias[d]
Krzeski et al,[56] 2007	Placebo	80	54 (70)	62.0 (8.1)	NR	NR	NR	12	Joint space width	All low
	PG-116800, 25 mg twice/d[i]	81	60 (75)	62.4 (7.7)						
	PG-116800, 50 mg twice/d[i]	80	61 (77)	62.6 (8.2)						
	PG-116800, 100 mg twice/d[i]	80	57 (71)	62.9 (8.5)						
	PG-116800, 200 mg twice/d[i]	80	49 (62)	63.1 (7.1)						
Laslett et al,[57] 2012	Placebo (intravenous infusion)	28	13 (46)	60.4 (7.3)	29.8 (5.8)	NR	NR	12	VAS global knee pain	Low; low; low; high; low; high; high
	Zoledronic acid, 5 mg/100 mL (1 intravenous infusion)	31	12 (39)	64.2 (8.2)	29.6 (4.4)					
Leighton et al,[58] 2014	Hyaluronic acid, 60 mg/3 mL (2 IA injections 6 mo apart)	221	111 (51)	61.9 (9.6)	28.2 (4.2)	2-3	4.7 (5.4)	12	WOMAC pain	Low; high; high; low; low; low; high
	Methylprednisolone, 40 mg/1 mL (1 IA injection) and hyaluronic acid, 60 mg/3 mL (1 IA injection after 6 mo)	221	102 (47)	61.5 (9.9)	28.3 (4.1)		4.9 (6.3)			
Listrat et al,[59] 1997	Placebo[h]	19	15 (79)	64.0 (8.0)	26.6 (3.6)	NR	2 (0-15)	12	VAS global knee pain, joint space width	Unclear; unclear; high; unclear; low; unclear; high
	Hyaluronic acid, 20 mg/2 mL (1 IA injection/wk for 3 wk every 3 mo)	20	11 (55)	60.0 (7.0)	27.5 (3.8)		4 (0-26)			
Lohmander et al,[60] 2014	Placebo (IA injection)	42	29 (69)	61.3 (7.5)	30.1 (4.8)	2-3	7.0 (4.6)	12	WOMAC pain and physical function, joint space width	Low; low; low; low; low; unclear; low
	Sprifermin, 10 µg (1 IA injection/wk for 3 wk repeated 3 mo apart)	21	14 (67)	60.6 (10.5)	31.2 (4.4)		6.1 (5.9)			
	Sprifermin, 30 µg (1 IA injection/wk for 3 wk repeated 3 mo apart)	42	30 (71)	61.4 (9.4)	33.3 (5.6)		6.8 (6.7)			
	Sprifermin, 100 µg (1 IA injection/wk for 3 wk repeated 3 mo apart)	63	43 (68)	61.1 (9.1)	30.3 (5.0)		5.8 (5.2)			
Mathieu,[61] 2002	Placebo	150	78 (52)	63.1 (10.7)	28.1 (5.5)	1-3	NR	24	Joint space width	Unclear; unclear; low; unclear; high; unclear; high
	Chondroitin sulfate, 800 mg/d	150	76 (51)	62.5 (9.1)	27.7 (5.2)					
McAlindon et al,[62] 2013	Placebo	73	40 (54)	63.0 (9.3)	30.8 (6.4)	2-4	NR	24	WOMAC pain and physical function, joint space width	Low; low; low; unclear; low; unclear; unclear
	Vitamin D, 2000-8000 IU/d (escalating dose)	73	49 (67)	61.8 (7.7)	30.5 (5.0)					
McAlindon et al,[63] 2017	Placebo (IA injection)	70	38 (54)	57.2 (7.6)	31.7 (6.6)	2-3	NR	24	WOMAC pain and physical function	Low; low; low; unclear; low; high; unclear
	Triamcinolone, 40 mg/1 mL (1 IA injection given every 12 wk)	70	37 (53)	59.1 (8.3)	30.8 (5.1)					
Michel et al,[64] 2005	Placebo	150	78 (52)	63.1 (10.7)	28.1 (5.5)	1-3	NR	24	Joint space width	Low; low; low; unclear; low; unclear; unclear
	Chondroitin sulfate, 800 mg/d	150	76 (51)	62.5 (9.1)	27.7 (5.2)					
Ozturk et al,[65] 2006	Hyaluronic acid, 15 mg/2 mL (1 IA injection/wk for 3 wk repeated 6 mo apart)	24	24 (100)	58.0 (7.7)	31.5 (5.0)	2-3	NR	12	WOMAC pain	Low; low; low; unclear; high; low; unclear
	Hyaluronic acid, 15 mg/2 mL (1 IA injection/wk for 3 wk repeated 6 mo apart) and triamcinolone, 40 mg/1 mL (1 IA injection given twice 6 mo apart)	16	15 (94)	58.1 (10.3)	30.3 (4.9)					

(continued)

Table. Characteristics of Trials Included in the Analysis and Summary Trial Quality Assessment (continued)

Source	Type of Intervention and Dose	No. of Patients	Women, No. (%)	Age, y[a]	BMI[a,b]	Grade[c]	Duration of Knee Osteoarthritis, y[a]	Follow-up, mo	Outcome Measure	Cochrane Collaboration Risk of Bias[d]
Pavelká et al,[66] 2002	Placebo	101	77 (76)	63.5 (6.9)	25.7 (1.8)	2-3	11.0 (6.8)	36	WOMAC pain and physical function, joint space width	Low; low; low; low; low; unclear; low
	Glucosamine sulfate, 1500 mg/d	101	80 (79)	61.2 (7.3)	25.7 (2.1)		10.1 (8.1)			
Pellettier et al,[67] 2016	Chondroitin sulfate, 1200 mg/d	97	53 (55)	61.4 (9.3)	30.1 (5.8)	2-3	NR	24	WOMAC pain and physical function	Low; low; low; low; low; high; low
	Celecoxib, 200 mg/d	97	61 (63)	61.3 (8.5)	32.3 (5.8)					
Pham et al,[68] 2004	Placebo (oral dose and IA injection)	85	52 (61)	64.9 (7.7)	NR	0-4	NR	12	VAS global knee pain	Low; low; low; low; low; unclear; low
	Hyaluronic acid, 25 mg/2.5 mL (1 IA injection/wk for 3 wk given every 3 mo)	131	93 (71)	64.9 (8.4)						
	Diacerein, 50 mg twice/d	85	59 (69)	64.5 (7.8)						
Raynauld et al,[69] 2003	Placebo (IA injection)	34	21 (61)	63.3 (9.0)	NR	2-3	8.7 (6.8)	24	WOMAC pain and physical function, joint space width	Low; low; low; high; low; unclear; high
	Triamcinolone, 40 mg/1 mL (1 IA injection given every 3 mo)	34	25 (74)	63.1 (9.1)			9.8 (7.2)			
Raynauld et al,[70] 2009	Licofelone, 200 mg twice/d	177	104 (71)	60.4 (8.6)	32.7 (6.4)	2-3	NR	24	WOMAC pain	All low
	Naproxen, 500 mg twice/d	178	100 (65)	60.3 (8.1)	31.2 (5.8)					
Reginster et al,[71] 2001	Placebo	106	83 (78)	65.5 (7.5)	27.4 (2.7)	2-3	7.6 (7.5)	36	WOMAC pain and physical function, joint space width	All low
	Glucosamine sulfate, 1500 mg/d	106	79 (75)	66.0 (8.1)	27.3 (2.6)		8.0 (7.5)			
Reginster et al,[72] 2007	Etoricoxib, 60 mg/d	434	322 (72)	62.6 (9.8)	NR	NR	NR	12	WOMAC pain	Low; unclear; low; unclear; low; unclear; unclear
	Naproxen, 500 mg twice/d	404	314 (71)	62.7 (9.7)						
Reginster et al,[73] 2013	Placebo	559	326 (69)	62.8 (7.3)	29.6 (5.1)	1-3	6.4 (6.4)	36	WOMAC pain and physical function, joint space width	Low; low; low; unclear; low; unclear; unclear
	Strontium ranelate, 1000 mg/d	558	309 (69)	62.3 (7.0)	30.1 (5.1)		6.7 (6.5)			
	Strontium ranelate, 2000 mg/d	566	311 (69)	63.1 (7.3)	29.7 (4.8)		6.3 (6.4)			
Saag et al,[74] 2000	Diclofenac, 50 mg 3 times/d	230	188 (82)	63 (38-85)	NR	NR	9 (1-47)	12	WOMAC pain	Low; low; low; high; high; low; high
	Rofecoxib, 12.5 mg/d	231	187 (81)	62 (39-85)			8 (1-57)			
	Rofecoxib, 25 mg/d	232	180 (78)	62 (39-79)			9 (1-37)			
Sawitzke et al,[75] 2008[j]	Placebo	114	45 (64)	56.6 (8.4)	NR	2-3	9.4 (8.7)	24	Joint space width	Unclear; unclear; low; low; high; low; unclear
	Celecoxib, 200 mg/d	122	51 (64)	58.3 (10.7)			10.3 (9.5)			
	Glucosamine, 500 mg 3 times/d	119	47 (61)	56.7 (10.4)			9.2 (9.4)			
	Chondroitin sulfate, 400 mg 3 times/d	107	51 (72)	56.4 (9.2)			8.8 (8.9)			
	Glucosamine (500 mg) and chondroitin (400 mg) 3 times/d	110	33 (56)	56.5 (9.9)			10.5 (9.8)			

