Antidepressant Use in Chronic Pain Management: Is There Evidence of a Role for Duloxetine?

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Background: Duloxetine is a novel antidepressant that is anticipated to be clinically available soon. It exerts simultaneous noradrenergic and serotonergic neurotransmitter effects. Because of these influences, it is postulated to have a role in management of pain.

Data Sources: An Index Medicus search from 1997 to 2003 was conducted using the search terms *duloxetine*, *Cymbalta*, and *pain*.

Data Analysis: Preclinical animal studies suggest that duloxetine may have a direct analgesic role. Premarketing studies have emphasized its utility in alleviating somatic, specifically pain, complaints among patients with major depression.

Conclusion: Although promising, these results cannot be generalized to patients with pain disorders; the reasons for this are discussed herein. While duloxetine may be useful among somatizing depressed patients and possibly chronic pain patients with comorbid depression, its analgesic role has yet to be elucidated in future research.

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The new antidepressant duloxetine is expected to receive U.S. Food and Drug Administration approval in the coming months. Initial work has demonstrated its efficacy in reducing severity of depression, an effect that is comparable to that of antidepressants of the selective serotonin reuptake inhibitor (SSRI) class, e.g., paroxetine and fluoxetine.[1,2] In premarketing trials of duloxetine, there has been a concerted effort to frame a unique niche for duloxetine's efficacy, i.e., emphasizing its utility for patients with major depression accompanied by pain.[3–5] The appropriateness of the theoretical rationale for linking its antidepressant efficacy with pain reduction in such paradigms is questionable.

The manner in which the clinical efficacy of duloxetine is described in articles previewing its effects lends itself to the presumption that duloxetine may have a significant role to play in the management of pain, especially chronic pain. An Index Medicus search from 1997 to 2003 was conducted using the search terms *duloxetine*, *Cymbalta*, and *pain*. This article will provide an overview of the literature thus far accumulated on the efficacy of duloxetine against the backdrop of the current literature on the efficacy of antidepressants as analgesics to determine whether, in fact, there is a role for duloxetine in chronic pain management.

ASSOCIATION BETWEEN DEPRESSION AND PAIN

The association between depression and pain is, at best, blurred. The tendency to report somatic symptoms, including pain, is a feature frequently encountered among depressed patients. Conversely, depression often accompanies and complicates the chronic pain condition. It is conceivable that dysregulation of neurotransmitter systems common to depression and pain mediation underlies both entities.[6,7]

For patients with chronic pain, depression is often a complicating comorbid condition. Clinical depression, or depressive symptoms, can emerge as a reaction to the chronicity of the painful condition, the disability associated with the painful condition, the loss of perceived self-efficacy arising from the pain and disability, the strained relationships emerging from the disabling conditions, and the reaction to having received a diagnosis of a chronic debilitating disorder.[7]

The presence of comorbid depression in chronic pain states can complicate the afflicted individual's course of illness and adaptation as well. Depressed patients with acute or chronic pain tend to rate their pain severity higher than those without depression,[8] termed as *pain scale augmentation*. The mere presence of an underlying depression can color pain patients' perceptions of their condition, prognosis, environment, and relationships. Hence,

depressed pain patients may view their condition as unremitting, that no self-initiated activity can restore reasonable functioning, that others lack understanding for them, and that their expectations of care often exceed what is optimally available.

While the goal of treatment of chronic pain states may not entirely involve cure, efforts can be directed at mitigating pain in quality and quantity, improving adaptive functioning and pursuit of normally pleasurable activities and relationships. As a result, it has become customary to invoke the use of antidepressants as part of the treatment for several chronic pain disorders. On the one hand, antidepressants may offer an indirect pain-mitigating effect by reducing the comorbid depressive (and anxiety) symptoms that may lead to exacerbations of pain-and/or perceptions of increased severity associated with pain. On the other hand, some antidepressants have direct pain-mitigating effects, independent of effects on mood. In addition, antidepressants can also function to improve or restore sleep and appetite that may have otherwise been disturbed by the chronic pain disorder.

