The Role of Duloxetine in the Treatment of Depression and Associated Painful Physical Symptoms

Sir: The recent article by Leo and Barkin[1] raises a number of interesting questions concerning the role of antidepressants in the treatment of painful physical symptoms associated with depression and the treatment of pain in nondepressed patients. The authors focus on published data for the antidepressant duloxetine and set out to determine "whether, in fact, there is a role for duloxetine in chronic pain management."[1(p118)] We wish to reply to the points raised in the article, clarify some of the statements made by the authors, and add new data that were not in the public domain at the time of submission of the article.

Collectively, these new results support the following conclusions: (1) duloxetine is an antidepressant that effectively treats painful physical symptoms in depressed patients[2–4]; (2) alleviation of painful physical symptoms in depressed patients significantly increases these patients' probability of achieving remission[5]; (3) approximately 50% of duloxetine's effect on pain in depressed patients occurs independently of changes in core emotional symptoms of depression (M. Fava, M.D.; C. H. Mallinckrodt, Ph.D.; M.M.W., et al., manuscript submitted); and (4) duloxetine effectively treats pain associated with diabetic neuropathy in nondepressed patients.[6]

First and foremost, duloxetine is an effective antidepressant. While some studies have investigated duloxetine's efficacy in pain states, the primary focus of our clinical development program has been the treatment of major depressive disorder (MDD). Results from double-blind, placebo-controlled studies,[2–4,7] in addition to a long-term, open-label study,[8] have established duloxetine as a safe and effective treatment for MDD. Leo and Barkin state that "its [duloxetine's] efficacy in reducing severity of depression . . . is comparable to that of antidepressants of the selective serotonin reuptake inhibitor (SSRI) class, e.g., paroxetine and fluoxetine."[1(p118)] In fact, an analysis of pooled data from comparator-controlled studies has shown that, in patients with a baseline 17-item Hamilton Rating Scale for Depression score of ≥ 19, remission rates for duloxetine are significantly higher than those for the SSRI comparators paroxetine and fluoxetine.[9]

Duloxetine is a balanced and potent reuptake inhibitor of both serotonin and norepinephrine. In addition to their role in the neurobiology of depression, these neurotransmitters act as pain modulators in the descending pain pathways of the spinal cord.[10] In placebo-controlled studies, duloxetine has demonstrated efficacy in the treatment of painful physical symptoms in depressed patients, as assessed using visual analog scales for pain.[2–4]

The authors correctly state that in the studies conducted to date, the nature of the pain complaints was not established, nor was the etiology of the pain. Patients were required to meet DSM-IV criteria for MDD, but were not screened for the presence or severity of pain. The rationale behind this was straightforward. The clinical studies were designed to investigate the efficacy and safety of duloxetine in the treatment of MDD and associated painful physical symptoms. Our intent was not to study chronic pain with comorbid depression, as implied by the authors.

We agree with Leo and Barkin that the relationship between pain and depression is complex and is not fully understood. Pain complaints, such as headache, back pain, and diffuse musculoskeletal pain, are common in depressed patients[11] and have an incidence similar to that of anxiety symptoms.[12] Higher baseline pain severity among depressed patients has been associated with an increased risk of antidepressant treatment failure.[13] These painful physical symptoms represent an important component of depressive illness, and their successful treatment may be expected to facilitate a patient's return to normal functioning, as would the treatment of other symptoms of depression (e.g., depressed mood, anhedonia, anxiety, sleep and appetite disturbance). However, it is commonly believed that antidepressants exhibit no direct effect on pain. Improvements in pain severity brought about by antidepressant treatment are often regarded as merely a secondary, or pseudospecific, effect resulting from improvement in the depressive illness as a whole. In contrast, results obtained during clinical trials of duloxetine support its direct effect on pain in both depressed and nondepressed patients and demonstrate the importance of effective treatment of painful physical symptoms associated with depression.[2,3,5,6]

The authors suggest that "statistical analyses, e.g., path analysis . . . may help to demonstrate the independence of duloxetine's effects on mood versus pain."[1(p122)] We have performed a path analysis on pooled data from 2 clinical trials of duloxetine (60 mg q.d.) and demonstrated that approximately 50% of the improvement in pain severity in depressed patients is directly attributable to duloxetine treatment and occurs *independently* of improvement in depressive symptoms (M. Fava, M.D.; C. H. Mallinckrodt, Ph.D.; M.M.W., et al., manuscript submitted). Leo and Barkin consider such an analysis to be an "essential element" toward demonstrating the pain-mitigating effect of duloxetine.