(continued)

Table. Characteristics of Trials Included in the Analysis and Summary Trial Quality Assessment (continued)

Source	Type of Intervention and Dose	No. of Patients	Women, No. (%)	Age, y[a]	BMI[a,b]	Grade[c]	Duration of Knee Osteoarthritis, y[a]	Follow-up, mo	Outcome Measure	Cochrane Collaboration Risk of Bias[d]
Sawitzke et al,[76] 2010[j]	Placebo	131	86 (66)	56.9 (9.8)	NR	2-3	10.1 (9.4)	24	WOMAC pain and physical function	Unclear; unclear; low; low; high; high; unclear
	Celecoxib, 200 mg/d	142	93 (65)	57.6 (10.6)			10.2 (9.2)			
	Glucosamine, 500 mg 3 times/d	134	92 (69)	56.7 (10.5)			9.7 (10.3)			
	Chondroitin sulfate, 400 mg 3 times/d	126	92 (73)	56.3 (8.8)			9.0 (9.0)			
	Glucosamine (500 mg) and chondroitin (400 mg) 3 times/d	129	84 (65)	56.7 (10.7)			10.0 (9.4)			
Scott et al,[77] 2000	Placebo	303	572 (70)[f]	61.0 (27-87)[f]	NR	NR	5 (0.1-50.0)[f]	48	VAS global knee pain	Unclear; unclear; low; unclear; high; unclear; high
	Tiaprofenic acid, 300 mg twice/d	307								
	Indomethacin, 25 mg 3 times/d	202								
Spector et al,[78] 2005	Placebo	99	64 (65)	63.2 (8.1)	29.2 (3.8)	NR	NR	12	WOMAC pain and physical function, joint space width	Low; unclear; low; low; low; low; unclear
	Risedronate, 5 mg/d	96	56 (58)	62.9 (8.8)	29.0 (3.9)					
	Risedronate, 15 mg/d	90	49 (54)	63.8 (8.3)	29.2 (4.0)					
Trueba Davalillo et al,[79] 2015	Hyaluronic acid, 2.5 mL in 1% solution (1 IA injection/wk for 5 wk)	100	59 (61)	62.7 (5.9)	28.3 (4.9)	2-3	NR	12	WOMAC pain	Low; low; high; low; low; high; high
	Betamethasone, 1 mL (5.0 mg and 2.0 mg; 2 IA injections 4 wk apart)	100	57 (58)	62.8 (5.9)	26.3 (4.0)					
Uebelhart et al,[80] 2004	Placebo	60	46 (82)	63.7 (8.1)	NR	1-3	NR	12	VAS global knee pain, joint space width	Low; low; low; low; low; unclear; low
	Chondroitin sulfate, 800 mg/d	60	43 (80)	63.2 (9.1)						
Williams et al,[81] 1993	Acetaminophen, 650 mg 4 times/d	88	66 (75)	60.3 (11.4)	NR	NR	5.9 (6.4)	24	VAS pain during motion	Low; low; low; high; low; unclear; high
	Naproxen, 375 mg twice/d	90	68 (75)	58.8 (10.1)			7.4 (5.9)			
Wluka et al,[82] 2002	Placebo	69	33 (48)	63.7 (10.0)	29.5 (5.0)	1-3	NR	24	WOMAC pain and physical function	Low; low; low; unclear; low; low; unclear
	Vitamin E, 500 IU/d	67	42 (63)	64.3 (11.0)	28.7 (6.0)					

Abbreviations: BMI, body mass index; IA, intra-articular; NR, not reported; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

[a] Data expressed as mean (SD) or median (range).

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] The Kellgren and Lawrence classification[83] grades radiographic abnormalities at the tibiofemoral joint as: grade 0, no radiographic abnormalities; grade 1, doubtful joint space narrowing with possible osteophyte formation; grade 2, possible joint space narrowing with definite osteophyte formation; grade 3, definite joint space narrowing, moderate osteophyte formation, some sclerosis, and possible deformity of bone ends; grade 4, severe joint space narrowing, large osteophyte formation, marked sclerosis, and definite deformity of bone ends.

[d] Risk of bias tool domains: random sequence generation; allocation concealment; blinding of participants, personnel, assessments; incomplete outcome data addressed; selective outcome reporting; other potential threats; and overall, respectively. The overall risk of bias was considered low if risk of bias was low in all of the first 4 domains (considered the key domains); unclear if risk of bias was unclear in 1 or 2 of the 4 key domains; and high if risk of bias was high in 1 or more of the key domains or unclear in 3 or more of the key domains.

[e] Data are from 2 parallel studies conducted in the United States and Canada (North America; NA) and in the European Union (EU). Demographic information is reported separately for NA (n = 1232) and EU (n = 1251) but pooled for all interventions.

[f] Demographic data pooled for all treatment groups.

