Antidepressants as analgesics: a review of randomized controlled trials

Mary E. Lynch, MD

Data from 59 randomized controlled trials provide support for the notion that antidepressants produce significant pain relief in chronic pain conditions. The literature includes 5 good reviews of such actions,1–5 2 of these being quantitative meta-analyses.2,5 The reviews conclude that antidepressants clearly exhibit analgesic effects. The majority of these studies have examined the analgesic action of the tricyclic group of antidepressants; controlled trials regarding the analgesic efficacy of other classes of antidepressants are lacking. We review the current literature regarding analgesia by class of antidepressant.

Tricyclic antidepressants

Data from 41 controlled trials indicate that tricyclic antidepressants (TCAs) are effective analgesics (Table 1). Amitriptyline is the most thoroughly studied agent;
desipramine, imipramine, clomipramine and doxepine have also been well studied.

Thirteen controlled trials examined the analgesic effects of the TCAs in neuropathic pain. There is signif-

Table 1: Placebo-controlled trials of tricyclic antidepressants to treat chronic pain

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Drug</th>
<th>Dosage, mg/d</th>
<th>Pain diagnosis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lance and Curran</td>
<td>1964</td>
<td>Amitriptyline</td>
<td>75</td>
<td>Chronic tension headache</td>
<td>+</td>
</tr>
<tr>
<td>Evans et al.</td>
<td>1973</td>
<td>Doxepin</td>
<td>150</td>
<td>Pain on oral analgesics</td>
<td>-</td>
</tr>
<tr>
<td>Gomersall and Stewart</td>
<td>1973</td>
<td>Amitriptyline</td>
<td>60</td>
<td>Migraine</td>
<td>+</td>
</tr>
<tr>
<td>O'kasha et al.</td>
<td>1973</td>
<td>Amitriptyline</td>
<td>50</td>
<td>Psychogenic headache</td>
<td>+</td>
</tr>
<tr>
<td>O'kasha et al.</td>
<td>1973</td>
<td>Doxepin</td>
<td>40</td>
<td>Psychogenic headache</td>
<td>+</td>
</tr>
<tr>
<td>Gringras</td>
<td>1976</td>
<td>Imipramine</td>
<td>75</td>
<td>Arthritic</td>
<td>+</td>
</tr>
<tr>
<td>Jenkins et al.</td>
<td>1976</td>
<td>Imipramine</td>
<td>75</td>
<td>Low back pain</td>
<td>-</td>
</tr>
<tr>
<td>MacNeil and Dick</td>
<td>1976</td>
<td>Imipramine</td>
<td>75</td>
<td>Rheumatoid arthritis</td>
<td>+*</td>
</tr>
<tr>
<td>Sternbach et al.</td>
<td>1976</td>
<td>Amitriptyline</td>
<td>150</td>
<td>Chronic organic pain</td>
<td>-</td>
</tr>
<tr>
<td>Sternbach et al.</td>
<td>1976</td>
<td>Clomipramine</td>
<td>150</td>
<td>Chronic organic pain</td>
<td>+</td>
</tr>
<tr>
<td>Couch and Hassanein</td>
<td>1979</td>
<td>Amitriptyline</td>
<td>100</td>
<td>Migraine</td>
<td>+</td>
</tr>
<tr>
<td>Morland et al.</td>
<td>1979</td>
<td>Doxepin</td>
<td>100</td>
<td>Mixed headache</td>
<td>+†</td>
</tr>
<tr>
<td>Ganvir et al.</td>
<td>1980</td>
<td>Clomipramine</td>
<td>25</td>
<td>Arthralgia</td>
<td>-</td>
</tr>
<tr>
<td>Alcoff et al.</td>
<td>1982</td>
<td>Imipramine</td>
<td>150</td>
<td>Low back pain</td>
<td>-</td>
</tr>
<tr>
<td>Hameroff et al.</td>
<td>1982</td>
<td>Doxepin</td>
<td>300</td>
<td>Low back pain</td>
<td>+</td>
</tr>
<tr>
<td>Pilowsky et al.</td>
<td>1982</td>
<td>Amitriptyline</td>
<td>150</td>
