Antidepressants as analgesics: a review of randomized controlled trials

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This review provides an overview of 59 randomized placebo-controlled trials that examined the analgesic effect of antidepressants. To summarize, there is significant evidence that the tricyclic group of antidepressants is analgesic and that trazodone is not; the data regarding selective serotonin reuptake inhibitors are conflicting. To date, there are no randomized controlled trials examining the potential analgesic action of nefazodone or venlafaxine, but on the basis of initial clinical reports and its structural similarity to other analgesics, venlafaxine shows promise as an analgesic.

Cette analyse présente un aperçu de 59 études randomisées contrôlées par placebo au cours desquelles on a examiné l'effet analgésique de certains antidépresseurs. En résumé, d'importantes données probantes indiquent que les antidépresseurs tricycliques sont analgésiques et que le trazodone ne l'est pas. Les données portant sur les inhibiteurs spécifiques du recaptage de la sérotonine sont contradictoires. Jusqu'à maintenant, il n'y a pas eu d'étude contrôlée randomisée portant sur l'effet analgésique possible de la néfazodone ou de la venlafaxine, mais si l'on se fonde sur les premiers rapports cliniques et sur la ressemblance de sa structure à celle d'autres analgésiques, la venlafaxine semble prometteuse comme analgésique.

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;

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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

Study	Year	Drug	Dosage, mg/d	Pain diagnosis	Outcome
Lance and Curran[6]	1964	Amitriptyline	75	Chronic tension headache	+
Evans et al.[7]	1973	Doxepin	150	Pain on oral analgesics	–
Gomersall and Stewart[8]	1973	Amitriptyline	60	Migraine	+
Okasha et al.[9]	1973	Amitriptyline	50	Psychogenic headache	+
Okasha et al.[9]	1973	Doxepin	40	Psychogenic headache	+
Gringras[10]	1976	Imipramine	75	Arthritic	+
Jenkins et al.[11]	1976	Imipramine	75	Low back pain	–
MacNeill and Dick[12]	1976	Imipramine	75	Rheumatoid arthritis	+*
Sternbach et al.[13]	1976	Amitriptyline	150	Chronic organic pain ("usually musculoskeletal")	–
Sternbach et al.[13]	1976	Clomipramine	150	Chronic organic pain	+
Couch and Hassanein[14]	1979	Amitriptyline	100	Migraine	+
Morland et al.[15]	1979	Doxepin	100	Mixed headache	+†
Ganvir et al.[16]	1980	Clomipramine	25	Arthralgia	–
Alcoff et al.[17]	1982	Imipramine	150	Low back pain	–
Hameroff et al.[18]	1982	Doxepin	300	Low back pain	+
Pilowsky et al.[19]	1982	Amitriptyline	150	Chronic intractable pain	–
Sjaastad[20]	1982	Doxepin	175	Tension heacache	+
Watson et al.[21]	1982	Amitriptyline	75	Postherpetic neuralgia	+
Pheasant et al.[22]	1983	Amitriptyline	150	Low back pain	–
Hameroff et al.[23]	1984	Doxepin	300	Low back pain	+
Kvinesdal et al.[24]	1984	Imipramine	100	Diabetic neuropathy	+
Carette et al.[25]	1986	Amitriptyline	50	Primary fibrositis	+
Goldenberg et al.[26]	1986	Amitriptyline	25	Fibromyalgia	+
Macfarlane et al.[27]	1986	Trimipramine	75	Rheumatoid arthritis	+
Sharav et al.[28]	1987	Amitriptyline	30	Chronic oral facial pain	+
Sharav et al.[28]	1987	Amitriptyline	150	Chronic oral facial pain	+
Max et al.[29]	1987	Amitriptyline	25–150	Diabetic neuropathy	+
Frank et al.[30]	1988	Amitriptyline	1.5/kg	Rheumatoid arthritis	+
Frank et al.[30]	1988	Desipramine	1.5/kg	Rheumatoid arthritis	–
Max et al.[31]	1988	Amitriptyline	150	Postherpetic neuralgia	+
Leijon and Boivie[32]	1989	Clomipramine	150	Post-stroke pain	+
Loldrup et al.[33]	1989	Clomipramine	150	Various pain locations	+/–‡
Pilowsky and Barrow[34]	1990	Amitriptyline	—	Chronic intractable pain	+§
Panerai et al.[35]	1990	Clomipramine, Nortriptyline	25–100	Central pain	+
Max et al.[36]	1991	Desipramine	12.5–150	Diabetic neuropathy	+
Sindrup et al.[37]	1989	Imipramine	125–200	Diabetic neuropathy	+
Sindrup et al.[38]	1990	Clomipramine	50–75	Diabetic neuropathy	+
Sindrup et al.[38]	1990	Desipramine	50–200	Diabetic neuropathy	+
Kishore-Kumar et al.[39]	1990	Desipramine	167 (avg)	Postherpetic neuralgia	+
Sindrup et al.[38]	1990	Imipramine	25–350	Diabetic neuropathy	+
Sindrup et al.[40]	1992	Imipramine	25–350	Diabetic neuropathy	+