[g] Extracted as primary outcome (instead of WOMAC pain) as recommended by Fransen et al.[46]

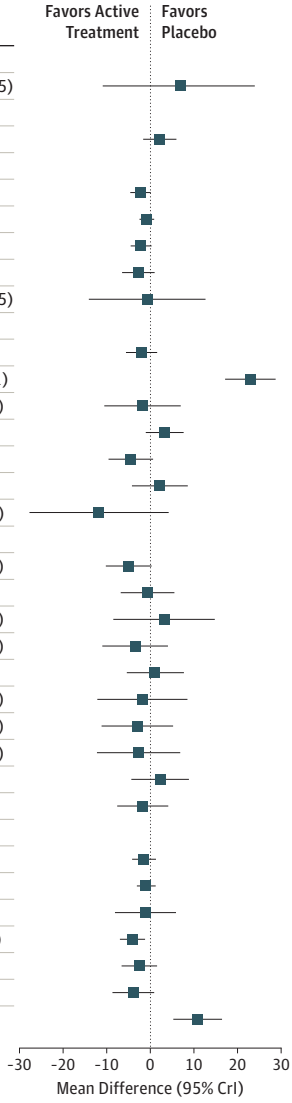
[h] Control group consisted of no treatment and was considered an oral placebo for this analysis.

[i] PG-116800 is a matrix metalloproteinase inhibitor.

[j] Included data from the same trial in both articles, but they considered different outcomes with different numbers of eligible patients. Therefore, they are reported as separate studies in this Table and throughout the article, including for the calculation of the total number of patients considered.

Figure 2. Forest Plot for the Estimates of Long-term Treatment Effects of Interventions on Knee Pain

Type of Intervention	No. of Trials	No. of Patients	Mean Difference (95% CrI)
Analgesics			
Acetaminophen	1	27	7.00 (-10.86 to 23.95)
Antioxidants			
Vitamin E	1	59	2.13 (-1.66 to 5.96)
Bone-acting agents			
Calcitonin	1	695	-2.25 (-4.58 to 0.08)
Risedronate	3	2087	-0.77 (-2.48 to 0.90)
Strontium ranelate	1	899	-2.11 (-4.51 to 0.29)
Vitamin D	2	310	-2.73 (-6.50 to 0.99)
Zoledronic acid	1	29	-0.64 (-14.14 to 12.65)
Intra-articular hyaluronate and corticosteroid injections			
Hyaluronic acid	12	1051	-1.97 (-5.56 to 1.53)
Betamethasone	1	98	23.04 (17.16 to 28.71)
Methylprednisolone	1	60	-1.90 (-10.57 to 6.96)
Triamcinolone	2	103	3.30 (-1.05 to 7.64)
Hyaluronic acid plus betamethasone	1	35	-4.45 (-9.57 to 0.64)
Hyaluronic acid plus methylprednisolone	1	169	2.20 (-4.19 to 8.61)
Hyaluronic acid plus triamcinolone	1	16	-11.79 (-27.72 to 4.18)
Nonsteroidal anti-inflammatory drugs			
Celecoxib	3	690	-4.93 (-10.23 to 0.30)
Diclofenac	5	1090	-0.58 (-6.81 to 5.54)
Etofenamate	1	29	3.18 (-8.48 to 14.75)
Etoricoxib	2	780	-3.40 (-10.92 to 4.05)
Indomethacin	1	202	1.07 (-5.38 to 7.47)
Licofelone	1	147	-1.82 (-12.19 to 8.51)
Naproxen	4	659	-2.98 (-11.21 to 5.22)
Nimesulide	1	183	-2.76 (-12.28 to 6.83)
Rofecoxib	2	979	2.25 (-4.37 to 8.82)
Tiaprofenic acid	1	307	-1.67 (-7.58 to 4.11)
Symptomatic slow-acting drugs in osteoarthritis and putative disease-modifying agents			
Chondroitin sulfate	5	731	-1.47 (-4.21 to 1.27)
Cindunistat	1	971	-0.94 (-3.10 to 1.22)
Diacerein	1	85	-1.07 (-8.13 to 5.94)
Glucosamine sulfate	2	207	-4.07 (-6.99 to -1.18)
Glucosamines	3	325	-2.54 (-6.59 to 1.55)
Glucosamines plus chondroitin sulfate	2	280	-3.85 (-8.72 to 0.87)
Sprifermin	1	122	10.86 (5.28 to 16.48)



Estimates are expressed on a 0 to 100 scale. Point estimates refer to the posterior mean. The bars indicate 95% credibility intervals (CrIs).

for assessing risk of bias. In contrast, 14 trials (30%) were at high risk of bias. A quantitative synthesis of the evidence through a network meta-analysis was deemed appropriate given the comparability in study design, outcome measures, patients involved, and inclusion and exclusion criteria. Homogeneity and consistency assumptions were confirmed.

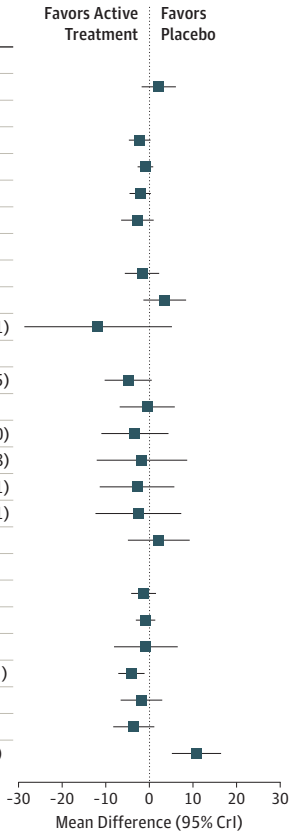
Primary Outcome

There were 31 pharmacological interventions. Of the 42 trials assessing pain, the most common outcome measure was WOMAC pain in 27 trials (64%), followed by VAS global knee pain in 7 trials (17%), and another VAS measure of pain in 8 trials (19%) (Table). The network plot for the primary outcome of knee pain appears in eFigure 1A in Supplement 2. There was a large amount of uncertainty around all the estimates and there was no association with improvement in pain (decrease) for 29 of the 31 interventions studied.

Associations with pain decrease were found for the NSAID celecoxib (SMD, −0.18 [95% CrI, −0.35 to −0.01]) and the symptomatic slow-acting drug in osteoarthritis glucosamine sulfate (SMD, −0.29 [95% CrI, −0.49 to −0.09]; eFigure 2 in Supplement 2). When the data were analyzed as a mean difference on a normalized scale from 0 to 100, celecoxib was no longer associated with improvement (decrease) in pain (mean difference, −4.93 [95% CrI, −10.23 to 0.30]), but the association of glucosamine sulfate with decreased pain remained (mean difference, −4.07 [95% CrI, −6.99 to −1.18]; **Figure 2**). When studies at high risk of bias were excluded (network plot appears in eFigure 1B in Supplement 2), there was no longer an association of celecoxib with improved pain, but glucosamine sulfate remained associated with pain improvement (SMD, −0.29 [95% CrI, −0.49 to −0.10] and mean difference, −4.10 [95% CrI, −7.14 to −1.12]; **Figure 3** and eFigure 3 in Supplement 2).

