

# Chondroitin for osteoarthritis (Protocol)

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[Intervention Protocol]

# Chondroitin for osteoarthritis

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## ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

The objective of this systematic review is to evaluate the effectiveness and safety of oral chondroitin for treatment of osteoarthritis compared to placebo or a comparator oral medication including Non-steroidal anti-inflammatory drug (NSAID), analgesic, opioid, glucosamine or other “herbal” medication.

## BACKGROUND

Osteoarthritis is the most common of all joint disorders and is one of the leading causes of disability in the USA (Gabriel 1995; Peyron 1992). Pathologically, osteoarthritis is characterized by softening and degeneration of articular cartilage and formation of new bone at joint margins and capsular fibrosis. Clinically, osteoarthritis manifests as joint pain, stiffness, deformity and loss of function. Clinical and radiographic surveys have found that the prevalence of osteoarthritis increases with age from 1% in people <30 years to 10% in those <40 years to more than 50% in individuals >60 years of age (Felson 1990; van Saase 1989). Autopsy studies show cartilage changes in almost all people above 65 years of age (Felson 1988). Osteoarthritis is equally common in men and women between 45-55 years, but more common in women after age of 55 years (Altman 1990). Risk factors for osteoarthritis include obesity, joint dysplasia (abnormal anatomy of the joint due to abnormal growth), trauma, occupational activity and family history among others (Solomon 2001). Osteoarthritis is classified as primary or secondary based on absence or presence of antecedent joint abnormality or injury. Primary osteoarthritis is further classified as generalized or localized to a joint area such as hand, knee, hip, spinal apophyseal (joints between spinal bones/vertebrae), foot and other joints (shoulder, elbow, wrist and ankle) (Solomon 2001).

Treatment of osteoarthritis is primarily directed at relieving pain and improving functional status. Various treatment options are available to patients with osteoarthritis including the following: (1) oral medications: analgesics such as acetaminophen, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids; (2) local therapies (applied as gels or creams): topical NSAIDs and capsaicin; (3) intra-articular therapies: corticosteroid and hyaluronic acid injections; (4) Non-pharmacological: physical therapy, aerobic therapy, strengthening exercises, transcutaneous electric nerve stimulation and wedged insoles; and (5) surgical treatment: joint replacement and arthroscopic debridement of the affected joint. However, frequent side effects, limited efficacy and variable rates of success limit the use of many non-surgical treatments.

In the last few years, various nutritional supplements including chondroitin, glucosamine, avocado/soybean unsaponifiables and diacerein have emerged as new treatment options for osteoarthritis (Deal 1999). These supplements are characterised by both a slow onset of action over 6-8 weeks and a carryover of effect for up to two months after withdrawal (Fajardo 2005). According to recent recommendations from the American College of Rheumatology and European League Against Rheumatism, drugs for treatment of osteoarthritis are classified as either symptom-modifying or structure-modifying drugs depending on their capacity to interfere with disease progression (Altman 2000; Pendleton 2000). The current body of evidence suggests that chondroitin falls in the symptom-modifying category (i.e. chondroitin has primary effect on improvement of pain and function) and glucosamine and diacerein in the structure-modifying category (Dougados 2000; Richy

2003) (i.e. they have an effect on progression of arthritis e.g. effect on joint space narrowing as assessed by radiography of the involved joint). One of the main proposed advantages of these medications over traditional medical therapies is their safety profile.

Chondroitin sulfate belongs to a family of heteropolysaccharides called glycosaminoglycans or GAGs. Chondroitin sulfate is found in human cartilage, bone, cornea, skin and arterial wall. The sources of chondroitin used in nutritional supplements include bovine trachea, pork byproducts, shark cartilage and whale septum (Hendler 2001). Proposed mechanisms of action of condition include restoration of extracellular matrix of cartilage and/or prevention of further cartilage degradation (Johnson 2001) and overcoming a dietary deficiency of sulphur-containing amino-acids that are essential building blocks for cartilage extracellular matrix molecules (Cordoba 2003). A large number of patients with osteoarthritis in the USA and around the world are already using chondroitin for relief of osteoarthritis-related joint pain alone or in combination with glucosamine. Both glucosamine and chondroitin are available over the counter as nutritional supplements and combination therapy of glucosamine and chondroitin has been used, but it is unclear if there is an additive or synergistic effect of these two supplements. A meta-analysis of glucosamine and chondroitin for treatment of osteoarthritis published in 2000 (McAlindon 2000) concluded that both supplements were effective for pain relief and functional outcomes with moderate to large effects, but quality issues and publication bias seemed to inflate the effect sizes. A recent updated Cochrane review of glucosamine for treating osteoarthritis concluded that studies using a non-Rotta preparation or adequate allocation concealment failed to show benefit in pain and function while those studies evaluating the Rotta preparation showed that glucosamine was superior to placebo in the treatment of pain and functional impairment resulting from symptomatic osteoarthritis (Towheed 2005). Meta-analyses of chondroitin for osteoarthritis (Leeb 2000) and glucosamine and chondroitin for knee osteoarthritis (Richy 2003) that included studies up to March 2002 concluded that chondroitin was effective for pain and function compared to placebo. A limitation noted in both these meta-analyses was that trials included in analyses allowed coadministration of analgesics or NSAIDs during the study leading to possible confounding of the results. Publication of additional studies of chondroitin in the last few years since the publication of meta-analyses necessitate an updated analysis and systematic review.