OVERVIEW OF EFFICACY OF ANTIDEPRESSANTS IN THE MANAGEMENT OF PAIN

The efficacy of some antidepressants in the treatment of chronic pain patients has been supported in the literature by demonstrations of pain reduction among non-depressed pain sufferers.[9] Among depressed pain patients, antidepressants can produce analgesia faster and at doses far lower than those required for antidepressant effects.[10] Hence, direct pain-mitigating effects arise from something other than the antidepressant effects of these medications.[10]

Pain is transmitted from peripheral sites along 2 sets of afferent nerves, i.e., the A delta and C fibers, which in turn synapse within the dorsal horn of the spinal cord. There, preliminary processing of the pain information is conducted before it is transmitted through ascending tracts to the thalamus and higher brain areas. Pain information, however, can be modulated by the activity of descending inhibitory fibers, passing from the brain to the spinal cord. The neurotransmitters primarily involved in the descending pathways, i.e., norepinephrine (NE) and serotonin (5-HT), act synergistically in reducing the transmission of pain information from the periphery to the central nervous system (CNS).[11–13] Analgesia produced by antidepressants is thought to be mediated by enhancing the activity of NE and 5-HT present within descending pain pathways. In the spinal cord, the synthesis and release of pain-promoting neurotransmitters, e.g., substance P and glutamate, are reduced by these neurotransmitters.

The antinociceptive influence of antidepressants can involve other mechanisms.[14] Certain antidepressants may augment opiate effects within the CNS. For example, morphine analgesia is potentiated by amitriptyline, imipramine, clomipramine, fluoxetine, sertraline, and nefazodone.[15–18] On the other hand, within the brain, the antidepressants reduce the extent of limbic output which may contribute to depression and anxiety that exacerbate underlying pain. Some antidepressants, e.g., tricyclic antidepressants (TCAs), also possess a sodium-channel blockade function, which can mitigate activity of pain-relaying neurons from the CNS, e.g., in sympathetically mediated and neuropathic pain.[19]

The bulk of the evidence has been directed at the utility of TCAs in the mitigation of pain. The efficacy of TCAs appears to be related to the reuptake inhibition of NE and 5-HT. Those TCAs with a broad spectrum of activity may have greater efficacy in pain reduction than those with neurotransmitter-specific effects.[20] Thus, amitriptyline and imipramine, both of which exert prominent NE and 5-HT influences, appear to be more effective than desipramine, which has a prominent NE effect, or clomipramine, which has a prominent 5-HT effect.

Unfortunately, the adverse effects of the TCAs, e.g., dry mouth, constipation, tachycardia, orthostasis, blurred vision, can limit their utility. The tertiary amine TCAs, e.g., amitriptyline and imipramine, have more troublesome side effects than the secondary amines, e.g., nortriptyline and desipramine. TCAs would be contraindicated in patients with several conditions, e.g., those with closed-angle glaucoma, recent myocardial infarction, or cardiac arrhythmias, among others.

The SSRIs offer the advantages of greater tolerability of side effects and relative safety in overdose as compared with TCAs. The efficacy of the SSRIs and other serotonergic antidepressants has been demonstrated to be less compelling and dramatic related to pain. However, the literature on the effectiveness of SSRIs and other serotonergic antidepressants in pain is limited by the small sample sizes and small dosage ranges employed in such studies.[21] There is some question that the reduced efficacy of the SSRIs and other antidepressants with prominent 5-HT effects (e.g., trazodone and nefazodone) as compared with TCAs may be related to their serotonin selectivity. In a study examining pain reduction among patients with neuropathic pain, fluoxetine was less effective than amitriptyline and desipramine and fared no better than placebo.[20]

Venlafaxine has a broad spectrum of activity including NE and 5-HT and displays some promise with respect to efficacy in certain pain disorders.[19,22–24] It lacks significant anticholinergic side effects, but may be associated with nervousness, insomnia, weight loss, and elevations in diastolic blood pressure. Venlafaxine has fewer risks of drug interactions as compared with other agents, e.g., fluoxetine and paroxetine. If TCAs are intolerable, venlafaxine may prove to be a viable alternative for the patient with chronic pain.