Figure 3. Forest Plot for the Estimates of Long-term Treatment Effects of Interventions on Knee Pain That Excluded Trials at High Risk of Bias

Type of Intervention	No. of Trials	No. of Patients	Mean Difference (95% CrI)
Antioxidants			
Vitamin E	1	59	2.13 (-1.77 to 6.08)
Bone-acting agents			
Calcitonin	1	695	-2.24 (-4.73 to 0.22)
Risedronate	2	2047	-0.93 (-2.70 to 0.85)
Strontium ranelate	1	899	-2.11 (-4.55 to 0.34)
Vitamin D	2	310	-2.73 (-6.48 to 1.00)
Intra-articular hyaluronate and corticosteroid injections			
Hyaluronic acid	5	605	-1.68 (-5.67 to 2.25)
Triamcinolone	1	70	3.50 (-1.41 to 8.44)
Hyaluronic acid plus triamcinolone	1	16	-11.91 (-28.71 to 5.11)
Nonsteroidal anti-inflammatory drugs			
Celecoxib	3	690	-4.81 (-10.26 to 0.55)
Diclofenac	4	860	-0.47 (-6.85 to 5.82)
Etoricoxib	2	780	-3.28 (-11.04 to 4.40)
Licofelone	1	147	-1.66 (-12.08 to 8.68)
Naproxen	3	624	-2.82 (-11.38 to 5.71)
Nimesulide	1	183	-2.53 (-12.38 to 7.31)
Rofecoxib	1	516	2.12 (-4.93 to 9.27)
Symptomatic slow-acting drugs in osteoarthritis and putative disease-modifying agents			
Chondroitin sulfate	5	731	-1.31 (-4.17 to 1.50)
Cindunistat	1	971	-0.92 (-3.17 to 1.34)
Diacerein	1	85	-0.90 (-8.16 to 6.45)
Glucosamine sulfate	2	207	-4.10 (-7.14 to -1.12)
Glucosamines	2	286	-1.81 (-6.56 to 2.95)
Glucosamines plus chondroitin sulfate	2	280	-3.60 (-8.31 to 1.09)
Sprifermin	1	122	10.78 (5.16 to 16.40)



Estimates are expressed on a 0 to 100 scale. Point estimates refer to the posterior mean. The bars indicate 95% credibility intervals (CrIs).

Among the high-quality trials, glucosamine sulfate had the highest probability of being the best long-term treatment (SUCRA value of 0.92 compared with 0.79 for celecoxib; **Figure 4**). The SUCRA and rankogram plots appear in eFigures 4-4C in Supplement 2. The intra-articular injection combination of hyaluronic acid with triamcinolone had a SUCRA value of 0.88. However, there was only 1 trial for this combined intervention and the results were limited by wide 95% CrIs (Figure 3). The 2 interventions administered alone (hyaluronic acid and triamcinolone) had lower SUCRA values (Figure 4). When all trials were included, the SUCRA and rankogram plots followed a similar pattern (eFigures 5-5C in Supplement 2).

In pairwise comparisons within the network of high-quality trials (eTable 3 in Supplement 2), glucosamine sulfate was associated with improved pain compared with some NSAIDs (ie, diclofenac and rofecoxib) and other compounds (eg, chondroitin sulfate), whereas other pairwise comparisons were not different from each other. Rofecoxib (which was withdrawn by the manufacturer in 2004) was associated with less improvement in pain compared with most NSAIDs and compared with other cyclooxygenase-2 selective agents (eg, celecoxib and etoricoxib). Pairwise comparisons when all trials were included appear in eTable 4 in Supplement 2.

Secondary Outcomes

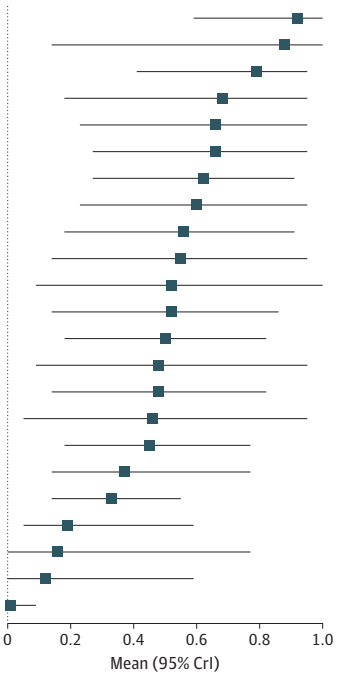
The secondary outcome results for the associations of long-term treatment efficacy compared with placebo were limited by considerable uncertainty. Data for physical function could be retrieved for 13 pharmacological interventions (eFigure 6 in Supplement 2). Compared with placebo, glucosamine sulfate was associated significantly with improvement in physical function (SMD, −0.32 [95% CrI, −0.52 to −0.12]; eFigure 7 in Supplement 2). The remaining interventions were not associated significantly with improved physical function.

Sixteen interventions were studied for their association with change in joint structure (eFigure 9 in Supplement 2). The following 3 interventions were significantly associated with improvement in JSN compared with placebo: glucosamine sulfate (SMD, −0.42 [95% CrI, −0.65 to −0.19]; mean difference, 0.27 mm [95% CrI, 0.12 to 0.42 mm]), chondroitin sulfate (SMD, −0.20 [95% CrI, −0.31 to −0.07]; mean difference, 0.16 mm [95% CrI, 0.07 to 0.25 mm]), and strontium ranelate (SMD, −0.20 [95% CrI, −0.36 to −0.05]; mean difference, 0.12 mm [95% CrI, 0.01 to 0.23 mm]) (eFigure 10 and eTable 7 in Supplement 2).

Glucosamine sulfate had the highest probability to be the best treatment for physical function based on the SUCRA value (eFigures 8-8C in Supplement 2). Glucosamine sulfate also was

Figure 4. Surface Under the Cumulative Ranking Curve for Knee Pain That Excluded Trials at High Risk of Bias

Type of Intervention	No. of Trials	Mean (95% CrI)
Glucosamine sulfate	2	0.92 (0.59-1.00)
Hyaluronic acid plus triamcinolone	1	0.88 (0.14-1.00)
Celecoxib	3	0.79 (0.41-0.95)
Vitamin D	2	0.68 (0.18-0.95)
Glucosamines plus chondroitin sulfate	2	0.66 (0.23-0.95)
Calcitonin	1	0.66 (0.27-0.95)
Strontium ranelate	1	0.62 (0.27-0.91)
Etoricoxib	2	0.60 (0.23-0.95)
Glucosamines	2	0.56 (0.18-0.91)
Naproxen	3	0.55 (0.14-0.95)
Nimesulide	1	0.52 (0.09-1.00)
Hyaluronic acid	5	0.52 (0.14-0.86)
Chondroitin sulfate	5	0.50 (0.18-0.82)
Diacerein	1	0.48 (0.09-0.95)
Cindunistat	1	0.48 (0.14-0.82)
Licofelone	1	0.46 (0.05-0.95)
Risedronate	2	0.45 (0.18-0.77)
Diclofenac	4	0.37 (0.14-0.77)
Placebo	21	0.33 (0.14-0.55)
Rofecoxib	1	0.19 (0.05-0.59)
Vitamin E	1	0.16 (0-0.77)
Triamcinolone	1	0.12 (0-0.59)
Sprifermin	1	0.01 (0-0.09)



The surface under the cumulative ranking curve would be 0 when a treatment is certain to be the worst and 1 when a treatment is certain to be the best.[27] The bars indicate 95% credibility intervals.

associated with improved physical function in pairwise comparisons with several of the treatments considered (eTable 5 in Supplement 2), including other glucosamines and their combination with chondroitin sulfate. Vitamin D had the next highest SUCRA value, but it had a small SMD. For the outcome of JSN, glucosamine sulfate had the highest probability to be the best treatment based on the SUCRA value (eFigures 11-11C in Supplement 2) and it was associated with joint structure improvement compared with most other treatments (eTable 8 in Supplement 2). The next highest SUCRA value was for chondroitin sulfate and strontium ranelate. Results for the secondary outcomes were similar when trials at high risk of bias were excluded (eTables 6 and 9 in Supplement 2).