## OBJECTIVES

The objective of this systematic review is to evaluate the effectiveness and safety of oral chondroitin for treatment of osteoarthritis compared to placebo or a comparator oral medication including Non-steroidal anti-inflammatory drug (NSAID), analgesic, opioid, glucosamine or other “herbal” medication.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised Controlled Trials (RCTs) of two weeks or longer duration will be included if they report clinical outcomes data, and are published in full in English. RCTs of shorter than two weeks duration will be excluded, since this time frame may be too short to assess safety and efficacy based on biological plausibility. We will include non-randomised post-marketing surveillance studies if they include  $\geq 500$  patients, report adverse events/safety data and are of  $\geq$  one year duration, since they may be better for detecting rare adverse events.

#### Types of participants

Adults (age  $>18$  years) with OA of any joint. Subgroup analysis for safety and efficacy will be done for age, race and gender.

#### Types of interventions

Chondroitin arm:

Use of oral chondroitin alone or in combination with glucosamine

Comparator arm:

Placebo or active medications including NSAID, analgesics (e.g. Acetaminophen), opioid pain-relieving, glucosamine or other "herbal" medication

#### Types of outcome measures

Primary outcomes:

1. Mean change in Pain: Pain subscale of the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) (Bellamy 1988), rest pain and pain on motion in chondroitin vs. control/comparator

2. Percent achieving Minimal Clinically Important Improvement (MCII) on WOMAC (Tubach 2005) in chondroitin vs. control/comparator

Secondary Outcomes:

1. Clinical Efficacy outcomes:

a. Pain on walking for index joint, pain in index joint during activities other than walking

b. Physical function - Both performance-based (e.g., 50-foot walk) and patient-based (WOMAC (total and subscale scores))

c. Patient and physician global assessment

d. OMERACT-OARSI response criteria (Dougados 2000, Pham 2004)

e. Need for use of concomitant medications

f. Lequesne index (Lequesne 1997)

g. Need for joint surgery or arthroscopy

h. Quality of life as assessed by specific (Health Assessment Questionnaire (HAQ)) and generic questionnaires (Short-Form-36 (SF-36) and others)

2. Radiographic outcomes: Radiological changes in joint space width/narrowing in mm, or other radiographic criteria

3. Safety will be measured by:

a. Specific adverse effects (gastrointestinal, cardiac, renal, hematologic and other side-effects) and total number of adverse effects/events

b. Total number of withdrawals and withdrawals judged to be due to adverse effects in each group

c. Number of deaths.

We will search the Food and Drug Administration (FDA) web site for obtaining the adverse effect data.

Pharmacoeconomics:

Wherever data is applicable, we will perform analyses comparing chondroitin to comparator regarding the cost of drugs per month and the number needed to treat (NNT) to prevent one patient from having an adverse event and NNT to have one patient achieve MCII on WOMAC. We will analyze direct medical and nonmedical costs as well as indirect medical costs in the analysis and report indirect costs (productivity losses) separately (Gabriel 2003).

### Search methods for identification of studies

Electronic Searches: The trials search coordinator (TSC) will carry out the searches of The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, LILACS, CINAHL, AMED and Current Controlled Trials. There will be no language or date restrictions in the search for trials and the databases will be searched from inception to present date. The search will be updated before the completion of the review to ensure inclusion of new trials in the intervening period.

Manual Searches: The reference lists of the studies included in the review will be searched for further trials. Since numerous International Nutraceutical companies market chondroitin, we believe it will be impossible to contact each of them for unpublished data. We will not search conference proceedings or journals specifically for the review.