*Improved joint tenderness in imipramine group, but no change in rheumatoid factor.
†Significant reduction in headache indices and in consumption of analgesic; 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,[1] Onghena and Van Houdenhove,[2] Max [3] and McQuay et al.[5]

icant consistent evidence that the TCAs are analgesic in painful diabetic neuropathy[24,29,36–38,40,41] and postherpetic neuralgia[21,36,39] and that they have exhibited analgesic efficacy in central pain[35] and post-stroke pain.[32] Other conditions for which there is evidence for TCA analgesia include tension-type headache,[6,9,15] migraine[8,14] and chronic oral-facial pain.[28] The data are less clear for arthritic pain[2,4] and chronic low back pain.[1,2,4]

The analgesic effect occurs in the absence of depression or where there was no antidepressant effect,[2–5] at doses lower than those used for depression,[2–5] and with an earlier onset of effect (i.e., within 1 week) than that required for an antidepressant effect.[3–5] Antidepressants were found to relieve brief lancinating pain as well as constant steady pain.[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.[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.[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.[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.[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.[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.[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.[46] Another trial found that 7 days of preoperative desipramine, but not amitriptyline, prolonged morphine analgesia.[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 no better than placebo.[48–50] 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;[51] in the 2 smaller studies, paroxetine[41] and citalopram[40] 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,[53] and a larger one found no significant analgesic effect with fluoxetine.[52] In a third trial, there was no significant analgesic effect with citalopram.[54] Two trials have examined the action of zimelidine,[55,56] 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;[55] however, a second trial involving 20 patients who received 250 mg of zimelidine per day reported no analgesic effect.[56] A trial of 23 women with chronic pelvic pain found that sertraline (100 mg/day) was no different than placebo in providing analgesia.[58]

In studies examining both SSRIs and TCAs, the analgesia obtained with TCAs was superior in every case. Sindrup and colleagues[41] found imipramine to be better than paroxetine in treating painful diabetic neuropathy; Max and coworkers[51] found desipramine and amitriptyline, but not fluoxetine, to be effective in treatment of diabetic neuropathy, and Bendsten et al[48] demonstrated an improvement in tension headache with amitriptyline, but not with citalopram. Also, Atkinson et al[59] 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.[60] Dirkson et al[61] 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 2: Placebo-controlled trials of selective serotonin reuptake inhibitors to treat chronic pain