Sensitivity Analyses

The sensitivity analyses were consistent with the results of the main analysis (eTables 10-10B2 in Supplement 2). The results did not change when the analyses for all interventions on the 3 outcomes were restricted to studies using only an oral placebo or an intra-articular injection placebo, when the analyses were limited to blinded studies, when imputation methods were not applied, or when alternative statistical methods were used.

Discussion

In this systematic review and network meta-analysis of long-term (≥12 months) trials, celecoxib (an NSAID) and glucosamine sulfate (a symptomatic slow-acting drug in osteoarthritis) were associated with improvement in pain, but the association for celecoxib was small and was no longer observed in a subgroup analysis of high-quality trials. Both celecoxib and glucosamine sulfate were associated with large uncertainty in the estimates compared with placebo. Glucosamine sulfate was associated with improvement in the secondary outcomes of physical function and joint structure.

NSAIDs are the most widely used medications for osteoarthritis.[84] They are associated with a moderate effect on pain compared with placebo or acetaminophen in RCTs with a duration of 12 weeks or less,[85,86] and are recommended by international guidelines.[5,6] However, they are recommended for short-term or intermittent use due to safety considerations.[87] In the present meta-analysis, celecoxib was the only NSAID associated with long-term pain improvement, but the SMD was small and the association was not observed after trials at high risk of bias were excluded from the analyses, or when the results were based on a scale from 0 to 100.

There was no association of celecoxib with improved physical function. Celecoxib is associated with better long-term gastrointestinal tolerability than nonselective NSAIDs and is not associated with a higher risk of cardiovascular events than nonselective NSAIDs.[88] Nevertheless, given persistent safety concerns vs placebo, the small association with benefit, and the lack of an association of other NSAIDs with improved outcomes in the data reported herein, it may be premature to recommend any NSAID beyond short-term or intermittent treatment. None of the NSAIDs were associated with improvement in JSN.

Glucosamine sulfate was consistently associated with improvement in pain, physical function, and JSN. Other

glucosamines were not associated with benefit. This finding is consistent with previously published conventional meta-analyses that mainly included short-term studies.[9,34,35] Glucosamine sulfate had a small to moderate effect size.

The combination of intra-articular injections of hyaluronic acid and corticosteroids had a moderately beneficial but highly variable association with pain. A previous conventional meta-analysis[89] showed a different trajectory of intra-articular injections of corticosteroids compared with intra-articular injections of hyaluronic acid for their association with knee osteoarthritis pain improvement. Intra-articular injections of corticosteroids were associated with greater benefit during the first few weeks of treatment and intra-articular injections of hyaluronic acid were associated with greater benefit at 3- and 6-month follow-up.

However, the results reported herein show no association of hyaluronic acid with long-term pain improvement. Intra-articular injections of corticosteroids are currently used for acute exacerbation of knee osteoarthritis. The results reported herein showed no association of intermittent injections with improvement in pain over long-term follow-up. Acetaminophen is an inexpensive analgesic,[5] but it was not associated with long-term pain improvement in the present study. Moreover, current practice guidelines question its safety long term.[6,87]

In the secondary analyses, glucosamine sulfate was associated with improvement in JSN, followed by chondroitin sulfate and strontium ranelate. An international task force[87] has recommended prescription-grade glucosamine sulfate or chondroitin be used as a first step in the long-term pharmacological management of knee osteoarthritis. There was no association with long-term improvement in symptoms with chondroitin.

Strontium ranelate is approved only in Europe for osteoporosis, and its use is currently restricted due to cardiovascular safety concerns. Bone-acting agents are tested in osteoarthritis RCTs because of their potential benefit in subchondral bone turnover.[90] However, none of the other bone-acting agents showed an association with improvement in JSN. The same was true for other medications, including putative disease-modifying drugs in osteoarthritis.

However, the data on sprifermin should be considered with caution because the compound is under development as a potential disease-modifying drug based on magnetic resonance imaging structural parameters. Future drug trials are likely to use magnetic resonance imaging to detect joint structure changes in osteoarthritis because radiological measures of JSN have limitations[91] and the clinical significance of joint structure changes on imaging is debated within the scientific community.

Limitations

This study has several limitations. First, there was large uncertainty regarding all the estimates. Second, although 47 long-term RCTs were retrieved, including approximately 22 000 patients and studying a large number of drug classes, only 13 of 33 interventions were studied in 2 or more trials and there were relatively few direct comparisons.

Third, fewer than 60% of trials included more than 100 participants per group, which may introduce bias due to small study effects. Fourth, 30% of the studies were of low methodological quality and had features of high risk of bias. A subgroup analysis excluding these studies resulted in the loss of a significant association of celecoxib with improvement in pain.

Fifth, data were pooled from the longest available follow-up after at least 12 months. However, evidence from some of the included trials[48,51,63,66,76] that had repeated measurements showed that pain patterns stabilized after 12 months. Therefore, it may be reasonable to combine data irrespective of study duration after 12-month follow-up.

Sixth, the SUCRA curve was used to estimate a ranking probability of comparative effectiveness between the different therapies, but it has limitations and the results should be interpreted with caution. Seventh, safety was not an outcome measure in the present study.

Eighth, this network meta-analysis did not consider nonpharmacological or procedure-based interventions. In these types of studies, blinding, randomization, and finding a suitable control are more difficult and this often results in short-term or small studies.[92]

Conclusions

In this systematic review and network meta-analysis of studies of patients with knee osteoarthritis and at least 12 months of follow-up, there was uncertainty around the estimates of effect size for change in pain for all comparisons with placebo. Larger RCTs are needed to resolve the uncertainty around efficacy of medications for knee osteoarthritis.

ARTICLE INFORMATION

Accepted for Publication: November 19, 2018.

Author Contributions: Drs Gregori and Rovati had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Gregori, Giacovelli, Rovati.
Acquisition, analysis, or interpretation of data: Minto, Barbetta, Gualtieri, Azzolina, Vaghi.
Drafting of the manuscript: Gregori, Giacovelli, Rovati.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Gregori, Giacovelli, Minto, Barbetta, Azzolina, Vaghi.
Obtained funding: Gregori, Rovati.
Administrative, technical, or material support: Gualtieri.
Supervision: Gregori, Rovati.

Conflict of Interest Disclosures: Drs Giacovelli and Rovati reported participating in clinical trials of glucosamine sulfate and hyaluronic acid as scientists and employees of Rottapharm (a pharmaceutical company). Rottapharm no longer exists and its commercial interests and operations have been taken over by another pharmaceutical company (Mylan). Drs Giacovelli and Rovati are now scientists at Rottapharm Biotech, which is the research and development spin-off of the former Rottapharm company and an independent corporate entity. Rottapharm Biotech is engaged in the development of new drugs for osteoarthritis, but has no commercial or other interest in any marketed drug and, in particular, in glucosamine sulfate, hyaluronic acid, or any other marketed or experimental pharmaceutical agents considered in the present study. Mss Barbetta, Gualtieri, and Vaghi are also scientists and employees of Rottapharm Biotech. No other disclosures were reported.

Funding/Support: This study was supported by grant BIRD 2016 DCTV from the University of Padova and by financial support from Rottapharm Biotech.

Role of the Funders: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Meeting Presentation: Presented in part at the American College of Rheumatology meeting; November 13, 2016; Washington, DC.

Additional Contributions: We are grateful to Lisa Buttle, PhD (Medscript Ltd), for providing editorial assistance. Dr Buttle was not compensated for her contribution.