Compared with other antidepressants with analgesic effects, duloxetine likewise simultaneously and directly affects noradrenergic and serotonergic neurotransmission. Such neurotransmitter influences would be expected to confer upon duloxetine a co-analgesic effect as well as its antidepressant effect. Initial animal studies have been employed to assess its pain-mitigating effects.[25,26]

EFFICACY OF DULOXETINE IN ANIMAL MODELS OF CHRONIC PAIN

There are several animal paradigms that are customarily employed to assess the pain relieving or antinociceptive effect of a medication. These include tests of introducing a long-lasting noxious/inflammatory substance, i.e., formalin, and models that simulate neuropathic pain.

In tests to simulate persistent inflammation, the agent formalin is injected beneath the footpad of an animal.[27] The formalin induces pain for approximately 1 hour, divided into 2 phases. The first of these is a relatively brief phase, lasting up to approximately 15 minutes. In this phase, animals so treated will "protect" the injected paw, elevating it, resisting the tendency to place it on the cage floor. The second phase is more persistent, lasting approximately 45 minutes, during which the animal engages in behaviors to stimulate the affected paw, e.g., shaking and licking behaviors. The first brief phase is believed to be mediated by stimulation of pain-transmitting nerve fibers, i.e., A delta and C fibers, simulating an acute pain process. The second phase, on the other hand, is believed to be related to changes within the dorsal horn of the spinal cord brought on by the barrage of activity emanating from C fibers. When assessing the antinociceptive effects of a drug in this paradigm, the observer will generally look for decreases in the frequencies of the aforementioned animal behaviors.

Rats that are administered duloxetine and subjected to formalin stimulation have reduced phase 2 activity, as measured by the reduced frequencies of paw elevations and licking and shaking behaviors. This effect appeared to be dose dependent, with greatest effects notable at higher doses, e.g., 20 mg/kg, as compared with lower doses, e.g., 3 or 10 mg/kg.[25,26] The serotonin-specific agent paroxetine did not result in any significant reductions in pain-related behaviors, whereas other antidepressants, e.g., amitriptyline, duloxetine, and venlafaxine, did. Comparatively, the effect of reducing pain-related behaviors was greatest with duloxetine. The effect observed with duloxetine was not attributable to other drug influences, e.g., motor impairments that interfere with the aforementioned behavioral measures and could potentially be misinterpreted as an antinociceptive effect. Amitriptyline, on the other hand, did impair the rats' motor abilities.[25,26]

Animal models of neuropathy are somewhat more complex. Such maneuvers require ligation of a spinal nerve, and after a few days of recovery, testing the animal's responsiveness to non-noxious tactile stimulation, i.e., referred to clinically as *allodynia*. An analogous situation in humans would be painful burning sensations that arise in the leg of a patient with neuropathy with non-noxious sensation, e.g., pulling clothing on or off. The tactile stimulation of the skin receptors of the affected neuropathic nerve distribution is interpreted within the CNS as painful. Again, duloxetine reduced pain-related behaviors in rats subjected to tactile stimulation after L5–L6 spinal nerve ligation. While venlafaxine (at 100- and 300-mg/kg doses) demonstrated an effect on reducing allodynia in the affected rats, the duloxetine effect was achieved at comparatively lower doses, e.g., 30 mg/kg.[25]

LIMITATIONS OF CURRENT STUDIES ON PAIN REDUCTION USING DULOXETINE

Despite the preliminary evidence obtained from animal models of pain, no studies have thus far demonstrated analgesic efficacy among chronic pain patients using duloxetine. Rather, the data presented to date have focused on the efficacy of duloxetine among depressed patients who also manifest somatic (albeit pain) complaints. Researchers requested that patients rate pain severity throughout the course of treatment with duloxetine, much as would be done in conventional pain research assessing the efficacy of a potential analgesic agent, suggesting that depression and pain relief were simultaneously achieved.[3–5]

