

**Moore RA, Straube S, et al. Pregabalin for acute and chronic pain in adults. Cochrane Database of Systematic Reviews 2009, Issue 3, Art No CD007076.**

Design: Meta-analysis

PICOS:

- Patients: adults age 18 or over with (1) acute pain in a setting where it is anticipated (e.g., postoperative), (2) neuropathic pain, including from diabetes (DM), postherpetic neuralgia (PHN), central neuropathic pain (CNP), (3) other chronic pain such as fibromyalgia (FM)
- Intervention: Pregabalin in any dose to achieve analgesia
- Comparator: Placebo or any active control
- Outcome: For acute pain: pain relief at 6 hours post-treatment; for chronic pain: pain relief at 2 weeks, 4 weeks, 6 months, using several pain relief measures: 30% or greater, 50% or greater, Patient Global Impression of Change (PGIC) and adverse effects (somnolence, dizziness, etc)
- Study types: Randomized clinical trials reported to be double blind

Study search and selection:

- Electronic searches of MEDLINE, EMBASE, and Cochrane CENTRAL
- References from retrieved articles
- Internet searches for reports not available as full publications
- <http://www.clinicalstudyresults.org/>, the PhRMA clinical results database
- All studies were read independently by two authors for risk of bias (randomization, blinding, follow-up adequacy) with disagreements resolved by consensus

Results:

- 6 articles on acute pain did not show a sufficiently homogeneous set of trials to allow a meta-analysis; there was no clear benefit of pregabalin
- For several chronic neuropathic pain conditions, pregabalin was effective, but a majority of patients did not have substantial benefit
- For PHN, there were 4 studies included in the analysis; for DM, there were 4 studies, for CNP, there were 2 studies, and for FM, there were 4 studies<sup>o</sup>
- For post-herpetic neuralgia (PHN), pregabalin was superior to placebo, but moderate benefit (30% relief) was obtained by only 39% of patients at a dose of 150 mg, by 49% of patients at a dose of 300 mg, and by 62% of patients at a dose of 600 mg
- For PHN, substantial benefit (50% relief) was obtained by 25% of patients at a dose of 150 mg, by 32% at a dose of 300 mg, and by 41% at a dose of 600 mg; similarly Patient Global Impression of Change (PGIC) was "Much of very much improved" for 27% of patients at 150 mg, by 32% of patients at a dose of 300 mg, and by 37% of patients at a dose of 600 mg
- For DM, a pattern broadly similar to that of PHN was seen, with a slightly higher percentage of patients having substantial benefit, e.g., 50% pain relief

in 46% of patients at a dose of 600 mg, and pregabalin superior to placebo (relative benefit of 1.5)

- For CNP, pregabalin was still more effective than placebo at producing 50% pain relief (relative benefit was 3.6), but only 25% of patients on 600 mg of pregabalin had pain relief of 50% or more
- For FM, pregabalin was again superior to placebo (e.g., relative benefit of 1.6 for 50% pain relief at 600 mg), but only 24% of FM patients taking 600 mg actually had this level of relief
- For serious adverse effects (not defined), about 3-4% of both pregabalin and placebo groups experienced them, with no difference between pregabalin and placebo
- Somnolence and dizziness occurred commonly in pregabalin than in placebo, and were more common in 600 mg doses (e.g., dizziness in 13% of PHN patients taking 150 mg, but in 35% of those taking 600 mg)

#### Authors' conclusions:

- Pregabalin shows no evidence of benefit in acute pain
- Pregabalin is superior to placebo for chronic pain, but a minority of patients taking it experience high levels of benefit
- At doses of 150 mg, pregabalin is generally not more effective than placebo, except for PHN
- PHN and DM respond to pregabalin better than do CNP and FM
- The included studies had adequate control of bias, but there was inconsistent reporting of some outcomes (e.g., 30% or more improvement of pain)
- Studies shorter than 8 weeks may over-estimate pregabalin efficacy, compared to studies longer than 8 weeks
- 18 of the 19 studies of pregabalin for chronic pain were sponsored by either Pfizer or by Parke-Davis; most evidence has been generated for regulatory purposes, and more evidence is needed to guide decisions about which patients are likely to benefit from its use
- It is not likely that there is a substantial amount of completed but unpublished work in neuropathic pain; it would require about three times as many participants in trials with zero effect to substantially reduce the effect of 600 mg pregabalin for PHN or DM pain