REFERENCES

1. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1545-1602. doi:10.1016/S0140-6736(16)31678-6

2. Mokdad AH, Ballestros K, Echko M, et al; US Burden of Disease Collaborators. The state of US health, 1990-2016: burden of diseases, injuries, and risk factors among US states. *JAMA*. 2018;319(14):1444-1472. doi:10.1001/jama.2018.0158

3. Glyn-Jones S, Palmer AJ, Agricola R, et al. Osteoarthritis. *Lancet*. 2015;386(9991):376-387. doi:10.1016/S0140-6736(14)60802-3

4. Lane NE, Brandt K, Hawker G, et al. OARSI-FDA initiative: defining the disease state of osteoarthritis. *Osteoarthritis Cartilage*. 2011;19(5):478-482. doi:10.1016/j.joca.2010.09.013

5. Hochberg MC, Altman RD, April KT, et al; American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)*. 2012;64(4):465-474. doi:10.1002/acr.21596

6. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage*. 2014;22(3):363-388. doi:10.1016/j.joca.2014.01.003

7. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods*. 2012;3(2):80-97. doi:10.1002/jrsm.1037

8. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med*. 2015;162(11):777-784. doi:10.7326/M14-2385

9. Newberry SJ, FitzGerald J, SooHoo NF, et al. Treatment of osteoarthritis of the knee: an update review. https://effectivehealthcare.ahrq.gov/topics/osteoarthritis-knee-update/research-2017. Accessed November 20, 2018.

10. Core Outcome Measures in Effectiveness Trials Initiative. Core outcome measures in effectiveness trials. http://www.comet-initiative.org. Accessed March 21, 2018.

11. Juhl C, Lund H, Roos EM, Zhang W, Christensen R. A hierarchy of patient-reported outcomes for meta-analysis of knee osteoarthritis trials: empirical evidence from a survey of high impact journals. *Arthritis*. 2012;2012:136245. doi:10.1155/2012/136245

12. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*. 1988;15(12):1833-1840.

13. Guyot P, Ades AE, Ouwens MJNM, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol*. 2012;12:9. doi:10.1186/1471-2288-12-9

14. Higgins JPT, Altman DG, Gøtzsche PC, et al; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. doi:10.1136/bmj.d5928

15. Nüesch E, Trelle S, Reichenbach S, et al. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. *BMJ*. 2010;341:c3515. doi:10.1136/bmj.c3515

16. Abrams KR, Gillies CL, Lambert PC. Meta-analysis of heterogeneously reported trials assessing change from baseline. *Stat Med*. 2005;24(24):3823-3844. doi:10.1002/sim.2423

17. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making*. 2013;33(5):607-617. doi:10.1177/0272989X12458724

18. Glass GV, McGaw B, Smith ML. *Meta-analysis in Social Research*. Beverly Hills, CA: Sage Publications; 1981.

19. Cohen J. *Statistical Power Analysis for the Behavioural Sciences*. 2nd ed. Mahwah, NJ: Lawrence Erlbaum Associates; 1988.

20. Reginster JY, Reiter-Niesert S, Bruyère O, et al. Recommendations for an update of the 2010 European regulatory guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis and reflections about related clinically relevant outcomes: expert consensus statement. *Osteoarthritis Cartilage*. 2015;23(12):2086-2093. doi:10.1016/j.joca.2015.07.001

21. Spiegelhalter DJ, Abrams KR, Myles JP. *Bayesian Approaches to Clinical Trials and Health-Care Evaluation*. Vol 13. New York, NY: John Wiley & Sons; 2004.

22. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med*. 2010;29(7-8):932-944. doi:10.1002/sim.3767

23. van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. *Res Synth Methods*. 2012;3(4):285-299. doi:10.1002/jrsm.1054

24. Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence synthesis for decision making 3: heterogeneity—subgroups, meta-regression, bias, and bias-adjustment. *Med Decis Making*. 2013;33(5):618-640. doi:10.1177/0272989X13485157

25. Schwarzer G, Carpenter JR, Rücker G. *Meta-analysis With R*. New York, NY: Springer-Verlag; 2015.

26. Brooks SP, Gelman A. General methods for monitoring convergence of iterative simulations. *J Comput Graph Stat*. 1998;7(4):434-455. doi:10.2307/1390675

27. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol*. 2011;64(2):163-171. doi:10.1016/j.jclinepi.2010.03.016

28. RStudio Team. RStudio integrated development for R. https://www.rstudio.com/. Accessed November 20, 2018.

29. van Valkenhoef G, Kuiper J. gemtc: network meta-analysis using Bayesian methods: R package version 0.8. http://cran.r-project.org/web/packages/gemtc/index.html. Accessed November 20, 2018.

30. Lunn D, Jackson C, Best N, Thomas A, Spiegelhalter D. *The BUGS Book: A Practical Introduction to Bayesian Analysis*. Boca Raton, FL: Chapman & Hall/CRC; 2012.

31. Lequesne M, Brandt K, Bellamy N, et al. Guidelines for testing slow acting drugs in osteoarthritis. *J Rheumatol Suppl*. 1994;41:65-71.

32. De Wan M, Volpi G. A method of preparing mixed glucosamine salts: US patent 5,847,107. https://patents.google.com/patent/US5847107A/en. Accessed November 20, 2018.

33. Altman RD. Glucosamine therapy for knee osteoarthritis: pharmacokinetic considerations. *Expert Rev Clin Pharmacol*. 2009;2(4):359-371. doi:10.1586/ecp.09.17

34. Towheed T, Maxwell L, Anastassiades TP, et al. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev*. 2005;2:CD002946.

35. Eriksen P, Bartels EM, Altman RD, Bliddal H, Juhl C, Christensen R. Risk of bias and brand explain the observed inconsistency in trials on glucosamine for symptomatic relief of osteoarthritis: a meta-analysis of placebo-controlled trials. *Arthritis Care Res (Hoboken)*. 2014;66(12):1844-1855. doi:10.1002/acr.22376

36. Arden NK, Cro S, Sheard S, et al. The effect of vitamin D supplementation on knee osteoarthritis, the VIDEO study: a randomised controlled trial. *Osteoarthritis Cartilage*. 2016;24(11):1858-1866. doi:10.1016/j.joca.2016.05.020

37. Bingham CO III, Buckland-Wright JC, Garnero P, et al. Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medial compartment osteoarthritis of the knee: results of the two-year multinational knee osteoarthritis structural arthritis study. *Arthritis Rheum*. 2006;54(11):3494-3507. doi:10.1002/art.22160

38. Bisicchia S, Bernardi G, Tudisco C. HYADD 4 versus methylprednisolone acetate in symptomatic knee osteoarthritis: a single-centre single blind prospective randomised controlled clinical study with 1-year follow-up. *Clin Exp Rheumatol*. 2016;34(5):857-863.

39. Brandt KD, Mazzuca SA, Katz BP, et al. Effects of doxycycline on progression of osteoarthritis:

results of a randomized, placebo-controlled, double-blind trial. *Arthritis Rheum*. 2005;52(7):2015-2025. doi:10.1002/art.21122

40. Buckland-Wright JC, MacFarlane DG, Lynch JA, Jasani MK. Quantitative microfocal radiography detects changes in OA knee joint space width in patients in placebo controlled trial of NSAID therapy. *J Rheumatol*. 1995;22(5):937-943.