Study	Year	Drug	Dosage, mg/d	Pain diagnosis	n	Outcome
Bendtsen et al.[48]	1996	Citalopram	20	Tension headache	40	–
Zeeberg et al.[49]	1981	Famoxetine	300	Migraine	59	–
Orholm et al.[50]	1986	Famoxetine	200–600	Migraine	65	–
Max et al.[51]	1992	Fluoxetine	40	Diabetic neuropathy	46	–
Sindrup et al.[41]	1990	Paroxetine	40	Diabetic neuropathy	19	+
Sindrup et al.[40]	1992	Citalopram	40	Diabetic neuropathy	18	+
Wolfe et al.[52]	1994	Fluoxetine	20	Fibromyalgia	42	–
Goldenberg et al.[53]	1996	Fluoxetine	20	Fibromyalgia	19	+
Nørregaard et al.[54]	1995	Citalopram	20–40	Fibromyalgia	22	–
Johansson and Von Knorring[55]	1979	Zimelidine	200	Chronic pain	40	+
Gourlay et al.[56]	1986	Zimelidine	250	Chronic pain	20	–
Rani et al.[57]	1996	Fluoxetine	20	Chronic rheumatic pain	59	+
Engel et al.[58]	1998	Sertraline	100	Pelvic pain	23	–
Atkinson et al.[59]	1999	Paroxetine	10–30	Low back pain	74	–

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.

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*-demethylamino 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 al[73] 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 Rowbotham[70] report on a series of 12 patients with various chronic pain diagnoses, all of whom experienced relief of pain taking venlafaxine. Nascimento[74] describes an

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

Study	Year	Dose per day	Pain diagnosis	*n*	Outcome
Frank et al.[30]	1988	1.5 mg/kg	Rheumatoid arthritis	47	–
Davidoff et al.[62]	1987	150 mg	Traumatic myelopathy	18	–
Battistella et al.[63]	1993	1 mg/kg	Pediatric migraine prophylaxis	35	+
Goodkin et al.[64]	1990	200 mg	Chronic low back pain	42	–

