

**Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database of Systematic Reviews 2007; Issue 4, Art No CD005454.**

Design: Meta-analysis of randomized trials

**PICOS:**

- **Patients:** Adults with any neuropathic pain; migraine and headache excluded
- **Intervention:** Any use of antidepressant drug, exclusive of lithium
- **Comparison:** Active treatment of any kind or placebo
- **Outcomes:** Patient-reported pain relief or global improvement, measured on any scale; overall quality of life measures, adverse effects; sleep and depression parameters
- **Study types:** Randomized trials in any setting; studies with fewer than 10 participants excluded

**Study search and selection:**

- Databases searched were MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Pain Palliative and Supportive Care Trials Register: all searched through the end of 2005
- Study quality was based on concealment of allocation, adequacy of randomization, adequacy of blinding, and description of withdrawals; two authors assessed the studies independently, and disagreements were resolved by discussion
- 115 reports were identified; 61 were initially selected, but 6 of these were excluded

**Results:**

- For tricyclic antidepressants (TCA), 31 placebo-controlled trials were included; 17 of these reported outcomes in terms of global change or at least moderate improvement, allowing combination of studies with a summary measure of effect (relative benefit and number needed to treat-NNT)
- 13 of the 31 TCA trials reported only means (many without standard deviations), allowing only combination with a vote-counting method
- Of the 17 placebo-controlled TCA studies, 13 reported TCA significantly better than placebo; the 4 exceptions were of TCA in HIV neuropathic pain (2 studies), chronic pain without specific organic cause (1 study), and prevention of post-stroke pain (1 study)
- Of the 13 studies which reported only mean data, 14 comparisons were made between TCA and placebo; 11 of the 14 comparisons reported more pain relief with TCA than with placebo; the 3 exceptions were amitriptyline for spinal cord injury, clomipramine for diabetic neuropathy, and mianserin for diabetic neuropathy
- 12 studies compared different TCAs with one another; 6 of these reported outcomes in terms of global improvement or pain response; and no differences were found in overall effectiveness

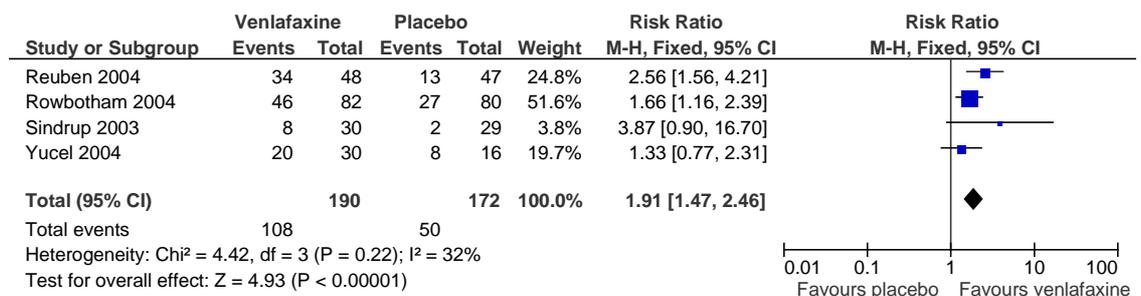
- 6 studies comparing different TCAs with one another reported results only in terms of mean data; some of these reported differences between TCAs, but the reporting of only mean data left the authors classifying the studies as having “no evaluable data”
- TCAs were compared with other active treatments in 13 studies, with numerous drug comparisons:
  - o Tramadol was as effective as clomipramine for postherpetic neuralgia (PHN)
  - o Clomipramine and aspirin were equally effective for neuropathic pain of traumatic or surgical origin
  - o Amitriptyline and mexiletine were both ineffective for HIV pain
  - o Amitriptyline was superior to lorazepam for PHN
  - o Capsaicin cream (low dose qid) was as effective as amitriptyline for diabetic neuropathy
  - o Morphine or methadone were superior to desipramine or nortriptyline for PHN
  - o TCAs and anticonvulsants (amitriptyline vs. gabapentin, amitriptyline vs. carbamazepine) did not differ in effectiveness for diabetic neuropathy or post-stroke pain
- SSRIs (fluoxetine, paroxetine, and citalopram) were superior to placebo in 4 studies of diabetic neuropathy and idiopathic facial pain
- The SNRI venlafaxine was superior to placebo in 3 studies, and was equal to imipramine and superior to placebo in one study of a variety of neuropathic conditions
- Other antidepressants (phenelzine, bupropion, St. John’s Wort) were compared to placebo in single studies; trazodone was not superior to placebo in 2 studies
- Adverse effects leading to withdrawal from the study occurred in 13% of all the participants in the included studies; dry mouth, drowsiness, dizziness, GI upset, urinary retention, and headache were commonly reported
- There appeared to be no correlation between depression and pain relief; the drugs appeared to have an independent analgesic action