<td>Chronic intractable pain</td>
<td>-</td>
</tr>
<tr>
<td>Sjaastad</td>
<td>1982</td>
<td>Doxepin</td>
<td>175</td>
<td>Tension headache</td>
<td>+</td>
</tr>
<tr>
<td>Watson et al.</td>
<td>1982</td>
<td>Amitriptyline</td>
<td>75</td>
<td>Postherpetic neuralgia</td>
<td>+</td>
</tr>
<tr>
<td>Pheasant et al.</td>
<td>1983</td>
<td>Amitriptyline</td>
<td>150</td>
<td>Low back pain</td>
<td>-</td>
</tr>
<tr>
<td>Hameroff et al.</td>
<td>1984</td>
<td>Doxepin</td>
<td>300</td>
<td>Low back pain</td>
<td>+</td>
</tr>
<tr>
<td>Kinesdal et al.</td>
<td>1984</td>
<td>Imipramine</td>
<td>100</td>
<td>Diabetic neuropathy</td>
<td>+</td>
</tr>
<tr>
<td>Carette et al.</td>
<td>1986</td>
<td>Amitriptyline</td>
<td>50</td>
<td>Primary fibrositis</td>
<td>+</td>
</tr>
<tr>
<td>Goldenberg et al.</td>
<td>1986</td>
<td>Amitriptyline</td>
<td>25</td>
<td>Fibromyalgia</td>
<td>+</td>
</tr>
<tr>
<td>Macfarlane et al.</td>
<td>1986</td>
<td>Tramipramine</td>
<td>75</td>
<td>Rheumatoid arthritis</td>
<td>+</td>
</tr>
<tr>
<td>Sharav et al.</td>
<td>1987</td>
<td>Amitriptyline</td>
<td>30</td>
<td>Chronic oral facial pain</td>
<td>+</td>
</tr>
<tr>
<td>Sharav et al.</td>
<td>1987</td>
<td>Amitriptyline</td>
<td>150</td>
<td>Chronic oral facial pain</td>
<td>+</td>
</tr>
<tr>
<td>Max et al.</td>
<td>1987</td>
<td>Amitriptyline</td>
<td>25-150</td>
<td>Diabetic neuropathy</td>
<td>+</td>
</tr>
<tr>
<td>Frank et al.</td>
<td>1988</td>
<td>Amitriptyline</td>
<td>1.5/kg</td>
<td>Rheumatoid arthritis</td>
<td>+</td>
</tr>
<tr>
<td>Frank et al.</td>
<td>1988</td>
<td>Desipramine</td>
<td>1.5/kg</td>
<td>Rheumatoid arthritis</td>
<td>-</td>
</tr>
<tr>
<td>Max et al.</td>
<td>1988</td>
<td>Amitriptyline</td>
<td>150</td>
<td>Postherpetic neuralgia</td>
<td>+</td>
</tr>
<tr>
<td>Leijon and Boivie</td>
<td>1989</td>
<td>Clomipramine</td>
<td>150</td>
<td>Post-stroke pain</td>
<td>+</td>
</tr>
<tr>
<td>Loldrup et al.</td>
<td>1989</td>
<td>Clomipramine</td>
<td>150</td>
<td>Various pain locations</td>
<td>+/-†</td>
</tr>
<tr>
<td>Pilowsky and Barrow</td>
<td>1990</td>
<td>Amitriptyline</td>
<td>—</td>
<td>Chronic intractable pain</td>
<td>+§</td>
</tr>
<tr>
<td>Panerai et al.</td>
<td>1990</td>
<td>Clomipramine, Nortriptyline</td>
<td>25-100</td>
<td>Central pain</td>
<td>+</td>
</tr>
<tr>
<td>Max et al.</td>
<td>1991</td>
<td>Desipramine</td>
<td>12.5-150</td>
<td>Diabetic neuropathy</td>
<td>+</td>
</tr>
<tr>
<td>Sindrup et al.</td>
<td>1989</td>
<td>Imipramine</td>
<td>125-200</td>
<td>Diabetic neuropathy</td>
<td>+</td>
</tr>
<tr>
<td>Sindrup et al.</td>
<td>1990</td>
<td>Clomipramine</td>
<td>50-75</td>
<td>Diabetic neuropathy</td>
<td>+</td>
</tr>
<tr>
<td>Sindrup et al.</td>
<td>1990</td>
<td>Desipramine</td>
<td>50-200</td>
<td>Diabetic neuropathy</td>
<td>+</td>
</tr>
<tr>
<td>Kishore-Kumar et al.</td>
<td>1990</td>
<td>Desipramine</td>
<td>167 (avg)</td>
<td>Postherpetic neuralgia</td>
<td>+</td>
</tr>
<tr>
<td>Sindrup et al.</td>
<td>1990</td>
<td>Imipramine</td>
<td>25-350</td>
<td>Diabetic neuropathy</td>
<td>+</td>
</tr>
<tr>
<td>Sindrup et al.</td>
<td>1992</td>
<td>Imipramine</td>
<td>25-350</td>
<td>Diabetic neuropathy</td>
<td>+</td>
</tr>
</tbody>
</table>

