

**Bannuru RR, Schmid CH, et al. Comparative Effectiveness of Pharmacologic Interventions for Knee Osteoarthritis: A Systematic Review and Network Meta-analysis. Ann Intern Med. 2015;162:46-54.**

Design: Network meta-analysis of randomized clinical trials

Study question: What are the efficacies of pharmacologic treatments of knee osteoarthritis (OA) compared to one another?

PICOS:

- Adults with clinical or radiologic diagnosis of symptomatic knee OA
- Interventions and comparisons: Both orally administered and intra-articular (IA) injected medications in multiple comparisons, direct and indirect
  - o Acetaminophen vs. oral placebo
  - o Diclofenac vs. oral placebo
  - o Ibuprofen vs. oral placebo
  - o Naproxen vs. oral placebo
  - o Celecoxib vs. oral placebo
  - o Acetaminophen vs. diclofenac
  - o Acetaminophen vs. ibuprofen
  - o Acetaminophen vs. naproxen
  - o Acetaminophen vs. celecoxib
  - o Diclofenac vs. celecoxib
  - o Diclofenac vs. IA hyaluronic acid
  - o Diclofenac vs. IA placebo
  - o Ibuprofen vs IA hyaluronic acid
  - o Naproxen vs. celecoxib
  - o Naproxen vs. IA hyaluronic acid
  - o Naproxen vs. IA placebo
  - o IA hyaluronic acid vs. IA corticosteroids
  - o IA Hyaluronic acid vs. IA placebo
  - o IA corticosteroids vs IA placebo
- Outcomes: primarily pain, function, and stiffness at 3 months after randomization
- Study types: Randomized trials which compared at least 2 interventions of interest and reported extractable data on at least one measure of pain, function, and stiffness

Study selection:

- Databases included MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, Google Scholar, and Web of Science from inception through August 15, 2014
- Two reviewers independently screened all titles and abstracts for inclusion, and assessed study quality using the Cochrane Risk of Bias tool, resolving discrepancies by consensus and investigating the effects of study quality on results in a separate sensitivity analysis
- A clinically important effect size was defined as an absolute change of 20 points or more on a 100 point scale such as for pain or function
- Many treatment comparisons are not in the main text of the article but are in a separate data supplement which accompanies the article
- Effect sizes were reported as median values with 95% central credible intervals (CrI), which are used in Bayesian analysis in place of 95% confidence intervals and indicate a 95% probability that the true effect size is between the upper and lower bounds of the CrI
  - o Most effect size comparisons were reported not in absolute terms (such as WOMAC points), but as standardized mean differences (SMD)

#### Results:

- 4122 literature citations were found; 497 full-text reports were retrieved, and 137 studies, with 33,243 participants, were judged to have met inclusion criteria for a network meta-analysis
- 13 studies had 3 trial groups; the rest had 2 trial groups
- The median age of patients was 62, the median proportion of women in the studies was 67%
- 90% of trials were industry-sponsored
- 129 trials contributed to the analysis of pain-related outcomes, with oral placebo as the intervention against which all other treatments were compared
  - o All pharmacologic treatments were better than oral placebo
  - o All treatments except acetaminophen met prespecified criteria for clinically significant improvement
  - o Naproxen, ibuprofen, diclofenac, IA hyaluronic acid, and IA corticosteroids were superior to acetaminophen
  - o IA placebo was superior to oral placebo (SMD 0.29 SD with 95% CrI from 0.04 to 0.54)
  - o IA treatments were superior to oral treatments when treatments were ranked in order of effectiveness
- 76 trials contributed to the analysis of physical function outcomes
  - o All interventions except IA corticosteroids were superior to oral placebo
  - o NSAIDs including celecoxib were superior to acetaminophen

- IA placebo was not significantly better than oral placebo
- IA hyaluronic acid was superior to IA placebo (SMD was 0.30 with 95% CrI from 0.20 to 0.40)
- 55 trials contributed data for stiffness outcomes
  - NSAIDs were superior to acetaminophen and oral placebo, but acetaminophen was not superior to oral placebo
  - IA hyaluronic acid was superior to IA placebo (SMD was 0.23 with 98% CrI from 0.13 to 0.34)
- Sensitivity analyses were done to detect the influence of study size on effect sizes; the effect sizes for IA treatments with 100 or more patients were smaller than 100 patients
- Adverse effects occurred for some treatments; oral nonselective NSAIDs led to more gastrointestinal adverse effects than acetaminophen or oral placebo or celecoxib
  - Cardiovascular events were not reported on in most trials, but the short exposure time of 2 to 3 months may account for this
  - IA therapies sometimes led to transient local reactions, but among the 29 trials reporting on septic arthritis, only 1 patient out of 3152 IA patients had this outcome

