Clinical experience with dual action antidepressants in different chronic pain syndromes

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A common psychopharmacology between pain and depression suggests that compounds inhibiting the reuptake of serotonin and/or noradrenaline are likely to produce relief from chronic pain. Indeed tricyclic antidepressants have been a standard treatment of chronic pain for many years. In spite of their improved tolerance, selective serotonin reuptake inhibitors do not appear to be particularly effective in the treatment of pain. Recently, a number of open and controlled trials with members of the new selective serotonin and noradrenaline reuptake inhibitor class of antidepressants, such as venlafaxine, milnacipran and duloxetine, suggest that these compounds may be more effective in relieving pain than selective inhibitors of serotonin reuptake. Wherever valid comparisons have been made the newer dual action drugs appear to be as effective as the tricyclics and considerably better tolerated. Dual action antidepressants are thus likely to become a widely used treatment of chronic pain both associated with and independent of depression. Copyright © 2004 John Wiley & Sons, Ltd.

**Key words** — pain; noradrenaline; serotonin; venlafaxine; milnacipran; duloxetine

**INTRODUCTION**

A common psychopharmacology between pain and depression (Briley, 2003) suggests that compounds inhibiting the reuptake of serotonin and/or noradrenaline are likely to produce relief from chronic pain. Following the empirical discovery of their efficacy, tricyclic antidepressants (TCA) have come to be considered for a long time to be the standard treatment for a variety of neuropathic pain syndromes including diabetic neuropathy (Davis et al., 1977) but also other somatic syndromes. A meta-analysis (O’Malley et al., 1999) evaluated 94 placebo-controlled studies in which the patients’ physical symptoms such as headache, fibromyalgia, gastrointestinal pain, tinnitus and chronic fatigue were treated with a variety of antidepressants including TCA, selective serotonin reuptake inhibitors (SSRI) as well as various combinations of antidepressants. The meta-analysis found all antidepressants to be effective in relieving the symptoms with no clear difference between the various classes of antidepressant. Similar results were found in a subsequent meta-analysis of 13 placebo-controlled studies in fibromyalgia (O’Malley et al., 2000).

It has been assumed that the action of these antidepressants on the reuptake of noradrenaline and/or serotonin was responsible for their action. Early studies suggested that the inhibition of the reuptake of noradrenaline was probably the most important property (Max et al., 1992). Subsequent studies confirmed that an action on the noradrenergic system alone or an inhibition of both noradrenaline and serotonin reuptake gave better results than selective inhibition of serotonin reuptake. Chronic neuropathic pain syndromes, such as postherpetic neuralgia and diabetic neuropathy, appear to respond to dual action antidepressants such as TCA and venlafaxine, whereas SSRI are not effective (Max, 1994). In another series of studies on diabetic neuropathy and postherpetic neuralgia comparing a variety of antidepressants, amitriptyline and desipramine were found to be effective, whereas the SSRI, zimelidine, which has subsequently been withdrawn from the market for toxicity reasons, and fluoxetine were without effect (Max, 1994). Similarly, trazodone, which is a weak serotonin reuptake inhibitor with additional 5-HT2 receptor antagonism,
appeared to be ineffective (Max, 1994). The SSRIs, paroxetine and citalopram, however, had some activity although this was less than that of the dual action compounds. Interestingly, the pain relieving activity of antidepressants was independent of whether the patients were suffering from co-morbid depression (Max, 1994), suggesting that the treatment of pain is a direct effect.

A meta-analysis of seven studies of antidepressants in the treatment of chronic lower back pain found that tricyclic and tetracyclic antidepressants, which inhibit noradrenaline reuptake, appeared to produce moderate symptom reduction. In contrast, SSRIs did not appear to be beneficial (Staiger et al., 2003).

In a structured review of the animal and clinical literature, Fishbain et al. (2000) analysed 22 animal studies and five human clinical studies that compared the pain-relieving effects of dual acting reuptake inhibitors, SSRIs and noradrenaline reuptake inhibitors (NRI). The authors came to the conclusion that, overall, dual acting antidepressants were more active than NRI, which were more active than SSRIs. Although they are clearly effective, the use of TCA in the treatment of chronic pain syndromes is compromised by the high level of adverse effects that limited the doses which can be used and probably the compliance.