*Improved joint tenderness in imipramine group, but no change in rheumatoid factor.
†Significant reduction in headache indices and in consumption of analgesics; no significant decrease in number of headache days.
‡For headache; — for burning mouth and abdominal pain.
§Varied results: amitriptyline somewhat effective in reducing pain intensity.

Source: Magni, Ongena and Van Houdenhove; Max; and McQuay et al.
significant consistent evidence that the TCAs are analgesic in painful diabetic neuropathy\textsuperscript{24,29,36–38,40,41} and postherpetic neuralgia\textsuperscript{21,36,39} and that they have exhibited analgesic efficacy in central pain\textsuperscript{35} and post-stroke pain.\textsuperscript{32} Other conditions for which there is evidence for TCA analgesia include tension-type headache,\textsuperscript{6,9,15} migraine\textsuperscript{8,14} and chronic oral-facial pain.\textsuperscript{28} The data are less clear for arthritic pain\textsuperscript{24} and chronic low back pain.\textsuperscript{1,2,4}

The analgesic effect occurs in the absence of depression or where there was no antidepressant effect,\textsuperscript{2–5} at doses lower than those used for depression,\textsuperscript{2–5} and with an earlier onset of effect (i.e., within 1 week) than that required for an antidepressant effect.\textsuperscript{3–5} Antidepressants were found to relieve brief lancinating pain as well as constant steady pain.\textsuperscript{3,5}

**Concentration–response**

There is very little work in the area of concentration–response relationships. The majority of studies have focused on the question of efficacy per se. However, 2 studies have addressed this issue. In a single-blinded imipramine dose-titration study of 15 patients with diabetic neuropathy, imipramine doses were individually adjusted until doses yielded plasma concentrations of imipramine and desipramine well above 400 nmol/L or until all neuropathy symptoms disappeared.\textsuperscript{38} Visual analog scores for pain were plotted against plasma TCA concentration, as well as the cumulative number of patients who reached 95% of maximum pain relief at a given concentration. Most patients noted optimum relief at or below 400 nmol/L. All but 1 subject experienced marked relief of pain. In the 14 responding patients, much of the effect occurred at plasma levels of imipramine and desipramine below 100 nmol/L. There was considerable variation, however, and concentrations of 400–500 nmol/L were required to ensure a maximum analgesic response in all patients. (Therapeutic doses for depression are 700–1100 nmol/L.\textsuperscript{42})

In another study, in a randomized, double-blind, multiple-dose, crossover study with 3-week treatment periods, the analgesic efficacy and adverse effects of amitriptyline in oral doses of 25, 50 and 75 mg/day in 29 patients with chronic pain were compared. A 75-mg dose exhibited significantly greater analgesic efficacy with no significant difference in depression scores. At this dose, side effects, including dry mouth and sedation, were more frequent than at the lower doses.\textsuperscript{43}

**Combination therapy using TCAs and neuroleptics**

In the past, clinicians had a tendency to add a low dose of a neuroleptic drug such as fluphenazine, in an effort to improve the analgesic effect of TCAs. This was based, primarily, on results of open uncontrolled trials.\textsuperscript{44} The 1 double-blind controlled trial comparing an amitriptyline–flupenthixol combination with amitriptyline alone found no significant difference in pain reduction between the 2 regimens.\textsuperscript{44} Thus, there is no support for using antidepressant–neuroleptic combinations to treat pain.

