

**RCT**  
**Potential PURL Review Form**  
**PURL Jam Version**

**PURLs Surveillance System**  
**Family Physicians Inquiries Network**

**SECTION 1: Identifying Information for Nominated Potential PURL**  
**[to be completed by PURLs Project Manager]**

- A. Citation: Roman-Blas JA, Castañeda S, Sánchez-Pernaute O, Largo R, Herrero-Beaumont G; CS/GS Combined Therapy Study Group. Combined Treatment With Chondroitin Sulfate and Glucosamine Sulfate Shows No Superiority Over Placebo for Reduction of Joint Pain and Functional Impairment in Patients With Knee Osteoarthritis: A Six-Month Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Arthritis Rheumatol.* 2017 Jan;69(1):77-85. doi: 10.1002/art.39819. Erratum in: *Arthritis Rheumatol.* 2017 Oct;69(10 ):2080. PubMed PMID: 27477804.
- B. Link to PubMed Abstract: <https://www.ncbi.nlm.nih.gov/pubmed/?term=27477804>
- C. First date published study available to readers: 1/9/2017
- D. PubMed ID: 27477804
- E. Nominated By: Jim Stevermer
- F. Institutional Affiliation of Nominator: University of Missouri
- G. Date Nominated: 1/13/2017
- H. Identified Through: POEMs
- I. PURLs Editor Reviewing Nominated Potential PURL: Corey Lyon
- J. Nomination Decision Date: 1/24/2017
- K. Potential PURL Review Form (PPRF) Type: RCT
- L. Assigned Potential PURL Reviewer: Corey Lyon
- M. Reviewer Affiliation: University of Colorado
- A. Abstract: Abstract

**OBJECTIVE:**

To assess the efficacy and safety of combination therapy with chondroitin sulfate (CS) and glucosamine sulfate (GS) compared to placebo in patients with symptomatic knee osteoarthritis (OA).

**METHODS:**

A multicenter, randomized, double-blind, placebo-controlled study was performed in 164 patients with Kellgren/Lawrence grade 2 or grade 3 radiographic knee OA and moderate-to-severe knee pain (mean  $\pm$  SD global pain score 62.1  $\pm$  11.3 mm on a 100-mm visual analog scale [VAS]). Patients were randomized to receive either combined treatment with CS (1,200 mg) plus GS (1,500 mg) or placebo in a single oral daily dose for 6 months. The mean change from baseline in the VAS global pain score was set as the primary end point. Secondary outcomes included the mean change in the investigator's global assessment of disease activity, total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), pain and function subscale scores on the WOMAC, responder rates based on the Outcome Measures in Rheumatology (OMERACT)-Osteoarthritis Research Society International (OARSI) 2004 response criteria, and rescue medication use. Adverse events were also recorded. A Data and Safety Monitoring Board was instituted to ensure patient safety and data accuracy.

**RESULTS:**

Intriguingly, in the modified intent-to-treat (mITT) population, CS/GS combination therapy was

inferior to placebo in the reduction of joint pain (mean  $\pm$  SD change in VAS global pain score over 6 months  $-11.8 \pm 2.4$  mm [19% reduction] in patients receiving CS plus GS versus  $-20.5 \pm 2.4$  mm [33% reduction] in patients receiving placebo; peak between-group difference in global pain score at 6 months 8.7 mm [14.2%],  $P < 0.03$ ), but no between-group differences were seen in the per-protocol completers. Both placebo treatment and CS/GS combination treatment improved to a similar extent the total WOMAC score as well as the pain and function WOMAC subscale scores, both in the mITT population and in the per-protocol completers. Neither the OMERACT-OARSI responder rate nor the frequency of rescue medication use differed between the treatment groups. Severe adverse events were uncommon and equally distributed.

#### CONCLUSION:

The results of this trial demonstrate a lack of superiority of CS/GS combination therapy over placebo in terms of reducing joint pain and functional impairment in patients with symptomatic knee OA over 6 months. Further research might fully elucidate the suitability of CS/GS combination therapy in patients with OA.