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

1. Magni G. The use of antidepressants in the treatment of chronic pain: a review of the current evidence. *Drugs* 1991; 42(5):730-48.
2. Onghena P, Van Houdenhove B. Antidepressant-induced analgesia in chronic non-malignant pain: a meta-analysis of 39 placebo-controlled studies. *Pain* 1992;49:205-20.
3. Max BM. Antidepressants as analgesics. *Prog Pain Res Manage* 1994;1:229-46.
4. Sindrup SH. Antidepressants as analgesics. *Anesth Biol Found* 1997;2B:987-97.
5. McQuay HJ, Tramer M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. *Pain* 1996;68:217-27.
6. Lance JW, Curran DA. Treatment of chronic tension headache. *Lancet* 1964;1:1236-9.
7. Evans W, Gensler F, Blackwell B, Galbrecht C. The effects of antidepressant drugs on pain relief and mood in the chronically ill. *Psychosomatics* 1973;14:214-9.
8. Gomersall JD, Stuart A. Amitriptyline in migraine prophylaxis: changes in pattern of attacks during a controlled clinical trial. *Neuro Neurosur Psychiat* 1973;36:684-90.
9. Okasha A, Ghaleb HA, Sadek A. A double-blind trial for the clinical management of psychogenic headache. *Br J Psychiat* 1973;122:181-3.
10. Gringras M. A clinical trial of tofranil in rheumatic pain in general practice. *J Int Med Res* 1976;4:(2 Suppl):41-9.
11. Jenkins DG, Ebbutt AF, Evans CD. Tofranil in the treatment of low back pain. *J Int Med Res* 1976;4:(2 Suppl):28-40.
12. MacNeill AL, Dick WC. Imipramine and rheumatoid factor. *J Int Med Res* 1976;4:(2 Suppl):23-7.
13. Sternback RA, Janowsky DS, Huey IY, Segal DS. Effects of altering brain serotonin activity on human chronic pain. In: Bonica JJ, Albe-Fessard DG, editors. *Advances in pain research and therapy*. vol 1. New York: Raven Press; 1976. p. 601-6.
14. Couch JR, Hassanein RS. Amitriptyline in migraine prophylaxis. *Arch Neurol* 1979;36:695-9.
15. Morland TJ, Storli OV, Mogstad TE. Doxepin in the prophylactic treatment of mixed "vascular" and tension headache. *Headache* 1979;19:382-3.
16. Ganvir P, Beaumont G, Seldrup J. A comparative trail of clomipramine and placebo as adjunctive therapy in arthralgia, *J Int Med Res* 1980;8 (3 Suppl):60-6.
17. Alcoff J, Jones E, Rust P, Newman R. Controlled trial of imipramine for chronic low back pain. *J Fam Pract* 1982;14:841-6.
18. Hameroff SR, Cork RC, Scherer K, Crago BR, Neuman C, Womble JR, et al. Doxepin effects on chronic pain, depression and plasma opioids. *J Clin Psychiat* 1982;43:22-7.
19. Pilowsky I, Hallet EC, Basset DL, Thomas PG, Penhall RK. A controlled study of amitriptyline in the treatment of chronic pain. *Pain* 1982;14:169-79.
20. Sjaastad O. So-called "tension headache" — the response to a 5-HT uptake inhibitor: femoxetine. *Cephalalgia* 1983;3:53-60.
21. Watson CP, Evans RJ, Reed K, Merskey H, Goldsmith L, Warsh J. Amitriptyline versus placebo in postherpetic neuralgia. *Neurology* 1982;32:671-3.
22. Pheasant H, Bursk A, Goldfarb J, Azen SP, Weiss JN, Borelli L. Amitriptyline and chronic low-back pain: a randomized double-blind crossover study. *Spine* 1983;8:552-7.
23. Hameroff SR, Weiss JL, Lerman JC, Cork RC, Watts KS, Crago BR, et al. Doxepin's effects on chronic pain and depression: a controlled study. *J Clin Psychiat* 1984;45:47-52.
24. Kvinesdale B, Molin J, Froland A, Gram LF. Imipramine treatment of painful diabetic neuropathy. *JAMA* 1984;251:1727-30.
25. Carette S, McCain GA, Bell DA, Fam AG. Evaluation of amitriptyline in primary fibrositis: a double-blind, placebo-controlled study. *Arthritis Rheum* 1986;29:655-9.
26. Goldenberg DL, Felson DT, Dinerman H. A randomized controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia. *Arthritis Rheum* 1986;29:1371-7.
27. Macfarlane JG, Jalali S, Grace EM. Trimipramine in rheumatoid arthritis: a double-blind trial in relieving pain and joint tenderness. *Curr Med Res Opin* 1986;10:89-93.
28. Sharav Y, Singer E, Schmidt E, Dionne RA, Dubner R. The analgesic effect of amitriptyline on chronic facial pain. *Pain* 1987;31:199-209.
29. Max MB, Culnane M, Schafer SC, Gracely RH, Walther DJ, Smoller B, et al. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. *Neurology* 1987;37:589-96.
30. Frank RG, Beck NC, Parker JC, Kashani JH, Elliott TR, Haut AE, et al. Depression in rheumatoid arthritis. *J Rheumatol* 1988; 15:920-5.
31. Max MB, Schafer SC, Culnane M, Smoller B, Dubner R, Gracely RH. Amitriptyline, but not lorazepam, relieves postherpetic neuralgia. *Neurology* 1988;38:1427-32.
32. Leijon G, Boivie J. Central post-stroke pain: controlled trial of amitriptyline and carbamazepine. *Pain* 1989;36:27-36.
33. Loldrup D, Langemark M, Hansen HJ, Olesen J, Bech P. Clomipramine and mianserin in chronic idiopathic pain syndrome: a placebo-controlled study. *Psychopharmacology* 1989; 99:1-7.
34. Pilowsky I, Barrow CG. A controlled study of psychotherapy and amitriptyline used individually and in combination in the treatment of chronic intractable, "psychogenic" pain. *Pain* 1990;40:3-19.
35. Panerai AE, Monza G, Movilia P, Bianchi M, Francucci BM, Tiengo M. A randomized, within patient, crossover, placebo-controlled trial on the efficacy and tolerability of the tricyclic antidepressants chlorimipramine and nortriptyline in central pain. *Acta Neurol Scand* 1990;82:34-8.
36. Max MB, Kishore-Kumar R, Schafer SC, Meister B, Gracely RH, Smoller B, et al. Efficacy of desipramine in painful diabetic neuropathy: a placebo-controlled trial. *Pain* 1991;45:3-9.
37. Sindrup SH, Ejlertsen B, Frøland A, Sindrup EH, Brøsen K, Gram LF. Imipramine treatment in diabetic neuropathy: relief of subjective symptoms without changes in peripheral and autonomic nerve function. *Eur J Clin Pharmacol* 1989;37:151-3.

