**Chappell AS, Ossanna MJ, et al. Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: A 13-week, randomized, placebo-controlled trial. Pain 2009;146:253-260.**

Design: randomized clinical trial

Study question: in the setting of knee osteoarthritis (OA), does duloxetine relieve pain more effectively than placebo?

Population/sample size/setting:

- 231 patients (151 women, 80 men, mean age 62) treated for knee OA at four centers in the United States
- Eligibility criteria were age over 40 who meet the American College of Rheumatology criteria for OA of the knee, with pain for at least 14 days of each month for at least 3 months with a mean pain score of at least 4 points on the 24 hour average pain scale, and were ambulatory without assistance
- Exclusion criteria were BMI over 40kg/$m^2$ , any confounding pain condition (such as inflammatory arthritis or autoimmune disorder), invasive therapy of the knee in the past 3 months, knee arthroscopy in the past year, use of crutches or a walker, psychiatric disorders such a major depression, pregnancy or breastfeeding, history of substance abuse or dependence, any history of seizures, glaucoma, acute liver injury, or sensitivity to duloxetine

Interventions:

- Randomization was to 60 mg duloxetine qd (n=111) or placebo (n=120)
    - Study was done in three phases
    - The first phase lasted one week during which patients were screened for eligibility
    - Study Period II (week 0) began with patients assigned to duloxetine taking 30 mg qd for one week and then titrating up to 60 mg qd through week 7
        - At week 7 all duloxetine patients were again randomized; duloxetine was continued, and randomization was based on dose: either continuing at 60 mg or titrating up to 120 mg
        - This continued through week 13 of the study
    - Study period III involved tapering the duloxetine for two weeks until duloxetine had been discontinued

Outcomes:

- The primary outcome was the weekly mean of the 24-hour pain score for each week
- Secondary measures included perceived improvement on the Patient Global Impression of Improvement (PGI-I) and the Western Ontario and McMaster University OA Index (WOMAC) physical function subscale
- A total of 173 (74.9%) of the patients completed the study: 80% of the placebo group and 69.4% of the duloxetine group
- The pain scores decreased more in the duloxetine group than in the placebo group
    - Pain reduction of 30% from baseline was reported in 59.3% of the duloxetine group and 44.5% of the placebo group
    - Pain reduction of 50% from baseline was reported in 47.2% of the duloxetine group and 29.4% of the placebo group
- Secondary outcomes such as PGI-I and WOMAC also were better in the duloxetine than the placebo group
    - Data are shown graphically rather than numerically
- Other outcome measures such as the body pain subscale of the SF-36 decreased in the duloxetine group more than in the placebo group
- 3 patients had serious adverse events (dehydration, MI, asthma, bronchitis, allergic rhinitis): 2 in the placebo group and1 in the duloxetine group
- After re-randomization at week 7, there were no differences between the 60 mg and the 120 mg doses of duloxetine; proportions of patients with 30% and with 50% pain improvement were equal between the two dosing schedules
- Groups (120 mg duloxetine, 60 mg duloxetine, and placebo) did not differ with respect to adverse events during the two week tapering phase of the study

Authors' conclusions:

- For knee OA, duloxetine is more effective than placebo for pain reduction
    - Age appeared to influence the treatment effect: patients over 65 had a significantly greater pain decrease with duloxetine than with placebo; for patients under 65, the decrease was not seen
    - This may have been due to the younger patients being more physically active, which could exacerbate knee pain; however, data on physical activity was not recorded, and this may have been due to chance rather than a true age effect
- The rate of dropouts was not statistically different between groups, although numerically more duloxetine than placebo patients discontinued the study

Comments:

- The primary outcome should be presented with actual numbers (means and standard deviations), either in a table or in the text of the article; a graph is not informative enough (Figure 3 does not show error bars)

- The study was sponsored by the manufacturer of the drug, and may have been done in order to obtain an additional FDA licensing indication
- A comparison of a centrally-acting drug with a placebo is expected to show more pain reduction with the drug, and is a fairly low bar to show efficacy of the drug
- Patients did continue with NSAID or acetaminophen, whichever drug they had been taking prior to the start of the trial; no treatment by subgroup interaction was seen; there is some post hoc speculation on this issue but this is not particularly valuable

Assessment: Adequate for evidence that duloxetine is more effective than placebo in decreasing pain from knee OA