Authors’ conclusions:

- There is robust evidence of the effectiveness of antidepressants for neuropathic pain
- TCAs (NNT=3.1) and venlafaxine (NNT=3) have the best evidence of effectiveness; SSRIs have more limited evidence, but are generally better tolerated, and more high quality studies are needed
- The evidence for PHN and diabetic neuropathy is better than for central pain and atypical facial pain
- Caution is needed when TCAs are used in the elderly or patients with heart disease
- The quality of the reporting limited the ability to combine data; many reports gave insufficiently detailed information for good meta-analysis

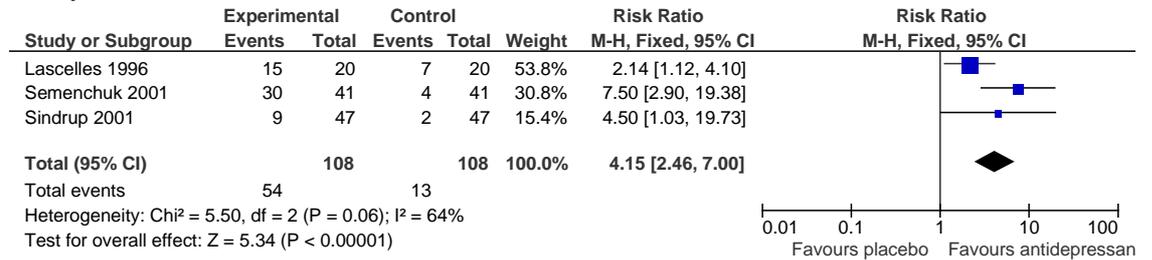
Comments:

- Search strategy and quality assessment are done in accordance with Cochrane methods and appear sound
- Publication bias is not addressed
- The authors are limited in being able to draw better inferences by the limited quality of much of the data reporting (e.g., means without standard deviations), and by the limited number of reports on some less commonly used antidepressants
- The NNT from meta-analyses need to be interpreted with caution when there is considerable variation in the placebo response rate in the included studies; for example, for venlafaxine, the placebo response rates vary from 6.8% to 50% and the NNT of 3 may be misleading
- The meaning of NNT is poorly stated in the abstract and in the conclusions; an NNT of 3 is discussed as signifying that one of three patients treated will respond, when the meaning of NNT of 3 is that there is approximately a 33% difference between the antidepressant and the placebo (only if the placebo response rate is zero will an NNT of 3 mean that one in three patients responds)
- There is an error in the main results section; it is stated that “no studies were found for SNRI antidepressants,” but venlafaxine, the best known SNRI, is then discussed in detail
- One study, Rowbotham 2004, is incorrectly characterized as being a comparison of amitriptyline and desipramine, when it is actually a comparison of venlafaxine and placebo; this leads to its omission from Analysis 1.6 on page 69
- Rowbotham can be added to Analysis 1.6 to produce a forest plot with a similar effect size to the one on page 69:

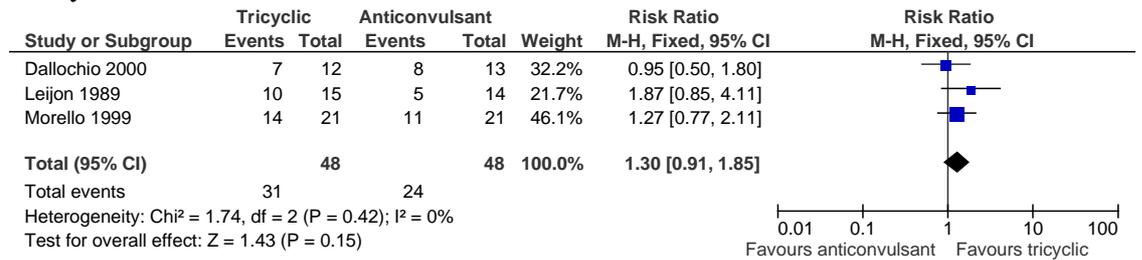


- The summary relative benefit for venlafaxine changes from 2.16 to 1.91, a small and inconsequential change; the value of  $I^2$  changes from 50% to 32%, which means less heterogeneity in the effect sizes
- The summary effect size is omitted from two analyses on page 68: for global improvement with other antidepressants vs. placebo (Analysis 1.4) and for tricyclics vs. anticonvulsants (Analysis 1.5). The completed forest plots are appended below:

- Analysis 1.4:



- Analysis 1.5:



- Analysis 1.5 shows no difference between gabapentin and TCA; Rintala 2007 is consistent with this conclusion, but it is a crossover study and cannot be readily combined with the above analysis

Assessment: Adequate for good evidence that TCA and venlafaxine are superior to placebo for neuropathic pain, and for good evidence that there is little difference in efficacy between tricyclics and gabapentin (although gabapentin may be better tolerated)