38. Sindrup SH, Gram LF, Skjold T, Frøland A, Beck-Nielsen H. Concentration–response relationship in imipramine treatment of diabetic neuropathy symptoms. *Clin Pharmacol Ther* 1990;47:509-15.
39. Kishore-Kumar R, Max MB, Schafer SC, Gaughan AM, Smoller B, Gracely RH, et al. Desipramine relieves postherpetic neuralgia. *Clin Pharmacol Ther* 1990;47:305-12.
40. Sindrup SH, Bjerre U, Dejgaard A, Brøsen K, Aaes-Jørgensen T, Gram LF. The selective serotonin reuptake inhibitor citalopram relieves the symptoms of diabetic neuropathy. *Clin Pharmacol Ther* 1992;52:547-52.
41. Sindrup SH, Gram LF, Brosen K, Eshoj O, Mogensen EF. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. *Pain* 1990;42: 135-44.
42. Reisby N, Gram LF, Bech P, Nagy A, Petersen GO, Ortmann J, et al. Imipramine: clinical effect and pharmacokinetic variability. *Psychopharmacology* 1977;54:263-72.
43. McQuay HJ, Carroll D, Glynn CJ. Dose–response for analgesic effect of amitriptyline in chronic pain. *Anaesthesia* 1993;49:281-5.
44. Zitman FG, Linssen ACG, Edelbroek PM, Van Kempen GMJ. Does addition of low-dose flupentixol enhance the analgetic effects of low-dose amitriptyline in somatoform pain disorder? *Pain* 1991;47:25-30.
45. Bowsher D. The effects of pre-emptive treatment of postherpetic neuralgia with amitriptyline: a randomized, double-blind, placebo-controlled trial. *J Pain Symptom Manage* 1997;13: 327-31.
46. Gordon NC, Heller PH, Levine JD. Enhancement of pentazocine analgesia by clonidine. *Pain* 1992;48:167-9.
47. Levine JD, Gordon NC, Smith R, McBryde R. Desipramine enhances opiate postoperative analgesia. *Pain* 1986;27:45-9.
48. Bendtsen L, Jensen R, Olesen J. A non-selective (amitriptyline), but not a selective (citalopram), serotonin reuptake inhibitor is effective in the prophylactic treatment of chronic tension-type headache. *Neurol Neurosurg Psychiatry* 1996;61:285-90.
49. Zeeberg I, Orholm M, Nielsen JD, Honore PL, Larsen JJ. Femoxetine in the prophylaxis of migraine — a randomised comparison with placebo. *Acta Neurol Scand* 1981;64:452-9.
50. Orholm M, Honoré PF, Zeeberg I. A randomized general practice group-comparative study of femoxetine and placebo in the prophylaxis of migraine. *Acta Neurol Scand* 1986;74:235-9.
51. Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med* 1992;326:1250-6.
52. Wolfe F, Cathey MA, Hawley DJ. A double-blind placebo-controlled trial of fluoxetine in fibromyalgia. *Scand J Rheumatol* 1994;23:255-9.
53. Goldenberg D, Mayskiy M, Mossey C, Ruthazer R, Schmid C. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. *Arthritis Rheum* 1986;39(11):1852-9.
54. Nørregaard J, Volkmann H, Danneskiold-Samsøe B. A randomized controlled trial of citalopram in the treatment of fibromyalgia. *Pain* 1995;61:445-9.
55. Johansson F, Von Knorring L. A double-blind controlled study of a serotonin uptake inhibitor (zimelidine) versus placebo in chronic pain patients. *Pain* 1979;7:69-78.