So as to avoid the pitfalls of overgeneralizing the efficacy of duloxetine in pain mitigation, one must be clear about which clinical population has been the focus of investigation. There is a vast difference between demonstrating reduced pain ratings after duloxetine treatment in patients with chronic pain, who may or may not be clinically depressed, and reducing "pain" complaints in somatizing depressed patients. Depression severity was measured using the Hamilton Rating Scale for Depression (HAM-D).[3–5] While this is a reasonable standard for the assessment of depression in clinical trials, it should be recognized that selected items within the HAM-D assess somatic concern (i.e., hypochondriasis) and pain complaints.[28,29] The latter in particular require that the investigator assess the extent to which the patient experiences symptoms such as "heaviness, backache, headache, and muscle ache." Therefore, more severely depressed patients would, by virtue of the manner in which the HAM-D is set up, endorse such symptoms.

Somatic complaints frequently accompany the symptom profiles of patients with major depression.[30–32] In one series, 69% of depressed patients reported only physical symptoms as the reason for seeking out medical care.[33] Common physical symptoms encountered among depressed patients include fatigue, asthenia, sleep and

appetite disturbances, constipation or other gastrointestinal problems, headache, and other nonspecific pain complaints.[34]

Sometimes depressed patients focus on somatic concerns to deny or disavow psychological distress. Because of fear of the perception that they are emotionally "weak" or ineffective at coping, the tendency to somatize may offer a face-saving mechanism to the individual seeking medical care. The depressed patient may be prone to a hypochondriacal focus on every sensation within their bodies. The presence of depression may predispose one to interpret the significance of the somatic sensations negatively, i.e., as signaling some pathologic state.[35] Thus, in distress, such patients may seek out the assistance of their primary care physicians. Somatic concerns may serve to legitimize the depressed person's behaviors, e.g., one's decline in interests or self-care, which can accompany the depressed state.

In the studies conducted to date, the nature of the pain complaints was never established or clarified, nor was there any attempt to define the etiology of the pain.[3–5] The categories of pain employed in these studies were extremely broad, e.g., "overall pain," "headache," "back pain," and "shoulder pain." It is never clear if these broadly classified pain complaints represent an epiphenomenon of the depression or if these reflect acute, chronic, or recurrent painful conditions. For example, among those with "headache," it is unknown if these were patients who experienced head and neck tension by virtue of the prevailing depression, and/or the headache constituted a disorder such as tension headache, migraine, or mixed-headache types. Thus, the experimental measures employed leave unanswered the question of whether one is measuring pain relief from a physical condition, or if one is measuring a reduction in somatic preoccupation accompanying relief of an underlying depression.

In addition, one must question the construct validity of pain instruments employed, i.e., whether the instrument measures what was intended or implied. Researchers requested that depressed subjects rate subjective pain severity using a visual analogue scale (VAS).[3–5] The VAS consists of a single 10-cm line, with anchors of "no pain" and "pain as bad as it could be." The subjects place a mark along the line, designating where they perceive their pain would be along the continuum between the 2 anchors. The measured distance (in mm) of the subjects' mark from the "no pain" anchor comprises the numeric value or score for the patient's pain rating used in statistical analysis.

While useful in a number of clinical and empirical settings,[36,37] ratings on the VAS can be subject to misinterpretation. The VAS, while brief and easy to administer and score, equates "pain" with a unidimensional experience. Because pain is a subjective experience, it is unclear whether a given subject is rating pain intensity, affective coloring (e.g., dysphoria) associated with the pain, or even cognitive appraisals (e.g., hopelessness) associated with the pain experience.

Since somatic complaints can occur within the context of depression, and apart from an actual diagnosable physical disorder, the use of the VAS as employed in the studies thus far cannot be said to intrinsically measure pain severity. Rather, the changes in the scores on the VAS during duloxetine treatment might only reflect the relief of psychological distress achieved with duloxetine. In other words, when the depression improves as a result of duloxetine treatment, there is a commensurate reduction in the somatic concerns that previously accompanied the depression. Such an effect should not be erroneously ascribed to intrinsic analgesic effects.

