

**Linde K, Rossnagel K. Propranolol for migraine prophylaxis. Cochrane Database of Systematic Reviews 2004; Issue 2, Art # CD003225.**

Design: Meta-analysis of clinical trials

PICOS:

- **Patient population:** Adult migraine sufferers; studies with mixed headache types were included if the results for migraine were reported separately
- **Intervention:** Oral propranolol in at least one arm of the study
- **Control/comparison intervention:** Placebo, other migraine prophylaxis drugs (including other beta-blockers); non-pharmacologic control interventions (e.g., biofeedback) were excluded; comparisons with different doses of propranolol were excluded
- **Outcomes:** Number of migraine attacks, headache index, pain intensity, number of headache days, or global response
- **Study types:** Randomized or quasi-randomized trials

Study type and selection:

- Databases included MEDLINE through May 2003; Cochrane Central Register of Controlled Trials through 2003; references of identified articles
- Two independent authors classified articles for data extraction and study quality, using questions which concern randomization, blinding, concealment of allocation, dropout rates, adequacy of reporting the main outcome, and analysis by intention-to-treat
- 58 trials with a total of 73 comparisons were considered relevant for the review; 26 trials had a comparison of propranolol with placebo

Results:

- Of the 26 trials comparing propranolol with placebo, only 9 furnished data on numbers of “responders,” in which a “responder” was defined as having a 50% improvement in some headache variable (number of migraine attacks, number of migraine days, global patient assessment)
  - o The overall response rate for propranolol was greater than for placebo; the pooled response ratio was 1.94 (95% confidence interval, 1.61 to 2.35) in favor of propranolol
- Other effect measurements, including headache intensity and frequency, were also estimated; although there was heterogeneity in the data, the trend in the trials was in favor of propranolol
- Propranolol was compared with calcium channel blockers in 13 trials; no evidence of any difference in effectiveness was seen
- Propranolol was compared with other beta-blockers in 10 trials; no other beta-blocker was shown to be superior to or inferior to propranolol

Authors' conclusions:

- Despite the methodological limitations of the majority of available trials, there is clear and consistent evidence that propranolol is superior to placebo for the prophylaxis of migraine
- The major problem in this review is the highly variable and often insufficient reporting of the outcome data
  - o Headache diaries, the most common method of monitoring therapeutic response in clinical trials, yield a variety of outcomes that can be extracted, over different time frames, reported as different effect sizes
  - o For this reason, the effect size estimates must be interpreted with great caution, leaving considerable uncertainty about the actual size of the propranolol effect in comparison with other medications
- The use of propranolol for the prophylaxis of migraine is justified

Comments:

- Most of the interpretive difficulties are discussed by the authors
  - o The authors had prespecified in their protocol that they would not do quantitative meta-analysis for a given comparison if fewer than half of the included trials provided usable data; for the comparison of propranolol with placebo, fewer than half of the trials included such data, and the quantitative pooling of results was done post-hoc
- Although there appears to be strong evidence of the superiority of propranolol to placebo, the authors' precautions about interpreting the effect size are justified
- Crossover trials were analyzed using comparisons of the responses to propranolol and control in the first period of the trial, effectively analyzing them as if they were parallel group studies; this will sacrifice the efficiencies of the crossover design and will tend to underestimate the treatment effect of propranolol, increasing the confidence that can be placed in the effectiveness of propranolol for migraine prophylaxis

Assessment: Adequate meta-analysis of consistent trial data to support a strong evidence statement that propranolol is superior to placebo for the prophylaxis of migraine