41. Cannon GW, Caldwell JR, Holt P, et al; Rofecoxib Phase III Protocol 035 Study Group. Rofecoxib, a specific inhibitor of cyclooxygenase 2, with clinical efficacy comparable with that of diclofenac sodium: results of a one-year, randomized, clinical trial in patients with osteoarthritis of the knee and hip. *Arthritis Rheum*. 2000;43(5):978-987. doi:10.1002/1529-0131(200005)43:5<978::AID-ANR4>3.0.CO;2-0

42. Curtis SP, Bockow B, Fisher C, et al. Etoricoxib in the treatment of osteoarthritis over 52-weeks: a double-blind, active-comparator controlled trial [NCT00242489]. *BMC Musculoskelet Disord*. 2005;6:58. doi:10.1186/1471-2474-6-58

43. Dahlberg LE, Holme I, Høye K, Ringertz B. A randomized, multicentre, double-blind, parallel-group study to assess the adverse event-related discontinuation rate with celecoxib and diclofenac in elderly patients with osteoarthritis. *Scand J Rheumatol*. 2009;38(2):133-143. doi:10.1080/03009740802419065

44. Dougados M, Nguyen M, Listrat V, Amor B. High molecular weight sodium hyaluronate (hyalectin) in osteoarthritis of the knee: a 1 year placebo-controlled trial. *Osteoarthritis Cartilage*. 1993;1(2):97-103. doi:10.1016/S1063-4584(05)80024-X

45. Ertürk C, Altay MA, Altay N, Kalender AM, Öztürk İA. Will a single periarticular lidocaine-corticosteroid injection improve the clinical efficacy of intraarticular hyaluronic acid treatment of symptomatic knee osteoarthritis? *Knee Surg Sports Traumatol Arthrosc*. 2016;24(11):3653-3660. doi:10.1007/s00167-014-3398-2

46. Fransen M, Agaliotis M, Nairn L, et al; LEGS Study Collaborative Group. Glucosamine and chondroitin for knee osteoarthritis: a double-blind randomised placebo-controlled clinical trial evaluating single and combination regimens. *Ann Rheum Dis*. 2015;74(5):851-858. doi:10.1136/annrheumdis-2013-203954

47. Güner S, Gökalp MA, Gözen A, Ünsal SŞ, Güner Şİ. Effectiveness of etofenamate for treatment of knee osteoarthritis: a randomized controlled trial. *Ther Clin Risk Manag*. 2016;12:1693-1699. doi:10.2147/TCRM.S114707

48. Hellio le Graverand M-P, Clemmer RS, Redifer P, et al. A 2-year randomised, double-blind, placebo-controlled, multicentre study of oral selective iNOS inhibitor, cindunistat (SD-6010), in patients with symptomatic osteoarthritis of the knee. *Ann Rheum Dis*. 2013;72(2):187-195. doi:10.1136/annrheumdis-2012-202239

49. Jørgensen A, Stengaard-Pedersen K, Simonsen O, et al. Intra-articular hyaluronan is without clinical effect in knee osteoarthritis: a multicentre, randomised, placebo-controlled, double-blind study of 337 patients followed for 1 year. *Ann Rheum Dis*. 2010;69(6):1097-1102. doi:10.1136/ard.2009.118042

50. Jubb RW, Piva S, Beinat L, Dacre J, Gishen P. A one-year, randomised, placebo (saline) controlled clinical trial of 500-730 kDa sodium hyaluronate (Hyalgan) on the radiological change in osteoarthritis of the knee. *Int J Clin Pract*. 2003;57(6):467-474.

51. Kahan A, Uebelhart D, De Vathaire F, Delmas PD, Reginster J-Y. Long-term effects of chondroitins 4 and 6 sulfate on knee osteoarthritis: the study on osteoarthritis progression prevention, a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2009;60(2):524-533. doi:10.1002/art.24255

52. Karlsson J, Sjögren LS, Lohmander LS. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis: a controlled, randomized, double-blind, parallel-design multicentre study. *Rheumatology (Oxford)*. 2002;41(11):1240-1248. doi:10.1093/rheumatology/41.11.1240

53. Karsdal MA, Byrjalsen I, Alexandersen P, et al; CSMC021C2301/2 Investigators. Treatment of symptomatic knee osteoarthritis with oral salmon calcitonin: results from two phase 3 trials. *Osteoarthritis Cartilage*. 2015;23(4):532-543. doi:10.1016/j.joca.2014.12.019

54. Kawasaki T, Kurosawa H, Ikeda H, et al. Additive effects of glucosamine or risedronate for the treatment of osteoarthritis of the knee combined with home exercise: a prospective randomized 18-month trial. *J Bone Miner Metab*. 2008;26(3):279-287. doi:10.1007/s00774-007-0813-5

55. Kriegel W, Korff KJ, Ehrlich JC, et al. Double-blind study comparing the long-term efficacy of the COX-2 inhibitor nimesulide and naproxen in patients with osteoarthritis. *Int J Clin Pract*. 2001;55(8):510-514.

56. Krzeski P, Buckland-Wright C, Bálint G, et al. Development of musculoskeletal toxicity without clear benefit after administration of PG-116800, a matrix metalloproteinase inhibitor, to patients with knee osteoarthritis: a randomized, 12-month, double-blind, placebo-controlled study. *Arthritis Res Ther*. 2007;9(5):R109. doi:10.1186/ar2315

57. Laslett LL, Doré DA, Quinn SJ, et al. Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomised controlled trial. *Ann Rheum Dis*. 2012;71(8):1322-1328. doi:10.1136/annrheumdis-2011-200970

58. Leighton R, Akermark C, Therrien R, et al; DUROLANE Study Group. NASHA hyaluronic acid vs methylprednisolone for knee osteoarthritis: a prospective, multi-centre, randomized, non-inferiority trial. *Osteoarthritis Cartilage*. 2014;22(1):17-25. doi:10.1016/j.joca.2013.10.009

59. Listrat V, Ayral X, Patarnello F, et al. Arthroscopic evaluation of potential structure modifying activity of hyaluronan (Hyalgan) in osteoarthritis of the knee. *Osteoarthritis Cartilage*. 1997;5(3):153-160. doi:10.1016/S1063-4584(97)80010-6

60. Lohmander LS, Hellot S, Dreher D, et al. Intraarticular sprifermin (recombinant human fibroblast growth factor 18) in knee osteoarthritis: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol*. 2014;66(7):1820-1831. doi:10.1002/art.38614

61. Mathieu P. Radiological progression of internal femoro-tibial osteoarthritis in gonarthrosis: chondro-protective effect of chondroitin sulfates ACS4-ACS6 [in French]. *Presse Med*. 2002;31(29):1386-1390.