#### ERRATUM IN

Errors in the Format of the Global Pain Score ( Visual Analog Scale) in the Article by Roman-Blas et al (Arthritis Rheumatol, January 2017)

B. Pending PURL Review Date: 12/14/2017

### **SECTION 2: Critical Appraisal of Validity [to be completed by the Potential PURL Reviewer]**

- A. Number of patients starting each arm of the study?  
Placebo – 78 (14 w/drawal)  
CS/GS – 80 (25 w/drawal)
  
- B. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)  
Pts with symptomatic knee OA, radiographic grade 2 or grade 3 knee OA according to the Kellgren/Lawrence scale; and moderate-to-severe knee pain (40-80mm on a 100mm VAS).  
Exclusions – obesity (BMI >35); concurrent arthritic conditions
  
- C. Intervention(s) being investigated?  
CS 1200 mg plus GS 1500mg
  
- D. Comparison treatment(s), placebo, or nothing?  
Placebo
  
- E. Length of follow-up? (Note specified end points, e.g., death, cure, etc.)  
6 months
  
- F. What outcome measures are used? List all that assess effectiveness.  
Primary – mean reduction from baseline on global pain score – 100mm VAS  
Secondary – mean reduction of WOMAC, as well as subscale of pain and function (0-100mm VAS)  
Percentage of treatment responders according to OMERACT

Use of rescue medications

G. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CU, p-values, etc.

164 patients were randomized and in the ITT (158 in mITT); statistical significance set at  $p=0.03$ )

Change in VAS global pain score from baseline to 6 months in mITT

- Placebo -20.5 mm vs CS/GS -11.8;  $P=.029$

No difference in

- Global assessment of disease activity (-21.7mm vs -15.1;  $p=.039$ )

- WOMAC scores (-14.8mm vs -8.9mm;  $p=0.47$ )

No difference in all outcomes in the per-protocol group

OMERACT treatment responders in placebo vs CS/GS

- All responders – 56% vs 50%;  $p=.419$

- Pain or function with 50% improvement (>20mm change) – 47% vs 27.5%;  $p=.01$

H. What are the adverse effects of intervention compared with no intervention?

No difference in AE or SAE between groups

More AE related to treatment (mainly GI symptoms) in the CS/GS group compared to placebo (19 vs 33 cases;  $p=.018$ )

I. The study addresses an appropriate and clearly focused question.  
(select one) Well covered

Comments:

J. Random allocation to comparison groups:  
(select one) Well covered

Comments:

K. Concealed allocation to comparison groups:  
(select one) Well covered

Comments:

L. Subjects and investigators kept “blind” to comparison group allocation:  
(select one) Well covered

Comments:

M. Comparison groups are similar at the start of the trial:  
(select one) Well covered

Comments:

N. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential sources of bias. (select one) Well covered

Comments:

- O. Were all relevant outcomes measured in a standardized, valid, and reliable way?  
(select one) Well covered  
Comments:
- P. Are patient oriented outcomes included? If yes, what are they?  
Yes, pain and function
- Q. What percent dropped out, and were lost to follow up? Could this bias the results? How?  
18% in placebo  
33% in Cs/GS  
mITT analysis uses
- R. Was there an intention-to-treat analysis? If not, could this bias the results? How?  
yes
- S. If a multi-site study, are results comparable for all sites?  
UNK
- T. Is the funding for the trial a potential source of bias? If yes, what measures were taken to ensure scientific integrity?
- U. To which patients might the finding apply? Include patients in the study and other patients to whom the findings may be generalized.  
Pt with moderate to severe OA
- V. In what care settings might the finding apply, or not apply?  
Primary care, ortho, rheum
- W. To which clinicians or policy makers might the finding be relevant?

### **SECTION 3: Review of Secondary Literature**

**[to be completed by the Potential PURL Reviewer]**

**[to be revised by the Pending PURL Reviewer as needed]**

**Citation Instructions:** For up-to-date citations, use style modified from [http://www.uptodate.com/home/help/faq/using\\_UTD/index.html#cite](http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite) & AMA style. Always use Basow DS on editor & current year as publication year.

Example: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: <http://www.uptodate.com>. {Insert date modified if given.} Accessed February 12, 2009. [whatever date PPRF reviewer did their search.]