56. Gourlay GK, Cherry DA, Cousins MJ, Love BL, Graham JR, McLachlan MO. A controlled study of a serotonin reuptake blocker, zimelidine, in the treatment of chronic pain. *Pain* 1986; 25:35-52.
57. Rani PU, Naidu MU, Prasad VB, Rao TR, Shobba JC. An evaluation of antidepressants in rheumatic pain conditions. *Anest Analg* 1996;83:371-5.
58. Engel CC, Walker EA, Engel AL, Bullis J, Armstrong A. A randomized, double-blind crossover trial of sertraline in women with chronic pelvic pain. *Psychosom Res* 1998;44(2):203-7.
59. Atkinson JH, Slater MA, Wahlgren DR, Williams RA, Zisook S, Pruitt SD, et al. Effects of noradrenergic and serotonergic antidepressants in chronic low back pain intensity. *Pain* 1999;83:137-45.
60. Gordon NC, Heller PH, Gear RW, Levine JD. Interactions between fluoxetine and opiate analgesia for postoperative dental pain. *Pain* 1994;58:85-8.
61. Dirksen R, Van Luijtelaar EL, Van Rijn CM. Selective serotonin reuptake inhibitors may enhance responses to noxious stimulation. *Pharmacol Biochem Behav* 1998;60(3):719-25.
62. Davidoff G, Guarracini M, Roth E, Sliwa J, Yarkony G. Trazodone hydrochloride in the treatment of dysesthetic pain in traumatic myelopathy: a randomized, double-blind, placebo-controlled study. *Pain* 1987;29(2):151-61.
63. Battistella PA, Ruffilli R, Cernetti R, Pettenazzo A, Baldin L, Bertoli S, et al. A placebo-controlled crossover trial using trazodone in pediatric migraine. *Headache* 1993;33(1):36-9.
64. Goodkin K, Gallion CM, Agras WS. A randomized, double-blind, placebo-controlled trial of trazadone hydrochloride in chronic low back pain syndrome. *J Clin Psychopharmacol* 1990; 10:269-78.
65. Ventafridda V, Caraceni A, Saita L, Bonezzi C, De Conno F, Guarise G, et al. Trazodone for deafferentation pain: comparison with amitriptyline. *Psychopharmacology* 1988;95:S44-9.
66. Lascelles RG. Atypical facial pain and depression. *Br J Psychiat* 1966;112:651-9.
67. Galer BS. Neuropathic pain of peripheral origin: advances in pharmacologic treatment. *Neurology* 1995;45(9 Suppl):S17-25.
68. Markowitz JS, Patrick KS. Venlafaxine–tramadol similarities. *Med Hypotheses* 1998;5:167-8.
69. Dwight MM, Arnold LM, O'Brien H, Metzger R, Morris-Park E, Keck PE. An open clinical trial of venlafaxine treatment of fibromyalgia. *Psychosomatics* 1998;39:14-7.
70. Taylor K, Rowbotham M. Venlafaxine hydrochloride and chronic pain. *West J Med* 1996;165:147-8.
71. Songer DA, Schulte H. Venlafaxine for the treatment of chronic pain [letter]. *Am J Psychiatry* 1996;153:737.
72. Fanelli J, Montgomery C. Use of the analgesic tramadol in antidepressant potentiation. *Psychopharm Bull* 1996;32:442.
73. Lang E, Hord AH, Denson D. Venlafaxine hydrochloride (Effexor™) relieves thermal hyperalgesia in rats with an experimental mononeuropathy. *Pain* 1996;68:151-5.
74. Nascimento ED. Prophylaxis of migraine: open study with venlafaxine in 42 patients [Portuguese]. *Arq Neuropsiquiatr* 1998;56(4):744-6.