With the arrival of the newer dual action selective serotonin and noradrenaline reuptake inhibitors (SNRI), venlafaxine, milnacipran and duloxetine, a number of studies have investigated the effectiveness of these ‘cleaner’ drugs in the treatment of various types of chronic pain, both associated with, and independent of, depression (Table 1).

VENLAFAXINE

A recent pooled analysis of 31 comparable, randomized, double-blind clinical studies comparing venlafaxine with SSRIs indicated that venlafaxine was significantly more effective than SSRI s in treating the somatic symptoms associated with depression (Entsuah, 2004). In 3273 patients on venlafaxine with 3217 on a SSRI, they compared the response and remission rates of the anxiety/somatization factor, which is an aggregate score of six items of the Hamilton depression rating scale. The proportion of patients with full remission of their somatic symptoms was significantly greater with venlafaxine than with a SSRI.

A placebo-controlled double-blind cross-over study in 16 healthy volunteers showed that venlafaxine increased the pain threshold for electrical stimulation (Enggaard et al., 2001). Open studies have demonstrated the effectiveness of venlafaxine in patients suffering from neuropathic pain (Taylor and Rowbotham, 1996) and peripheral diabetic neuropathy (Davis and Smith, 1999; Lithner, 2000; Kunz et al., 2000). A patient with neuropathic pain who was switched from amitriptyline to venlafaxine reported that equivalent pain relief was obtained with the SNRI but with considerably less adverse effects (Kiayias et al., 2000).

Venlafaxine XR has also been found to be effective in the treatment of painful peripheral diabetic neuropathy in a uraemic patient undergoing haemodialysis (Yilmaz et al., 2002).

A small randomized placebo-controlled cross-over study in 13 patients suffering from neuropathic pain following the treatment for breast cancer, showed that venlafaxine significantly reduced maximal pain intensity and significantly increased pain relief. Average pain intensity, on the other hand, was not modified (Tasmuth et al., 2002).

Table 1. Clinical studies of SNRIs in different types of pain

<table>
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<tr>
<th>SNRI</th>
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<th>Open studies</th>
<th>Double-blind controlled studies</th>
<th>Double-blind controlled studies</th>
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All of the above studies are referenced in the text.
A double-blind, placebo-controlled three-way cross-over trial in painful neuropathy compared the effectiveness of venlafaxine 225 mg and imipramine 150 mg with placebo (Sindrup et al., 2003). Of the 40 patients recruited 29 completed all three study periods of 4 weeks’ duration each. At the end of the trial period, the total pain scores on venlafaxine or imipramine were significantly lower than on placebo. Results with the two antidepressants were qualitatively similar and quantitatively they were not significantly different.

An open study of depressed patients with painful symptoms treated for 1 year with at least 150 mg/day venlafaxine XR has shown that the acute improvements in both pain and depression scores are maintained long term (Bradley et al., 2003).

Two open studies have suggested that venlafaxine may also be active in fibromyalgia. In the first trial of 15 patients with fibromyalgia, 11 completed an open 8-week trial. Six of the 11 patients who completed the study (40% of all enrolled patients) experienced a reduction of fibromyalgia symptoms of 50% or more (Dwight et al., 1998). The second study investigated 15 patients suffering from fibromyalgia with co-morbid depression and anxiety. Over the 12-week study there was a significant reduction in mean pain intensity and disability caused by fibromyalgia, as measured by the fibromyalgia impact questionnaire. Depression and anxiety scores were also significantly decreased during the study, although there was no correlation between the reduction in depressive or anxiety scores and the effects on pain or disability caused by fibromyalgia (Sayar et al., 2003).

MILNACIPRAN

An increasing number of reports suggest that milnacipran is effective in a wide range of chronic pain disorders. Glossodynia is an orolingual chronic pain syndrome which is characterized by a spontaneous burning sensation mainly affecting the tongue with clinically normal oral mucosa. Eleven patients with glossodynia and no history of significant psychiatric illness were treated with milnacipran on an open, variable dose, basis for 6 weeks (final mean dose 58.6 mg/day). Ten patients completed the study. Eight of these reported decreased pain intensity, six had a decrease of more than 50% and four reported negligible pain at the end of the study. For most patients the maximal benefit was achieved within the first week of treatment (Toyofuku, 2003). Similarly, Kamata et al. (2003) reported a case of a 72-year-old woman who had been suffering from persistent glossodynia for over 3 months. After 2 weeks treatment with milnacipran at 50 mg/day the level of pain subsided to a negligible and acceptable level.