#### Comments:

- The essential features of a good systematic review and meta-analysis are well documented and clearly presented
- However, some of the analyses must be interpreted cautiously
- In particular, there are pooled numbers needed to treat (NNT) for most of the dichotomous outcomes, e.g., 30% pain reduction, 50% pain reduction, patient global impression of change (PGIC) much or very much improved
- Because NNT is generally considered to be a "clinician-friendly" summary number, it is potentially valuable as a measure of effectiveness in practice
- The NNT are presented in some circumstances in which they are likely to be misleading—when the control group event rates (baseline risks) are different;

pooling of studies for NNT generally assumes that the control event rate is fixed across studies

- For example, in Analysis 2.1, Comparison 2, pregabalin 300 mg versus placebo for 30% relief, the subtotal for DM neuropathy pools two studies, one with a control event rate of 33%, the other with a control event rate of 52%; the risk differences are 29% (NNT =3.5) and 6% (NNT=16.7) respectively
- The pooled NNT of 6.8 from this analysis may not represent what can be expected in the treatment of any given population of patients with neuropathic pain
- For every meta-analysis with more than one study, heterogeneity is calculated, but it is not explored for an explanation, even when this may be an important issue
- For example, in the same analysis (Analysis 2.1, page 53) of DM neuropathy response to 300 mg pregabalin, the heterogeneity is significant with an  $I^2$  of 86%, which suggests that the studies have different effect sizes; this is not examined further
- A plausible explanation for the heterogeneity is that A0081071 2007, the study with the benefit ratio of 1.11 [0.91, 1.36] was done without enriched enrollment; Lesser 2004 used partial enriched enrollment
- Enriched enrollment randomizes patients who have shown some response to the test drug in an open-label setting or in a previous randomized trial; this strategy is felt to decrease the number of patients who withdraw from the study due to side effects, but may increase the apparent benefit of the drug, since only a drug-responsive subset of patients enter the trial
- The second author (Straube) cites his earlier systematic review (Straube S et al, Br J Clin Pharmacol 2008;66(2):266-275), in which partial enriched enrollment was not found to change estimates of the efficacy or harm of pregabalin; Lesser 2004 was included in this 2008 review, but A0081071 was not included
- Therefore, the hypothesis that enriched enrollment does not change estimates of effect size should not be accepted in the current study; the enriched enrollment study has changed the effect size and its statistical significance
- However, the play of chance may account for the “heterogeneity,” since the amount of evidence is not sufficient to establish that it is a real phenomenon [personal communication from the first author]
- The analyses of the 30% and 50% pain reductions are reported separately for the different doses of pregabalin; the 150 mg, 300 mg, and 300 mg doses are in three separate forest plots in three separate analyses
- Separate analyses by dose presents no difficulties, but the data from the three dose levels can be entered as if they arose from separate studies into the Cochrane RevMan software; when this is done, there is no heterogeneity for the 150, 300, and 600 mg doses for either van Seventer 2006 or for A0081071; the three dose levels have similar effects in relation to placebo
- In addition, the rate of 50% relief response is nearly identical for the van Seventer 2006 and the A0081071 studies; when all three dose categories are

aggregated, there were 83/272 responders for A0081071, and 83/275 responders for van Seventer—a 30% “success” rate in both studies

- A0081071 was done in Japan and van Seventer in Europe; they differed in the placebo response rates—15.5% for the Japanese study and 7.5% in Europe; the relative benefit in Japan is 1.97, while the relative benefit in Europe is 4.01
- Van Seventer 2010 was published after this Cochrane review was last updated; it reported a somewhat smaller relative benefit (studying a population with post-traumatic neuralgia); adding this data to the analysis does not materially change the estimates for relative benefit for 50% pain relief or for “much or very much improved” for relief of post-herpetic neuralgia
- Therefore, there is not a great demonstrated difference in response to pregabalin in post-traumatic and post-herpetic neuralgias
- The estimate of the effectiveness of pregabalin may be difficult to apply to patients if it is highly effective in a minority of patients and ineffective in others; the average pain relief may fail to guide decisions about the drug’s appropriate use

Assessment: High quality for evidence that pregabalin is more effective than placebo, and that it may provide substantial relief only in a minority of patients