Authors' conclusions:

- For pain outcomes, all NSAIDs and IA treatments, except for celecoxib, were superior to acetaminophen
- IA placebo was superior to oral placebo for pain outcomes, and IA treatments were more effective than oral treatments
  - The effect size for IA hyaluronic acid compared to IA placebo was nearly the same as for conventional pairwise meta-analysis (Rutjes 2012), which concluded that the difference between IA hyaluronic acid and IA placebo was short of the clinically important difference
  - However, the network meta-analysis had oral placebo as the reference category, and the total effect of IA hyaluronic acid can be seen as the sum of the effect of an IA active injection over IA placebo plus the effect of IA placebo over oral placebo
  - Regardless of the mechanism, the IA procedure contributes to the overall benefit seen in clinical practice
- Celecoxib was not superior to acetaminophen, which may call into question the use of celecoxib in patients with multiple comorbid conditions
- Nonpharmacological treatments could not feasibly be compared with pharmacologic treatments because the use of differing control groups affect the assumptions necessary for network meta-analysis to yield unbiased estimates of relative effectiveness

- One limitation is that while many therapies in clinical practice are used in various combinations, only monotherapies could be combined in a network meta-analysis
- The lack of long-term outcome data limits the interpretation to short-term effects
- Many patients with OA are older, and their risks from systemic pharmacological interventions may be greater than the risks from local interventions such as IA injections; the integrated IA placebo effect may contribute to the advantages of IA hyaluronic acid over NSAIDS or acetaminophen

Comments:

- IA placebo could be compared to oral placebo in a network meta-analysis even though there are no randomized trials comparing the two because they are connected in the network diagram in Figure 1, where IA placebo had been directly compared to both naproxen and diclofenac, and both of these had been compared with oral placebo; this illustrates how indirect comparisons in a network meta-analysis are intended to work
- Three month followup is too short to be very helpful in a guideline for a chronic condition such as knee OA, even though most of the available studies were short term in duration
- Glucosamine and chondroitin were not included in the network, even though they are often used in the setting of knee OA
  - o This could be because they are available without a prescription, but the same is true of acetaminophen and many preparations of naproxen and ibuprofen
- Sensitivity analyses were not done for risk of bias; for example, while Rutjes 2012 examined several factors for IA hyaluronic acid versus IA placebo
  - o Rutjes found that allocation concealment made a difference, finding that when it was done, the SMD in favor of IA hyaluronic acid was 0.18, considerably smaller than when it was not done and the SMD was 0.43
  - o Blinding of outcome assessment, when adequate, had a SMD in favor of IA hyaluronic acid of 0.25; when blinding was inadequate, the SMD was 0.66
  - o For IA hyaluronic acid, an unbiased analysis would probably be smaller than is reported by the authors here
- In meta-analyses of osteoarthritis trials, study size has been associated with the estimate of treatment effect; small studies tend to show larger effects than larger studies (Nuesch 2010), and trials with 100 or more participants per group did have smaller effect sizes than trials with fewer participants, suggesting that there is publication bias for many interventions, including glucosamine, chondroitin, opioids, and IA hyaluronic acid, but not for several nonpharmacologic interventions such as exercise and self-management
- In a separate analysis, Ruesch 2009 found that allocation concealment and blinding had important influences on effect sizes for OA trials

Assessment: Inadequate for the main comparisons, including for the effectiveness of IA hyaluronic acid (lack of adjustment for studies with high risk of bias); the effect sizes are probably inflated for many comparisons, but adequate for good evidence that acetaminophen is not more effective than placebo for the treatment of knee osteoarthritis

References:

Nuesch E, Reichenbach S, et al. The importance of allocation concealment and patient blinding in osteoarthritis trials: a meta-epidemiologic study. *Arthritis Rheum* 2009; 61(12):1633-41

Nuesch E, Trelle S, et al. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. *BMJ*. 2010 Jul 16;341:c3515

Rutjes AWS, Juni P, et al. Viscosupplementation for Osteoarthritis of the Knee: A Systematic Review and Meta-analysis. *Ann Intern Med*. 2012;157:180-191