**TCAs as pre-emptive analgesics**

There is some evidence that amitriptyline can be effective in pre-emptive analgesia in postherpetic neuralgia (i.e., the prevention of the onset of the neuropathic pain, not herpes zoster infection.) Seventy-two patients infected with acute herpes zoster were randomly assigned to receive either amitriptyline or placebo within days of the diagnosis; patients continued taking amitriptyline for 90 days. At 6-month follow-up, low-dose amitriptyline was found to decrease the prevalence of postherpetic neuralgia by more than half.\textsuperscript{45}

**Postoperative pain**

Long-term administration of TCAs may be effective in potentiating opioid analgesia in postoperative pain. Desipramine, given daily for 3–7 days preoperatively, was found to enhance postoperative morphine analgesia in dental pain paradigms. If administered for only 3 days, there was no effect, indicating desipramine had to be initiated 7 days before surgery to be effective.\textsuperscript{46} Another trial found that 7 days of preoperative desipramine, but not amitriptyline, prolonged morphine analgesia.\textsuperscript{47} On the other hand, a single dose of 50-mg desipramine on the first day postsurgically did not significantly enhance morphine analgesia when compared with placebo. Thus, it appears that desipramine, given for 3–7 days, as long as it is given 1 week preoperatively, can potentiate opioid analgesia.

**Selective serotonin reuptake inhibitors**

**Chronic pain**

Overall, the results regarding analgesic effects of the
selective serotonin reuptake inhibitor (SSRI) group of antidepressants have been disappointing (Table 2). These agents are not superior analgesics as was hoped in the late 1980s and early 1990s when it was assumed that analgesic mechanisms of the antidepressants were monoaminergic.

There are 7 controlled trials examining the analgesic action of SSRIs on headache. Only 3 of these included a placebo control group, however, and in these trials, the SSRI was not better than placebo. There are 3 controlled trials examining SSRIs in the treatment of painful diabetic neuropathy. The larger study \((n = 46)\) found no difference between fluoxetine and placebo; in the 2 smaller studies, paroxetine and citalopram were found to exhibit a greater analgesic effect than placebo. There have been mixed results in studies of fibromyalgia as well. One smaller study demonstrated an analgesic effect with fluoxetine, and a larger one found no significant analgesic effect with fluoxetine. In a third trial, there was no significant analgesic effect with citalopram. Two trials have examined the action of zimelidine, an SSRI not available in Canada, in a mixed group of patients with chronic pain. Forty patients who received zimelidine (200 mg/day) experienced a significant analgesic effect; however, a second trial involving 20 patients who received 250 mg of zimelidine per day reported no analgesic effect. A trial of 23 women with chronic pelvic pain found that sertraline (100 mg/day) was no different than placebo in providing analgesia.

In studies examining both SSRIs and TCAs, the analgesia obtained with TCAs was superior in every case. Sindrup and colleagues found imipramine to be better than paroxetine in treating painful diabetic neuropathy; Max and coworkers demonstrated an improvement in tension headache with amitriptyline, but not fluoxetine, to be effective in treatment of diabetic neuropathy, and Bendsten et al demonstrated an improvement in tension headache with amitriptyline, but not with citalopram. Also, Atkinson et al found that maprotiline (a norepinephrine reuptake inhibitor), but not paroxetine, led to a significant reduction in chronic low back pain when compared with placebo. Thus, the question of whether SSRIs improve chronic pain, independent of effects in coexisting depression, has not been clearly resolved; there are few controlled trials, and the results are conflicting.