For DynaMed, use the following style:

Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at <http://www.DynamicMedical.com>. Last updated February 4, 2009. {Insert date modified if given.} Accessed June 5, 2009. {search date}

#### A. DynaMed excerpts

##### Glucosamine and chondroitin:

- AAOS does not recommend glucosamine and chondroitin for patients with symptomatic OA of knee, based on lack of efficacy with low likelihood of achieving clinically important benefits ([AAOS Strong recommendation](#))<sup>(1)</sup>
- ACR recommends that chondroitin sulfate and glucosamine should not be used for initial management ([ACR Conditional recommendation](#))<sup>(6)</sup>
- **chondroitin sulfate may improve pain in adults with osteoarthritis of the knee ([level 2 \[mid-level\] evidence](#))**
  - based on Cochrane review limited by heterogeneity and trials with methodologic limitations
  - systematic review of 43 randomized trials evaluating oral chondroitin with trial duration of ≥ 2 weeks in 9,110 adults with osteoarthritis
  - most trials had ≥ 1 limitation including
    - unclear allocation concealment
    - unclear or no blinding
    - high dropout rate
  - trial duration ranged from 1 month to 3 years
  - most patients had osteoarthritis of the knee
  - comparing chondroitin sulfate ≥ 800 mg/day to placebo
    - chondroitin sulfate ≥ 800 mg/day associated with
      - decreased pain at < 6 months in analysis of 8 trials with 1,077 adults, results limited by significant heterogeneity
        - mean difference (MD) -10.14 points (95% CI -14.58 to -5.71 points) on 0-100 point pain scale
        - corresponds to NNT 5 (95% CI 3-8)
      - decreased pain at ≥ 6 months (MD -9 points, 95% CI -17.7 to -0.34 points) in analysis of 6 trials with 989 adults, results limited by significant heterogeneity
      - increase in ≥ 20% reduction in knee pain at ≥ 6 months in analysis of 2 trials with 1,253 adults
        - risk ratio 1.12 (95% CI 1.01-1.24)
        - NNT 16 (95% CI 9-136)
      - lower risk of serious adverse events (RR 0.4, 95% CI 0.19-0.82) in analysis of 6 trials with 954 adults
    - no significant difference in function at < 6 months (2 trials with 303 adults) and at ≥ 6 months (2 trials with 677 adults), results limited by significant heterogeneity
  - comparing chondroitin sulfate plus glucosamine to placebo
    - no significant difference in mean pain
      - at < 6 months in analysis of 3 trials with 332 adults
      - at ≥ 6 months in analysis of 2 trials with 719 adults
    - ≥ 20% reduction in knee pain at ≥ 6 months in 66.6% with chondroitin sulfate plus glucosamine vs. 60% with placebo (p = 0.091) in 1 trial with 630 adults
    - chondroitin sulfate plus glucosamine associated with nonsignificant improvement in function at ≥ 6 months (2 trials with 719 adults), but no significant difference at < 6 months (2 trials with 300 adults)
  - no significant differences in pain comparing
    - chondroitin sulfate 1,200 mg/day vs. [celecoxib](#) 200 mg/day in 1 trial with 635 adults
    - chondroitin sulfate 1,200 mg/day plus glucosamine 1,500 mg/day vs. celecoxib 200 mg/day in 1 trial with 271 adults
    - chondroitin sulfate ≥ 800 mg vs. avocado soybean unsaponifiable 300 mg/day in 1 trial with 357 adults
  - Reference - [Cochrane Database Syst Rev 2015 Jan 28;\(1\):CD005614](#)
- **glucosamine appears ineffective for reducing pain in patients with osteoarthritis of hip or knee ([level 2 \[mid-level\] evidence](#))**
  - based on multiple systematic reviews with heterogeneity
  - synthesis of results from multiple systematic reviews finds