DISCUSSION

Patients most commonly present to physicians with complaints of pain.[38] When the pain has no clear etiology, or when the complaints of pain exceed what is expected given the nature of the underlying physical source, psychological factors are often invoked to explain the patient's complaints. The well-meaning clinician may attempt to address the pain by prescribing a psychotropic agent. Given the manner in which the current premarketing literature presents the efficacy of duloxetine, it appears that the antidepressant would become a popular treatment option with large commercial implications.

There is evidence that agents comparable to duloxetine demonstrate an analgesic effect. Antidepressants with 5-HT and NE effects fare better than those with either neurotransmitter influence alone.[20] While animal studies suggest duloxetine's antinociceptive effect,[26,27] it is not clear how this generalizes to chronic pain in humans. Given that duloxetine exerts simultaneous influences on both 5-HT and NE, it is expected that duloxetine may demonstrate promise with regard to the treatment of depression and depression associated with chronic pain and may even exert some analgesic effect. However, at this juncture, no human investigations have established a clear, unequivocal direct analgesic effect produced by duloxetine.

The studies described herein are the first attempts to systematically assess changes in somatic symptoms in depression using an antidepressant. Comparable assessments have not been systematically conducted employing other antidepressants. It is not yet clear, therefore, whether the reduced tendency to somatize among depressed patients treated with duloxetine actually represents a unique indication or pharmacologic feature.

Duloxetine may, nonetheless, be a reasonable consideration for use among chronic pain patients with comorbid depression. It has a safety and tolerability profile that makes it desirable. Adverse effects most commonly asso-

ciated with its use include nausea, dry mouth, and somnolence.[3] It may, therefore, bypass some of the intolerable effects limiting the usefulness of other agents, e.g., TCAs. It may also be of benefit in those chronic pain patients who, by virtue of their comorbid depression, may tend to be so somatically preoccupied as to rate pain more severely.

On the basis of the available data, it is impossible to separate out any analgesic effects of duloxetine from its antidepressant effects. In order to establish any direct analgesic efficacy of duloxetine, it is imperative that patients with pain be studied. Pain conditions would need to be carefully defined. Ideally, homogeneous comparison groups would be employed, e.g., patients with migraine or patients with diabetic neuropathy. Demonstrating the utility of duloxetine in pain reduction ratings among nondepressed subjects with painful conditions would, perhaps, be most compelling. While there will always be vicissitudes in pain ratings contingent on the day-to-day mood fluctuations of being in chronic pain, use of a nondepressed population as suggested here would remove the potential confounds of pain ratings being influenced by a major psychiatric disorder.

In addition, it becomes critically important that measures employed to assess pain severity, or its relief, have construct validity. Thus, the measure, whether it is the VAS or, preferably, a multidimensional pain assessment instrument, should specifically measure pain reduction and not the affective and cognitive meaning of the pain. The essential element, however, would be to demonstrate that the pain-mitigating effect of duloxetine is uninfluenced by the alleviation of the mood disorder. This potential confound might be controlled by employing duloxetine in doses suboptimal for producing an antidepressant effect and determining if pain reductions are observed. In addition, changes in pain ratings would have to be temporally correlated with any observed reductions in depression severity. Statistical analyses, e.g., path analysis and stratification, may help to demonstrate the independence of duloxetine's effects on mood versus pain.

If analgesia is demonstrated with duloxetine use, it may be possible to assess the range of painful physical conditions that are responsive to duloxetine. If an analgesic effect is demonstrated, research endeavors would be required to assess whether duloxetine-associated analgesia is dose dependent, whether there is a ceiling dose for duloxetine beyond which no additional analgesia can be achieved, and whether analgesia correlates with serum duloxetine levels.

Drug names: amitriptyline (Elavil and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), nefazodone (Serzone), nortriptyline (Aventyl, Pamelor, and others), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

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