62. McAlindon T, LaValley M, Schneider E, et al. Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis: a randomized controlled trial. *JAMA*. 2013;309(2):155-162. doi:10.1001/jama.2012.164487

63. McAlindon TE, LaValley MP, Harvey WF, et al. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. *JAMA*. 2017;317(19):1967-1975. doi:10.1001/jama.2017.5283

64. Michel BA, Stucki G, Frey D, et al. Chondroitins 4 and 6 sulfate in osteoarthritis of the knee: a randomized, controlled trial. *Arthritis Rheum*. 2005;52(3):779-786. doi:10.1002/art.20867

65. Ozturk C, Atamaz F, Hepguler S, Argin M, Arkun R. The safety and efficacy of intraarticular hyaluronan with/without corticosteroid in knee osteoarthritis: 1-year, single-blind, randomized study. *Rheumatol Int*. 2006;26(4):314-319. doi:10.1007/s00296-005-0584-z

66. Pavelká K, Gatterová J, Olejarová M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. *Arch Intern Med*. 2002;162(18):2113-2123. doi:10.1001/archinte.162.18.2113

67. Pelletier J-P, Raynauld J-P, Beaulieu AD, et al. Chondroitin sulfate efficacy versus celecoxib on knee osteoarthritis structural changes using magnetic resonance imaging: a 2-year multicentre exploratory study. *Arthritis Res Ther*. 2016;18(1):256. doi:10.1186/s13075-016-1149-0

68. Pham T, Le Henanff A, Ravaud P, Dieppe P, Paolozzi L, Dougados M. Evaluation of the symptomatic and structural efficacy of a new hyaluronic acid compound, NRD101, in comparison with diacerein and placebo in a 1 year randomised controlled study in symptomatic knee osteoarthritis. *Ann Rheum Dis*. 2004;63(12):1611-1617. doi:10.1136/ard.2003.019703

69. Raynauld J-P, Buckland-Wright C, Ward R, et al. Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2003;48(2):370-377. doi:10.1002/art.10777

70. Raynauld J-P, Martel-Pelletier J, Bias P, et al; Canadian Licofelone Study Group. Protective effects of licofelone, a 5-lipoxygenase and cyclo-oxygenase inhibitor, versus naproxen on cartilage loss in knee osteoarthritis: a first multicentre clinical trial using quantitative MRI. *Ann Rheum Dis*. 2009;68(6):938-947. doi:10.1136/ard.2008.088732

71. Reginster JY, Deroisy R, Rovati LC, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet*. 2001;357(9252):251-256. doi:10.1016/S0140-6736(00)03610-2

72. Reginster JY, Malmstrom K, Mehta A, et al. Evaluation of the efficacy and safety of etoricoxib compared with naproxen in two, 138-week randomised studies of patients with osteoarthritis. *Ann Rheum Dis*. 2007;66(7):945-951. doi:10.1136/ard.2006.059162

73. Reginster J-Y, Badurski J, Bellamy N, et al. Efficacy and safety of strontium ranelate in the treatment of knee osteoarthritis: results of a

double-blind, randomised placebo-controlled trial. *Ann Rheum Dis*. 2013;72(2):179-186. doi:10.1136/annrheumdis-2012-202231

74. Saag K, van der Heijde D, Fisher C, et al; Osteoarthritis Studies Group. Rofecoxib, a new cyclooxygenase 2 inhibitor, shows sustained efficacy, comparable with other nonsteroidal anti-inflammatory drugs: a 6-week and a 1-year trial in patients with osteoarthritis. *Arch Fam Med*. 2000;9(10):1124-1134. doi:10.1001/archfami.9.10.1124

75. Sawitzke AD, Shi H, Finco MF, et al. The effect of glucosamine and/or chondroitin sulfate on the progression of knee osteoarthritis: a report from the Glucosamine/Chondroitin Arthritis Intervention Trial. *Arthritis Rheum*. 2008;58(10):3183-3191. doi:10.1002/art.23973

76. Sawitzke AD, Shi H, Finco MF, et al. Clinical efficacy and safety of glucosamine, chondroitin sulphate, their combination, celecoxib or placebo taken to treat osteoarthritis of the knee: 2-year results from GAIT. *Ann Rheum Dis*. 2010;69(8):1459-1464. doi:10.1136/ard.2009.120469

77. Scott DL, Berry H, Capell H, et al. The long-term effects of non-steroidal anti-inflammatory drugs in osteoarthritis of the knee: a randomized placebo-controlled trial. *Rheumatology (Oxford)*. 2000;39(10):1095-1101.

78. Spector TD, Conaghan PG, Buckland-Wright JC, et al. Effect of risedronate on joint structure and symptoms of knee osteoarthritis: results of the BRISK randomized, controlled trial [ISRCTN01928173]. *Arthritis Res Ther*. 2005;7(3):R625-R633. doi:10.1186/ar1716

79. Trueba Davalillo CÁ, Trueba Vasavilbaso C, Navarrete Álvarez JM, et al. Clinical efficacy of intra-articular injections in knee osteoarthritis: a prospective randomized study comparing hyaluronic acid and betamethasone. *Open Access Rheumatol*. 2015;7:9-18. doi:10.2147/OARRR.S74553

80. Uebelhart D, Malaise M, Marcolongo R, et al. Intermittent treatment of knee osteoarthritis with oral chondroitin sulfate: a one-year, randomized, double-blind, multicenter study versus placebo [published correction appears in *Osteoarthritis Cartilage*. 2007;15(8):979]. *Osteoarthritis Cartilage*. 2004;12(4):269-276. doi:10.1016/j.joca.2004.01.004

81. Williams HJ, Ward JR, Egger MJ, et al. Comparison of naproxen and acetaminophen in a two-year study of treatment of osteoarthritis of the knee. *Arthritis Rheum*. 1993;36(9):1196-1206. doi:10.1002/art.1780360904

82. Wluka AE, Stuckey S, Brand C, Cicuttini FM. Supplementary vitamin E does not affect the loss of cartilage volume in knee osteoarthritis: a 2 year double blind randomized placebo controlled study. *J Rheumatol*. 2002;29(12):2585-2591.

83. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis*. 1957;16:494-502.

84. Gore M, Tai KS, Sadosky A, Leslie D, Stacey BR. Use and costs of prescription medications and alternative treatments in patients with osteoarthritis and chronic low back pain in community-based settings. *Pain Pract*. 2012;12(7):550-560. doi:10.1111/j.1533-2500.2012.00532.x

85. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med*. 2015;162(1):46-54. doi:10.7326/M14-1231

86. da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet*. 2017;390(10090):e21-e33. doi:10.1016/S0140-6736(17)31744-0

87. Bruyère O, Cooper C, Pelletier JP, et al. An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: a report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). *Semin Arthritis Rheum*. 2014;44(3):253-263. doi:10.1016/j.semarthrit.2014.05.014

88. Nissen SE, Yeomans ND, Solomon DH, et al; PRECISION Trial Investigators. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. *N Engl J Med*. 2016;375(26):2519-2529. doi:10.1056/NEJMoa1611593

89. Bannuru RR, Natov NS, Obadan IE, Price LL, Schmid CH, McAlindon TE. Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis. *Arthritis Rheum*. 2009;61(12):1704-1711. doi:10.1002/art.24925

90. Baker-LePain JC, Lane NE. Role of bone architecture and anatomy in osteoarthritis. *Bone*. 2012;51(2):197-203. doi:10.1016/j.bone.2012.01.008

91. Pavelka K, Bruyere O, Rovati LC, Olejárova M, Giacovelli G, Reginster JY. Relief in mild-to-moderate pain is not a confounder in joint space narrowing assessment of full extension knee radiographs in recent osteoarthritis structure-modifying drug trials. *Osteoarthritis Cartilage*. 2003;11(10):730-737. doi:10.1016/S1063-4584(03)00166-3

92. Fernandes L, Hagen KB, Bijlsma JW, et al; European League Against Rheumatism (EULAR). EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Ann Rheum Dis*. 2013;72(7):1125-1135. doi:10.1136/annrheumdis-2012-202745