- no clinically relevant reduction in pain in analyses limited to largest trials and/or trials with highest methodological rigor
- trials suggesting statistically significant and clinically relevant reductions in pain are limited to smaller trials (< 200 patients) of Rotta preparation of glucosamine sulfate funded by manufacturer (Rotta Pharm); larger trials of Rotta preparation did not independently support clinically relevant pain reduction
- findings of selected systematic reviews
  - **glucosamine appears ineffective for reducing pain in patients with osteoarthritis of hip or knee (level 2 [mid-level] evidence)**
    - based on systematic review with limited trial coverage (excluding smaller trials)
    - systematic review of 10 randomized placebo-controlled trials (with at least 100 patients per treatment arm) evaluating glucosamine, chondroitin, or glucosamine plus chondroitin with 3,803 patients with osteoarthritis of hip or knee
      - 6 trials evaluated glucosamine vs. placebo
      - 3 trials evaluated chondroitin vs. placebo
      - 1 trial evaluated glucosamine vs. chondroitin vs. glucosamine plus chondroitin vs. placebo (GAIT trial)
    - all 4 trials evaluating chondroitin had high dropout rate or unclear allocation concealment
    - prespecified clinically important pain difference between treatments was -0.9 cm on 10-cm visual analog scale (VAS)
    - pain intensity on 10-cm VAS comparing intervention vs. placebo
      - -0.4 cm (95% CI -0.7 to -0.1 cm) with glucosamine in analysis of 7 trials with 1,939 patients
    - no significant differences between glucosamine or chondroitin vs. placebo in adverse events
    - no significant differences between any intervention vs. placebo in dropout due to adverse events
    - Reference - [BMJ 2010 Sep 16;341:c4675 full-text](#), commentary can be found in [Evid Based Med 2011 Apr;16\(2\):52](#)

B. DynaMed citation/ access date      Title. Author. In: DynaMed [database online]. Available at: [www.DynamicMedical.com](http://www.DynamicMedical.com) Last Updated: . Accessed

C. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)  
CS/GS not effective and not recommended.

D. UpToDate excerpts

E. UpToDate citation/ Always use Basow DS as editor & current year as publication year. Access date Title. Author. In: UpToDate [database online]. Available at: <http://www.uptodate.com>. Last updated: . Accessed

F. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)

G. Other excerpts (USPSTF; other guidelines; etc.)

H. Citations for other excerpts

I. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)

## SECTION 4: Conclusions

[to be completed by the Potential PURL Reviewer]

[to be revised by the Pending PURL Reviewer as needed]

- A. **Validity:** Are the findings scientifically valid? 2
- B. If **A** was coded 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?
- C. **Relevance:** Is the topic relevant to the practice of family medicine and primary care practice, including outpatient, inpatient, obstetrics, emergency and long-term care? Are the patients being studied sufficiently similar to patients cared for in family medicine and primary care in the US such that results can be generalized?  
1 (extremely well)
- D. If **C** was coded 4, 5, 6, or 7, please provide an explanation.
- E. **Practice changing potential:** If the findings of the study are both valid and relevant, are they not a currently widely accepted recommendation among family physicians and primary care clinicians for whom the recommendation is relevant to their patient care? Or are the findings likely to be a meaningful variation regarding awareness and acceptance of the recommendation?  
3
- F. If **E** was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.
- G. **Applicability to a Family Medical Care Setting:**  
Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc.), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, education or counseling a patient; or creating a system for implementing an intervention? 1 (definitely could be done in a medical care setting)
- H. If **G** was coded as a 4, 5, 6, or 7, please explain.
- I. **Immediacy of Implementation:**  
Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug, or other essentials available on the market? 1 (definitely could be immediately applied)

J. If **I** was coded 4, 5, 6, or 7, please explain why.

K. **Clinically meaningful outcomes or patient oriented outcomes:**

Do the expected benefits outweigh the expected harms? Are the outcomes patient oriented (as opposed to disease oriented)? Are the measured outcomes, if true, clinically meaningful from a patient perspective?

1 (definitely clinically meaningful or patient oriented)

L. If **K** was coded 4, 5, 6, or 7 please explain why.

M. In your opinion, is this a pending PURL?

3

1. Valid: Strong internal scientific validity; the findings appear to be true.
2. Relevant: Relevant to the practice of family medicine.
3. Practice Changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.
4. Applicability in medical setting.
5. Immediacy of implementation

N. Comments on your response for question M.