### Acute and postoperative pain, potential antianalgesic effect

In a randomized controlled trial of 70 patients, 7 days of fluoxetine administered preoperatively attenuated postoperative morphine analgesia, both in peak effect and duration. Dirkson et al examined the acute effects of various doses of fluoxetine and fluvoxamine on thermal and electrical stimulation induced pain in drug-naive rats and found enhanced withdrawal responses to noxious electrical stimulation, with no effect on heat-induced pain behaviour. The authors

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Drug</th>
<th>Dosage, mg/d</th>
<th>Pain diagnosis</th>
<th>n</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendtsen et al.</td>
<td>1996</td>
<td>Citalopram</td>
<td>20</td>
<td>Tension headache</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>Zeeberg et al.</td>
<td>1981</td>
<td>Famoxetine</td>
<td>300</td>
<td>Migraine</td>
<td>59</td>
<td>-</td>
</tr>
<tr>
<td>O’holm et al.</td>
<td>1986</td>
<td>Famoxetine</td>
<td>200–600</td>
<td>Migraine</td>
<td>65</td>
<td>-</td>
</tr>
<tr>
<td>Max et al.</td>
<td>1992</td>
<td>Fluoxetine</td>
<td>40</td>
<td>Diabetic neuropathy</td>
<td>46</td>
<td>-</td>
</tr>
<tr>
<td>Sindrup et al.</td>
<td>1990</td>
<td>Paroxetine</td>
<td>40</td>
<td>Diabetic neuropathy</td>
<td>19</td>
<td>+</td>
</tr>
<tr>
<td>Sindrup et al.</td>
<td>1992</td>
<td>Citalopram</td>
<td>40</td>
<td>Diabetic neuropathy</td>
<td>18</td>
<td>+</td>
</tr>
<tr>
<td>Wolfe et al.</td>
<td>1994</td>
<td>Fluoxetine</td>
<td>20</td>
<td>Fibromyalgia</td>
<td>42</td>
<td>-</td>
</tr>
<tr>
<td>Goldenberg et al.</td>
<td>1996</td>
<td>Fluoxetine</td>
<td>20</td>
<td>Fibromyalgia</td>
<td>19</td>
<td>+</td>
</tr>
<tr>
<td>Nørregaard et al.</td>
<td>1995</td>
<td>Citalopram</td>
<td>20–40</td>
<td>Fibromyalgia</td>
<td>22</td>
<td>-</td>
</tr>
<tr>
<td>Johansson and Von Knorring</td>
<td>1979</td>
<td>Zimelidine</td>
<td>200</td>
<td>Chronic pain</td>
<td>40</td>
<td>+</td>
</tr>
<tr>
<td>Gourlay et al.</td>
<td>1986</td>
<td>Zimelidine</td>
<td>250</td>
<td>Chronic pain</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>Rani et al.</td>
<td>1996</td>
<td>Fluoxetine</td>
<td>20</td>
<td>Chronic rheumatic pain</td>
<td>59</td>
<td>+</td>
</tr>
<tr>
<td>Engel et al.</td>
<td>1998</td>
<td>Sertraline</td>
<td>100</td>
<td>Pelvic pain</td>
<td>23</td>
<td>-</td>
</tr>
<tr>
<td>Atkinson et al.</td>
<td>1999</td>
<td>Paroxetine</td>
<td>10–30</td>
<td>Low back pain</td>
<td>74</td>
<td>-</td>
</tr>
</tbody>
</table>
concluded that there is no antinociceptive effect for the 2 SSRIs and raised the concern that SSRIs may actually enhance responses to noxious stimulation.

**Triazolopyridines**

**Trazodone**

There are 4 placebo-controlled trials examining trazodone as an analgesic (Table 3), which, in general, do not support an analgesic effect. A study involving 18 patients with traumatic myelopathy determined that trazodone (150 mg/day) was no better than placebo as an analgesic.62 Trazodone (1.5 mg/kg/day) given to 47 patients with rheumatoid arthritis was also no better than placebo in controlling pain,30 and 42 patients with chronic low back pain experienced no significant pain relief taking 200 mg of trazodone per day.64 There was 1 positive placebo-controlled trial involving 35 patients with pediatric migraine;63 in this study trazodone at 1 mg/kg/day reduced the frequency and duration of migraine. Another trial comparing amitriptyline and trazodone found that both agents exhibited similar efficacy in relieving deafferentation pain.65 Thus, trazodone does not appear to exhibit consistent analgesic effects.