Search Terms: We will use the following search strategy which has been developed in Medline (Appendix 1) and will be adapted for other databases.

1. exp OSTEOARTHRITIS/
2. osteoarthr\$.tw.
3. (degenerative adj2 arthritis).tw.
4. or/1-3
5. exp CHONDROITIN/
6. chondroitin.sh,rn,tw.
7. 5 or 6
8. 4 and 7
9. randomized controlled trial.pt.
10. controlled clinical trial.pt.
11. randomized controlled trials.sh.
12. random allocation.sh.
13. double blind method.sh.
14. single-blind method.sh.
15. clinical trial.pt.
16. clinical trials.sh.
17. clinical trial.tw.

18. ((singl\$ or doubl\$ or trebl\$ or tripl\$) and (mask\$ or blind\$)).tw.
19. placebos.sh.
20. placebo\$.tw.
21. random\$.tw.
22. Research Design/
23. comparative study.sh.
24. evaluation studies.sh.
25. follow-up studies.sh.
26. prospective studies.sh.
27. control\$.tw.
28. prospectiv\$.tw.
29. volunteer\$.tw.
30. or/9-29
31. (animal not human).mp.
32. 30 not 31
33. 8 and 32

### Data collection and analysis

All titles and abstracts of studies resulting from the searches will be undertaken by two reviewers (JAS and TJW) independently. The differences between the two reviewers will be resolved by consensus. The studies will not be masked for the identity of the report authors or trial location. A full copy of all possibly or definitely relevant studies will be obtained for further assessment. All the studies will be screened and reviewed for inclusion and exclusion criteria by two reviewers (JAS and TJW/RM). Authors will be contacted for clarifications and to obtain additional data in order to perform a systematic review, whenever necessary.

#### Data Collection

Reviewers will independently determine study eligibility and discrepancies will be resolved by discussion. For each study, we will extract the patient and study characteristics, and outcomes data. Predefined data extraction forms will be used to collect data and pilot tested.

#### Quality Assessment

We will assess percent of study participants lost to follow up. Each selected study will be evaluated for the following sources of bias: selection bias (allocation concealment), performance bias (masking of participants), detection bias and attrition bias, and each trial will be graded as A - adequate, B- unclear or C - inadequate on each criteria. We will assess the overall methodological quality including quality of concealment and study blinding methods of each study using the scale developed by Schulz which assigns a score of 1 for the poorest quality and 3 for the best quality (Schulz 1995). The randomization concealment method is scored on Schulz scale as follows: (1) Clearly adequate method is scored as 3: This includes centralized randomization by telephone, pharmacy-controlled randomization scheme, numbered or coded identical containers administered sequentially, on site computer system which can only be accessed after entering the characteristics of an enrolled participant or sequentially numbered sealed opaque en-

velopes; (2) Unclear is scored as 2: This includes sealed envelopes that are not sequentially numbered or opaque, other, list of random numbers read by someone entering the patient into trial or study noted to be "random" or "randomization" or "random allocation" but without details; and (3) Clearly inadequate: This includes alternation (odd-even, etc.), date of birth, date of week etc.

#### Data analysis

Data at the end of randomized studies will be analyzed. Interim analysis will be done whenever indicated, but in particular at 1, 3, 6, 12 months and at the end of the study. We will evaluate the short-term (< three months) and long-term effectiveness of chondroitin. We will analyze the studies of chondroitin separately from those that use both chondroitin and glucosamine.

For continuous data, results will be analyzed as weighted mean differences between the intervention and comparator group (WMD). The mean difference between treated group and control group is weighted by the inverse of the variance in the pooled treatment estimate. However, when different scales are used to measure the same conceptual outcome (e.g. functional status or pain), standardized mean differences (SMD) will be calculated instead. SMDs are calculated by dividing the WMD by the standard deviation, resulting in a unitless measure of treatment effect. For dichotomous data, a relative risk (RR) will be calculated. Homogeneity of the data will be calculated using a Chi square test at n-1 degrees of freedom with the significance level of < 0.05. Meta-analysis will be conducted according to a fixed effects model. Where heterogeneity exists, possible clinical sources of heterogeneity will be explored. We will assess for heterogeneity in the following characteristics: (1) Study-related: Quality, year, geography, duration; (2) Intervention-related: Dose, manufacturer, single vs. combination therapy, frequency; (3) Patient factors: gender, age, race; and (4) Disease-related: baseline severity, joint involvement, and unilateral vs. bilateral. If clinically appropriate, a random effects model will be used.

