DeLemos BP, Xiang J, et al. Tramadol hydrochloride extended-release once-daily in the treatment of osteoarthritis of the knee and/or hip: a double-blind, randomized, dose-ranging trial. Am J Therapeutics 2011;18:216-226.

Design: randomized clinical trial

Purpose of study: to compare the effectiveness of three different daily doses of extended release tramadol (100 mg, 200 mg, 300 mg) and celecoxib 200 mg with placebo for patients with osteoarthritis (OA) of the hip or knee

Reasons not to cite as evidence:

- The study is very large and the analysis repeatedly emphasizes p values at the expense of actual effect sizes, which are not reported in the text but which must be gleaned from figures and from Table 2
- Because a large sample size (n=1001) can report small p values with small treatment effects, the actual differences between tramadol and placebo must be evaluated separately from the p values
- The mean difference for the primary WOMAC pain score from baseline of the 300 mg tramadol dose was 117.8 and the difference for placebo was 94.9 (22.9 points), with the scale running from 0 to 500
    - This represents the equivalent of 0.45 points on a scale from 0 to 10
    - The smallest detectable difference (SDD) for WOMAC has been suggested by Angst 2001 as 0.51 points on a ten point scale, and the minimal clinically important difference (MCID) as 1.33 points
- The mean difference for the WOMAC physical function score, done on a scale from 0 to 1700 points, was 357.2 for 300 mg tramadol and 290.1 for placebo, a difference of 67.1 points, which does exceed the MCID for the WOMAC
- However, the study is set up with a very large list of exclusion criteria which characterize it as an explanatory rather than a pragmatic trial (Thorpe 2009), which influences its usefulness for a practice guideline
    - A pragmatic trial asks whether an intervention works under usual conditions, and an explanatory trial asks whether an intervention works under ideal conditions
    - A pragmatic trial includes all participants who have the condition of interest, while an explanatory trial strictly limits enrollment to those thought likely to be highly responsive to the experimental intervention
- Of the 201 patients randomized to 300 mg tramadol, 98 discontinued treatment, with 61 of these discontinuations being due to an adverse event and 22 due to lack of efficacy
    - In contrast, of 203 patients randomized to celecoxib, 67 discontinued treatment, 20 due to an adverse event, and 30 for a lack of efficacy

- The study is set up as a Phase III study for the licensing of a new extended release formulation of tramadol, and the superiority of the highest dose of tramadol to placebo is sufficient to accomplish this regulatory goal, but not helpful in guiding decision-making in a less strictly selected population
- Tramadol ER could be an option for patients who have serious adverse risks with NSAIDS, but this study does not provide evidence that its benefits are greater than its potential harms for patients treated under most real-world conditions

Reference:

Thorpe KE, Zwarenstein M, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. J Clin Epidemiol 2009;62:464-475.