**Nefazodone**

There are no human reports or randomized controlled trials examining an analgesic effect for nefazodone.

**Monoamine oxidase inhibitors**

In the 1 controlled trial in the literature, which involved 40 patients with atypical facial pain and depression, 45 mg of phenelzine led to significant improvements in both pain and depression.66 There are no controlled trials examining the analgesic effect of monoamine oxidase inhibitors in nondepressed patients.

### Table 3: Placebo-controlled trials of trazodone to treat chronic pain

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Dose per day</th>
<th>Pain diagnosis</th>
<th>n</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frank et al.60</td>
<td>1988</td>
<td>1.5 mg/kg</td>
<td>Rheumatoid arthritis</td>
<td>47</td>
<td>-</td>
</tr>
<tr>
<td>Davidoff et al.61</td>
<td>1987</td>
<td>150 mg</td>
<td>Traumatic myelopathy</td>
<td>18</td>
<td>-</td>
</tr>
<tr>
<td>Battistella et al.62</td>
<td>1993</td>
<td>1 mg/kg</td>
<td>Pediatric migraine prophylaxis</td>
<td>35</td>
<td>+</td>
</tr>
<tr>
<td>Goodkin et al.64</td>
<td>1990</td>
<td>200 mg</td>
<td>Chronic low back pain</td>
<td>42</td>
<td>-</td>
</tr>
</tbody>
</table>

**Selective serotonin–norepinephrine reuptake inhibitor: venlafaxine**

At present there are no published randomized controlled trials examining the analgesic action of venlafaxine. This agent is of particular interest for 2 reasons: (1) its broad neurotransmitter profile, similar to the tricyclic group, has led to speculation that it may have promise as an analgesic,67 and (2) it is similar in structure to tramadol, an analgesic with both opioid agonist and monoaminergic activity. The structural similarities between venlafaxine and tramadol are striking,68 both agents exhibit methoxyphenyl, N,N-dimethylamino and hydroxycyclohexyl groups. These groups can assume near super-imposable intramolecular orientations (depending on which enantiomers and conformations are compared).68 Venlafaxine and tramadol exhibit pharmacological similarities as well; both inhibit reuptake of serotonin and norepinephrine, both are enantioselectively metabolized by cytochrome oxidase isoenzyme P450 2D6 and both yield pharmacologically active O-desmethyl metabolites.68 Venlafaxine has been utilized to treat cases of chronic pain,69–71 and tramadol has shown promise as an antidepressant augmentation strategy.72

Although there are no published controlled trials with this agent, there are case reports, open trials and preclinical work of interest. Lang et al73 found venlafaxine to be effective in mitigating thermal hyperalgesia in rats caused by chronic constriction injury of the sciatic nerve. Songer and Schulte,71 in the first reported case discussing venlafaxine as an analgesic, describe a patient with radicular back pain and depression who had experienced resolution of depression but continued back pain on sertraline (200 mg/day). The patient was admitted to hospital and venlafaxine was started at a dose of 37.5 mg twice daily. Within 3 days, the patient’s back pain markedly decreased. Taylor and Rowbotham70 report on a series of 12 patients with various chronic pain diagnoses, all of whom experienced relief of pain taking venlafaxine. Nascimento74 describes an
open trial of 42 patients with migraine who experienced an 88% reduction in headaches while taking 18.75 mg to 37.5 mg of venlafaxine per day. Although randomized controlled trials are necessary, this agent shows considerable promise as an analgesic.

Summary

There is significant evidence that the TCAs are good analgesics, but data for the SSRIs are conflicting; data available to date indicate trazodone is not analgesic, and although venlafaxine shows significant promise, clinical trials are needed.

References