There have been two independent reports of cases of successful treatment of postherpetic neuralgia with milnacipran (Utsunomiya et al., 2002; Shimamoto et al., 2002).

Pain arising from a purely physical orthopaedic cause, such as degenerative spondylosis and osteoarthritis, has also been successfully treated with milnacipran. A series of 15 patients with a primary diagnosis of orthopaedic pain, including degenerative spondylosis, lumbar spinal canal stenosis and osteoarthritis of the knee with symptoms which included low back pain, ischialgia, intermittent claudication and lower limb arthralgia were administered milnacipran, at 50 mg/day for 8 weeks. Twelve of the 15 patients completed the study. Of these, symptomatic improvement was seen in ten patients while symptoms remained unchanged in two patients. In four patients pain was reduced by more than 80% (Tanikawa, 2002).

In a second study, 17 patients suffering from pain resulting from degenerative spondylosis were treated with milnacipran at flexible doses ranging from 25 to 75 mg/day for 8 weeks. Five patients discontinued, two because of adverse effects within the first 24 h, two for lack of improvement and one for a worsening of his pain. The 12 patients who completed the study all reported improved pain symptoms. In seven patients (58% of completers; 41% of all enrolled patients) the reduction of pain intensity was greater than 50% (Tanikawa, 2004).

A 39-year-old woman suffering from an extremely painful temporomandibular disorder which developed into a generalized fibromyalgia was treated with milnacipran, at a dose of 30 mg/day increasing progressively, over 6 months, to 120 mg/day. Dose and time-dependent improvements were observed in occlusal discomfort, generalized pain and the associated symptoms of sleep disorder, chronic fatigue, stiffness, numbness and depressed mood. The treatment enabled the rehabilitation of the patient with a major improvement in her quality of life (Toyofuku and Miyako, 2004). An open-label clinical trial has also shown milnacipran to be effective in relieving pain and other symptoms in patients with fibromyalgia syndrome with co-morbid depressive symptoms (Nagaoka et al., 2004).

Milnacipran is the only SNRI to have been tested in a double-blind placebo-controlled study in fibromyalgia (this volume Vitton et al., 2004). Twice as many milnacipran-treated patients (75%) reported overall
improvement compared with the placebo group (38%, \(p<0.01\)). Furthermore, over a third of the patients treated twice daily with milnacipran reported at least 50% reduction in pain intensity, compared with only 14% of placebo-treated patients (\(p<0.05\)).

**OTHER NON-TRICYCLIC DUAL ACTION DRUGS**

In a double-blind, placebo-controlled study in patients with major depression, 60 mg once daily duloxetine was shown to be significantly superior to placebo in reducing depression scores from the second week. The pain-relieving effects of duloxetine in these patients were evaluated by a visual analogue scale and the somatic symptom inventory. Compared with placebo, duloxetine produced a statistically significant reduction in pain severity (Detke et al., 2002; Goldstein et al., 2004; Wohlreich et al., 2004).

Sibutramine, which is a SNRI used in the treatment of obesity (Poston and Foreyt, 2004) has also been reported to relieve neuropathic pain associated with type 2 diabetes (Davis, 2000). This effect was demonstrated in a small open study. Patients, however, who stopped medication (because of its expense) had a rapid return of pain which was immediately relieved when medication was resumed.

**CONCLUSION**

Although most of the currently available data on the newer compounds are derived from case reports and open studies, there is a strong suggestion that the SNRI are capable of providing relief from chronic pain whether directly associated with depression or not. This is consistent with an action on the ascending and descending noradrenergic and serotonergic neuronal pathways described by Stahl (this volume). Their ability to improve psychological, somatic and physical symptoms is probably the basis of their superior efficacy and their capacity to produce higher rates of remission (Thase et al., 2001).

Full, placebo-controlled clinical trials are now required to confirm these promising suggestions of efficacy in a number of chronic pain disorders.

**REFERENCES**


