Prior MJ, Harrison DD, Frustaci ME. A randomized, double-blind, placebo-controlled 12 week trial of acetaminophen extended release for the treatment of signs and symptoms of osteoarthritis. Current Medical Research & Opinion 2014;30(11):2377–2387.

Design: randomized clinical trial

Purpose of study: to compare the effectiveness of extended release acetaminophen with placebo in the setting of osteoarthritis

Reasons not to cite as evidence:

- The authors emphasize p values as measures of effectiveness based on least squares statistical methods, but the actual effect sizes are fairly small, and the achievement of nominal statistical significance is likely based on large sample sizes, for which small p values can be reported even when clinically of marginal importance
    - That is, there were 267 patients randomized to acetaminophen and 257 randomized to placebo
    - This is likely to produce an overpowered trial which will produce statistically significant results with effect sizes of dubious importance
- The differences in the primary endpoint 100-point normalized WOMAC scores in Table 3 for pain and function are probably of small clinical significance
    - For pain, the group differences in change scores equal 4.21 points
    - For function, the group differences in change scores equal 5.35 points
- Further compromising even the small observed differences is the design of the study, which required the patients to discontinue their OA medications for five drug half-lives plus 48 hours, and then to have a 20% relative increase in their WOMAC scores from before that washout period; this is known as a “flare design” and is common in pharmacologic studies of OA
- However, a recent meta-analysis of the flare design (Trijau 2010) compared estimated treatment effects of NSAID studies (mostly coxibs) using a flare design with studies not using a flare design, using standardized mean differences as estimates of effect size, and found that effect sizes for the flare design are greater than for the non-flare design
    - The effect sizes were defined as is conventionally done, where an ES of 0.8 SD or more is large, an ES from 0.5 to 0.8 is moderate, and an ES of 0.2 to 0.5 is moderate
    - For WOMAC pain, the flare design effect size was 0.66 SD versus 0.45 for non-flare design
    - For WOMAC function, the flare design effect size was 0.50 versus 0.25 for the non-flare design
- From these considerations, even the trivial effect sizes achieved in this study are probably inflated over their true values

- Therefore, no evidence is supplied by this study to support effectiveness of extended release acetaminophen for OA

Reference:

Trijau S, Avouac J, et al. Influence of flare design on symptomatic efficacy of non-steroidal anti-inflammatory drugs in osteoarthritis: a meta-analysis of randomized placebo-controlled trials. Osteoarthritis Cartilage 2010;18:1012-1018.