Furthermore, if improvements in pain severity were simply a secondary result of improvement in overall depressive symptoms, it would be expected that the temporal course of changes in pain severity would be similar to, or possibly lag behind, changes in core mood symptoms. However, in our studies, the time course for improvement in painful physical symptoms is, if anything, more rapid than for improvement in core emotional symptoms.[14]

If painful physical symptoms truly represent an important component of MDD, it may be expected that the alleviation of these symptoms should contribute to a patient's recovery from depressive illness and thereby influence the probability that a patient will achieve remission. To further investigate this concept, we studied pooled data[5] from 2 clinical studies of duloxetine (60 mg q.d.). Results from these analyses demonstrated that improvement in pain severity was associated with an increased probability of achieving remission even after accounting for improvement in core emotional symptoms of depression.[5] These data are clearly inconsistent with Leo and Barkin's assertion that duloxetine may simply produce "a reduction in somatic preoccupation accompanying relief of an underlying depression."[1(p121)]

In their discussion, the authors state that "on the basis of the available data, it is impossible to separate out any analgesic effects of duloxetine from its antidepressant effects."[1(p122)] They propose that "demonstrating the utility of duloxetine in pain reduction ratings among nondepressed subjects with painful conditions would, perhaps, be most compelling" and, in particular, in a "homogeneous comparison group . . . e.g., . . . patients with diabetic

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neuropathy."[1(p122)] The results of just such a study have been presented recently.[6] In this 12-week double-blind, placebo-controlled study, duloxetine doses of 60 mg q.d. and 60 mg b.i.d. were significantly superior to placebo in alleviating pain associated with diabetic neuropathy in nondepressed patients. Efficacy was demonstrated on both the primary measure (the weekly mean of the 24-Hour Average Pain Score) and several secondary measures (including Brief Pain Inventory pain severity and interference items).

We hope that the additional results discussed here will clarify the role of duloxetine in the treatment of MDD and the painful physical symptoms associated with depression. Furthermore, while Leo and Barkin assert that "[duloxetine's] analgesic role has yet to be elucidated in future research,"[1(p118)] these results provide compelling evidence that duloxetine demonstrates efficacy in the treatment of pain symptoms in both depressed and nondepressed patients.

Drs. Wohlreich and Watkin are employees of Eli Lilly.

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Dr. Leo Replies

Sir: One would naturally question the suggestion that an analgesic, e.g., acetaminophen or an opiate, that reduces pain severity in a patient with chronic pain, and thereby reduces the patient's dysphoria, would be implied to have an antidepressant property. It is in this context that the article by Leo and Barkin was written.[1]

To summarize, Leo and Barkin advise readers that studies assessing the efficacy of duloxetine among patients with major depressive disorder who are simultaneously somatically preoccupied does not necessarily imply an analgesic role of duloxetine. Use of a standard pain assessment instrument, such as the visual analog scale (VAS),[2] in somatizing depressed patients is misleading. The VAS, a single-dimension pain-rating measure, is influenced by the vicissitudes of the rater's affect, prevailing mood, cognitions, and expectations. Each of these can be altered by the presence of a major depressive disorder, thereby leading to a magnification of pain severity ratings. Reduction in VAS scores is likely to be an artifact of the improvements in mood observed when depressed patients are given duloxetine. Thus, as depression is alleviated, so too is there a reduction in the amplification of somatic symptoms. Other studies have corroborated that the degree of physical symptom improvement among depressed patients is correlated with overall reduction of depression severity.[3,4]

Obviously, researchers at Eli Lilly are in agreement. To establish an analgesic effect of duloxetine in patients with diabetic neuropathy, they made certain to remove the potential confounds of comorbid depression. It is only when such confounds are controlled in experimental paradigms that one can begin to suggest that an agent like duloxetine exerts an analgesic effect. The suggestion that analgesic effects result from the effects of duloxetine on norepinephrine and serotonin neurotransmission is an interesting model but has, as yet, to be clarified. It may have been useful to study depressed and nondepressed patients with diabetic neuropathy. In this way, it might have been possible to demonstrate differences in the reductions in pain severity ratings between the 2 groups. Perhaps greater analgesia would be attained in those with depression as compared with those who are not depressed.

There is a continuum of depressive symptoms present among patients with chronic pain. Some patients have few depressive symptoms, while others may manifest the full gamut of symptoms to fulfill diagnostic criteria for a major depressive disorder or variant, e.g., dysthymic disorder. Use of duloxetine among chronic pain patients with comorbid depression would be a welcomed addition to the current armamentarium of antidepressants available for use among such patients. It would be an added benefit if duloxetine could be demonstrated to have an analgesic effect in selected pain disorders.

Preliminary animal studies,[5] as well as a recent examination of pain-mitigating effects among patients with diabetic neuropathy[6] (published after the submission of the 2003 Leo and Barkin article), suggest that duloxetine may have a role in pain management. However, many antidepressants and anticonvulsants have likewise demonstrated efficacy in neuropathy. Future research would be helpful in clarifying those patient subpopulations for whom duloxetine would be the preferred agent among the alternatives currently available. It may be possible to demonstrate the role of duloxetine in patients who have neuropathic pain with certain characteristics, e.g., dysesthetic or burning features, or certain neurovegetative symptoms of depression.

Dr. Leo reports no financial affiliation or other relationship relevant to the subject matter of this letter.

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