To assess for publication bias, inverted funnel plot technique (e.g. effect size against precision) will be used based on the data for the primary outcomes. Specific tests of publication bias will be employed, where appropriate (Egger 1997). Sensitivity analyses will be done to check if the results are consistent across various outcomes. Crossover vs. parallel RCT trials will be analyzed separately. Additional sensitivity analyses will take into account publication bias, if any, and the source of funding of the study.

#### Grading of the evidence

We will use the grading system described in the 2004 book Evidence-based Rheumatology (Tugwell 2004) and recommended by the Musculoskeletal Group:

Platinum: A published systematic review that has at least two individual controlled trials each satisfying the following :  
 Sample sizes of at least 50 per group - if these do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome.  
 Blinding of patients and assessors for outcomes.

Handling of withdrawals >80% follow up (imputations based on methods such as Last Observation Carried Forward (LOCF) are acceptable).

Concealment of treatment allocation.

Gold: At least one randomised clinical trial meeting all of the following criteria for the major outcome(s) as reported:

Sample sizes of at least 50 per group - if these do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome.

Blinding of patients and assessors for outcomes.

Handling of withdrawals > 80% follow up (imputations based on methods such as LOCF are acceptable).

Concealment of treatment allocation.

Silver: A systematic review or randomised trial that does not meet the above criteria. Silver ranking would also include evidence from at least one study of non-randomised cohorts that did and did not receive the therapy, or evidence from at least one high quality case-control study. A randomised trial with a 'head-to-head' comparison of agents would be considered silver level ranking unless a reference were provided to a comparison of one of the agents to placebo showing at least a 20% relative difference.

Bronze: The bronze ranking is given to evidence if at least one high quality case series without controls (including simple before/after studies in which patients act as their own control) or if the conclusion is derived from expert opinion based on clinical experience without reference to any of the foregoing (for example, argument from physiology, bench research or first principles).

#### **Clinical relevance tables**

Clinical relevance tables will be compiled under additional tables to improve the readability of the review. For dichotomous outcomes, the number needed to treat will be calculated from the control group event rate and the relative risk using the Visual Rx NNT calculator ([Cates 2003](#)). Continuous outcome tables will also be presented under additional tables. Absolute benefit will be calculated as the improvement in the intervention group minus the improvement in the control group, in the original units. Relative difference in the change from baseline will be calculated as the absolute benefit divided by the baseline mean of the control group.

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\* Indicates the major publication for the study

## APPENDICES

### Appendix I. MEDLINE search strategy

1. exp OSTEOARTHRITIS/
2. osteoarthr\$.tw.
3. (degenerative adj2 arthritis).tw.
4. or/1-3
5. exp CHONDROITIN/
6. chondroitin.sh,rn,tw.
7. 5 or 6
8. 4 and 7
9. randomized controlled trial.pt.
10. controlled clinical trial.pt.
11. randomized controlled trials.sh.
12. random allocation.sh.
13. double blind method.sh.
14. single-blind method.sh.
15. clinical trial.pt.
16. clinical trials.sh.
17. clinical trial.tw.
18. ((singl\$ or doubl\$ or trebl\$ or tripl\$) and (mask\$ or blind\$)).tw.
19. placebo.sh.
20. placebo\$.tw.
21. random\$.tw.
22. Research Design/
23. comparative study.sh.
24. evaluation studies.sh.
25. follow-up studies.sh.
26. prospective studies.sh.
27. control\$.tw.

- 28. prospectiv\$.tw.
- 29. volunteer\$.tw.
- 30. or/9-29
- 31. (animal not human).mp.
- 32. 30 not 31
- 33. 8 and 32

## WHAT'S NEW

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5 September 2008	Amended	Converted to new review format. CMSG ID: C116-P
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## HISTORY

Protocol first published: Issue 1, 2006

## CONTRIBUTIONS OF AUTHORS

Conceiving the review: JAS and TJW

Designing the review: JAS and TJW

Coordinating the review: JAS

Assessing search results: JAS, TJW and RM

Assessing quality of studies: JAS, TJW and RM

Obtaining further information about studies: JAS and RM

## DECLARATIONS OF INTEREST

No conflict of interest

## SOURCES OF SUPPORT

### Internal sources

- Center for Chronic Disease Outcomes Research and Center for Epidemiological and Clinical Research, Minneapolis VA Medical Center, Minneapolis, MN, USA.

## External sources

- No sources of support supplied