Evidence-based data on pain relief with antidepressants

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Authors' objectives
To systematically review the evidence for antidepressant pain efficacy, including clinical studies and recent meta-analyses (MA) studies. A secondary objective was to review the consistency of pain efficacy evidence for different pain syndromes, to determine what evidence, if any, exists for the superiority of subgroups of antidepressants and to propose some reasons why conflicting conclusions about pain efficacy have previously been reported in the literature.

Searching
MEDLINE, PsycINFO, Science Citation Index and PDQ databases were reviewed. The following MeSH terms were used: meta-analysis (MA) and pain, and antidepressants and pain, with each heading being exploded for all subheadings. All databases were searched from 1966 to 1999, except for the Science Citation Index that was searched from 1974 to 1999. No language restrictions were imposed on the searches. A manual search of key pain journals was also performed (list supplied in review) and three pain textbooks (listed) consulted for additional references.

Study selection
Study designs of evaluations included in the review
All placebo-controlled studies which reported the result of a statistical analysis of treatment effect were selected for inclusion in the review and were grouped by type of pain treated except those which addressed neuropathic pain, psychogenic pain or somatoform pain disorder, which were excluded due to the existence of MAs relating to them.

Specific interventions included in the review
Antidepressant drugs used for the treatment of acute or chronic pain. Specific agents discussed in the review were: amitriptyline, desipramine, clomipramine, fluoxetine, imipramine, trazodone, doxepin, nortripylline, maprotiline, sertraline, paroxetine, mianserin, fenoxetin, amitripyllineoxide, s-adenosylmethionine, trimipramine, citalopram, cyclobenzaprine, zimelidine. They were classified into noradrenergic (NA), serotonergic (S) and serotonergic-noradrenergic (S-NA) subgroups. All were compared to placebo except one study which compared clomipramine to pentazocine.

Participants included in the review
Patients receiving antidepressant drug therapy for the relief of chronic pain, (chronic low back pain; headaches; pelvic pain; pain associated with cancer; oseoarthritis or rheumatoid arthritis pain; fibroisitis or fibromyalgia pain; facial pain; ulcer healing; pain associated with irritable bowel syndrome; pain of mixed aetiologies; neuropathic pain; and pain associated with psychogenic pain or somatoform pain disorder) or acute pain (acute low-back pain, pre- and post-operative pain and chest pain with normal coronary arteries).

Outcomes assessed in the review
Antinociceptive (analgesic) effect. The outcome measure referred to was whether or not the treatment effect was statistically significantly more effective than placebo. How this was assessed in the individual trials was not detailed in the review.

How were decisions on the relevance of primary studies made?
The author does not state how many reviewers performed the selection.

Assessment of study quality
The author does not state that they assessed validity.

The author states that only placebo-controlled studies were included in the review, although data from MAs and from one comparator-controlled study were included.
Data extraction
The author does not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. Categories of data extracted were: patient numbers, type of pain, drug, dose and effect.

Methods of synthesis
How were the studies combined?
The trials were combined in a narrative.

How were differences between studies investigated?
Heterogeneity between the studies was not formally addressed, but the studies were grouped first by type of pain and then by subgroup of antidepressant.

Results of the review
95 placebo controlled studies were included in the review (n=5382 plus two studies where the number of patients was not stated). In addition data from four MAs were included, but the number of patients was not stated. The number of studies addressing the subgroups of pain were: six for acute pain, 13 for chronic low back pain, 28 for headache, one for chronic pelvic pain, two for pain associated with cancer, 13 for pain of osteoarthritis or rheumatoid arthritis, 12 for pain associated with fibrositis or fibromyalgia, two for facial pain, eight for ulcer healing, two for pain associated with irritable bowel syndrome and seven for pain of mixed aetiology.

Acute pain: 3 of 5 studies using S-NA drugs found the active treatment to be more effective than placebo. The one NA study found a positive treatment effect, whilst the one S study had a negative treatment effect.

Chronic low back pain: 8 of 10 S-NA trials found a positive treatment effect, as did 3 of 5 NA studies, whilst both S trials found a negative effect.

Headache: 15 of 18 S-NA trials found a positive treatment effect, as did 8 of 15 S trials and the one NA study.

Chronic pelvic pain: the one study which utilised a S antidepressant found a negative treatment effect.

Pain associated with cancer: of the two studies in this indication which both used a S-NA drug one gave positive and one gave a negative effect.

Oseoarthritic and rheumatoid arthritis: 7 or 11 S-NA trials found a positive treatment effect, as did half of the S trials (2 of 4). The one NA study reported a negative treatment effect. S-Adenosylmethionine (mechanism unknown) gave a positive effect.

Pain associated with fibrositis or fibromyalgia: All 10 S-NA studies reported a positive treatment effect, whilst 1 of 3 S studies reported a positive treatment effect. S-Adenosylmethionine (mechanism unknown) gave a positive effect.

Facial Pain: One trial with a S-NA and one with a S drug both found positive treatment effects. Ulcer healing: six of 8 trials that used a S-NA drug reported positive treatment effect. No other studies for this indication were included.

Pain associated with irritable bowel syndrome: Both studies, one with a S-NA and one with a NA antidepressant, reported positive treatment effects.

Pain of mixed aetiology: three of five S-NA trials found a positive treatment result, whilst one S trial found a positive, and one found a negative treatment effect.

The MA studies indicate that antidepressant drugs do have an anti-nociceptive effect, but because they pooled studies of different subgroups of antidepressants, they cannot provide information on the relative antinociceptive efficacy of the different subgroups.
Authors’ conclusions
The author concluded that antidepressant drugs do have an antinociceptive effect. The evidence was consistent in indicating that overall antidepressants may have an antinociceptive effect in chronic pain and that these drugs are effective for neuropathic pain. There was also some evidence that these drugs could be effective for psychogenic or somatoform disorder-associated pain. This evidence also strongly suggested that S-NA antidepressants may have a more consistent antinociceptive effect than the S antidepressants. Finally, this evidence indicated that antidepressants could be effective in pain associated with some specific pain syndromes, such as chronic low back pain, osteoarthritis and rheumatoid arthritis, fibrositis of fibromyalgia, and ulcer healing.

CRD commentary
The review addressed a specific appropriate question regarding the antinociceptive effect of antidepressants and used adequate criteria for this purpose, although their decision to include only placebo-controlled studies is questionable. The search strategy used was fairly comprehensive using a combination of electronic and manual searches. Although not all possible databases were searched it is probable that few relevant articles were missed. Thus, an unknown number of studies that reported no treatment effect have been excluded from this review, rendering the results effectively meaningless. The validity of studies included in the review was not assessed. Furthermore, it appears that the selection and reviewing of the papers included in this review were all performed by the single author (although this is not stated). If this is the case, it may have resulted in significant interpretation bias. Details of the papers included in the review are tabulated and the narrative synthesis used is appropriate.

Given the methodological flaws in this review, the conclusions drawn cannot be fully justified.

Implications of the review for practice and research
Practice: The author states that 'there are now consistent data that antidepressants do have an antinociceptive effect for various forms of chronic pain' and suggests the use of these agents for the treatment of chronic pain, irrespective of whether the patients suffer from depression. These conclusions should be accepted with caution in accordance with the comments above.

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