Cepeda MS, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD005522

Design: meta-analysis of randomized clinical trials

Purpose of study: To compare effectiveness of tramadol with both placebo and active control interventions for the control of pain and improvement of function in patients with osteoarthritis (OA).

PICOS:

- Patient population: Adults with primary or secondary (to trauma or obesity) OA of the hip and/or knee
- Interventions: Tramadol with or without acetaminophen
- Comparisons: Another pharmacological treatment, either placebo or an active treatment
- Outcomes:
    - Pain
        - Pain intensity reported by the patient
        - Pain relief reported by the patient
    - Patient global assessment of function
    - Physical function
        - Self-reported function
        - Performance-based measures of function
        - Any physical function scale such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)
    - Safety of tramadol (adverse effects)
    - Joint imaging
- Study types: randomized clinical trials only

Study selection:

- Searches were carried out through September of 2005
- Databases included MEDLINE, EMBASE, LILACS, and the Cochrane Central Register of Controlled Trials
- Two authors independently assessed articles for inclusion and for study quality, using the Cochrane Risk of Bias tool for quality (description of randomization, allocation concealment, withdrawal rates of 20% or less, baseline similarity of compared groups, and intention-to-treat analysis of outcomes)
- Level of evidence was rated as platinum, gold, silver, or bronze depending on the quality and size of the studies
    - 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
        - Blinding of patients and assessors for outcomes
        - Handling of withdrawals >80% follow up
        - Concealment of treatment allocation
    - Gold: At least one randomized clinical trial meeting all of the following criteria for the major outcome(s) as reported:
        - Sample sizes of at least 50 per group
        - Blinding of patients and assessors for outcomes
        - Handling of withdrawals > 80% follow up
        - Concealment of treatment allocation
    - Silver: A systematic review or randomized trial that does not meet the above criteria
    - Bronze: at least one high quality case series without controls, or conclusions based on expert opinion

Results:

- 11 RCTs were selected, with a total of 1019 patients receiving either tramadol or tramadol/acetaminophen combination and 920 patients who received either placebo or another active comparison intervention
    - 10 of the included studies were sponsored by the pharmaceutical industry
    - 6 studies used placebo controls, and five studies used an active control (acetaminophen alone, diclofenac, dihydrocodeine, dextropropoxyphene, or pentazocine)
    - All but one study blinded the investigators, but only one study described allocation concealment, and two studies lost more than 20% of patients to followup
- Pain intensity was the reported outcome in 3 placebo controlled trials
    - The results were homogeneous enough to permit pooling of results
    - The pooled difference in pain intensity favored tramadol by a margin of 8.5 units on a scale of 0 to 100, with 95% confidence intervals from 4.9 to 12.05 points
- Pain intensity was the reported outcome in 4 active controlled trials, but only two studies reported data on a 0 to 10 or 0 to 100 point scale
    - Tramadol and dextropropoxyphene had very similar pain intensity (5 points in favor of tramadol, but 95% CI was between 11.27 points in favor of tramadol to 1.27 points in favor of dextropropoxyphene)
    - Tramadol at a dose of 150 mg/day was less effective than acetaminophen 1500 mg/day (20 points in favor of acetaminophen with 95% CI between 1.36 and 38.64 points on a 100 point scale)

- Global improvement (moderate improvement or better) was reported by four placebo-controlled studies, and tramadol increased by 37% the probability that such improvement would be reported (95% CI from 20% to 50%)
- Tramadol was superior to placebo in 4 studies which reported function on the WOMAC scale
    - WOMAC scores were normalized to have a range of scores from 0 to 10
    - The four studies reported differences between tramadol and placebo for the combined WOMAC scores, and the four between-group differences were pooled so that an average difference could be estimated
    - This estimate of composite WOMAC group differences was 0.34 points on a 10 point scale in favor of tramadol, with 95% CI between 0.19 and 0.49 points
- Tramadol and diclofenac were compared in one trial only, and there was no difference between the two drugs with respect to WOMAC scores at the end of the study
- Tramadol had no life-threatening adverse effects, but adverse events leading to patients stopping treatment were 2.6 times as common with tramadol (143 of 710) than with placebo (49 of 626)
    - In a trial comparing tramadol with diclofenac or dextropropoxyphene, adverse events leading to stopping treatment were more common (53 of 189) with tramadol than with the other drugs (15 of 183)
    - However, tramadol had fewer such adverse events (9 of 30) than with pentazocine (11 of 30)

Authors' conclusions:

- There is gold level evidence that tramadol is more effective than placebo in reducing pain intensity and improving function in the setting of hip OA, but these benefits are small
    - The maximum reduction in pain intensity would not be likely to exceed 12.5 points on a 100 point scale
- About one of eight patients taking tramadol may be expected to stop treatment because of adverse effects, but a slow titration period may improve this situation
- However, NSAIDS can have life-threatening adverse events such as GI bleeding, perforated ulcer, and renal failure
- There is limited evidence that traditional opioids are not more effective than tramadol fo r OA
- There was not enough data to estimate the duration of effectiveness of tramadol, since the longest study followup was three months; medications which bind to opioid receptors often lose effectiveness over time
- Acetaminophen was more effective than tramadol in regard to analgesia

- Adverse effects could limit the usefulness of tramadol, which points to a disadvantage of tramadol unless slow titration is done at the beginning of its use

Comments:

- The effects of tramadol on pain and function do appear to be small and may not exceed minimal effective differences with placebo
    - A treatment difference of 12.5 points on a scale of 0 to 100 is generally considered small
    - Angst 2001 studied the WOMAC and suggested an effect size of 0.51 points on a scale of 0 to 10 to represent the smallest detectable difference and a difference of 1.33 points to represent a minimal clinically effective difference; the estimated pooled effect of tramadol compared to placebo was 0.34 points, and was 8.5% of baseline
- The description of the method for pooling the WOMAC scores is sketchy, and the standard deviations for the change scores would have to be calculated for that analysis
    - Such calculations depend on assumptions about the correlation coefficients of baseline and final scores, and these assumptions are not mentioned in the methods section
    - However, the conclusion that the effect size for tramadol is small is not undermined by these ambiguities
- "Gold" level evidence is approximately equivalent to "good" evidence for the Workers' Compensation levels of evidence, since it would represent one high quality study

Assessment: an adequate meta-analysis which supports good evidence that in the setting of hip OA, the analgesic effects of tramadol compared to placebo are likely to be small enough to be clinically unimportant, and that the effects on hip function are similar. Adverse events can be expected to lead to stopping treatment unless careful dose titration is done, but there may be fewer life-threatening adverse events with tramadol than with commonly used NSAIDS

Reference:

Angst, F, Aeschlimann A, Stucki G. Smallest Detectable and Minimal Clinically Important Differences of Rehabilitation Intervention With Their Implications for Required Sample Sizes Using WOMAC and SF-36 Quality of Life Measurement Instruments in Patients With Osteoarthritis of the Lower Extremities. Arthritis Care and Research 2001;45:384-391