Efficacy and Tolerability of Duloxetine, a Novel Dual Reuptake Inhibitor, in the Treatment of Major Depressive Disorder

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Although highly selective antidepressants such as the selective serotonin reuptake inhibitors represent an advance over older drugs with respect to tolerability, they are not more effective than previous agents. Antidepressants that enhance transmission in more than one monoamine system may have greater efficacy than highly selective drugs, while equaling or improving their adverse effect profiles. This article reviews the properties of duloxetine, a potent and balanced inhibitor of norepinephrine and serotonin reuptake. Controlled studies indicate a high degree of efficacy, tolerability, and safety for duloxetine in the treatment of major depressive disorder. In particular, rapid therapeutic onset and high remission rates have been noted. Duloxetine appears to have significant benefit in the treatment of the painful physical symptoms associated with depression. The continued presence of such symptoms may predict relapse. Accordingly, it is hoped that duloxetine therapy may reduce the likelihood of depressive relapse. *(J Clin Psychiatry 2003;64[suppl 13]:30–37)*

SELECTIVE DUAL REUPTAKE INHIBITORS IN THE TREATMENT OF DEPRESSION

The previous decade witnessed the ascendance of antidepressant agents developed for their relative selectivity. This group of drugs, which includes the selective serotonin reuptake inhibitors (SSRIs) and various relatively selective atypical agents such as nefazodone, has largely supplanted its predecessors due to more favorable side effects. These second-generation agents generally lack the anticholinergic and cardiovascular effects of the tricyclic antidepressant (TCA) class, and they are much less likely to be toxic in overdose. They are also free of the dietary restrictions imposed by the monoamine oxidase inhibitors (MAOIs), which carry the risk of potentially lethal hypertensive crisis when combined with tyramine-containing foodstuffs.

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Nonetheless, the shortcomings of the selective second-generation agents have become increasingly clear. First, they are not generally more efficacious in relieving the symptoms of major depressive disorder (MDD) than are earlier antidepressants, and in fact may be less effective than some members of the TCA class, especially in severely depressed patients or patients with atypical depression.[1] SSRIs seem to have little effect on some symptoms commonly seen in depression, particularly pain and other physical complaints. This is important, given that incomplete symptom remission in MDD is associated with a higher probability of relapse.[2,3] Furthermore, as with the older drugs, therapeutic effects require 2 to 4 weeks to become evident. Finally, the more selective drugs, while safer than their predecessors, are not without their own characteristic adverse effects, most notably the sexual dysfunction that is associated with SSRIs—an effect that may or may not be transient.[4] Another effect associated with long-term SSRI treatment is an apathy syndrome marked by emotional blunting and decreased motivation.[5]

As the shortcomings of the second generation of agents have become apparent, attempts have been made to develop antidepressants that combine the therapeutic range of the less selective TCAs and MAOIs with the safety profiles of the SSRIs and have a rapid onset of therapeutic action. Some newer agents have been developed on the principle that a broader spectrum of activity may lead to increased efficacy. Some studies indicate that clomipramine may be more effective than paroxetine or citalopram.[6,7] Other investigators have provided preliminary evidence that serotonergic-noradrenergic polypharmacy

may be effective in refractory depression.[8,9] A group of newer drugs, the selective serotonin-norepinephrine reuptake inhibitors (SNRIs), constitute a form of "intramolecular polypharmacy"[10] that potentially offers a faster onset of therapeutic action,[11,12] improved efficacy,[12] and ultimately, perhaps, greater tolerability than antidepressants that inhibit only one monoamine reuptake system. Among these dual reuptake inhibitors are venlafaxine, introduced in 1993 in the United States; milnacipran, approved in Europe and Japan; and duloxetine (Eli Lilly and Company, Indianapolis, Ind.), which is in advanced clinical trials in the United States.

COMPARATIVE PHARMACOLOGY OF DULOXETINE

Duloxetine is the most potent and the most balanced of the dual reuptake inhibitors. Milnacipran has a relatively greater affinity for norepinephrine (NE) than serotonin (5-HT) reuptake transporters, while the reverse is true for venlafaxine.[13] A study of the binding properties of duloxetine to human NE and 5-HT transporters in vitro found inhibition constant (K_i) values of 7.5 nM and 0.8 nM, respectively, with a K_i ratio of 9.[14] In contrast, the corresponding values for venlafaxine were 2480 nM and 82 nM, with a K_i ratio of 30. This indicates both greater potency of blockade for both types of transporters, as well as a more balanced binding profile for duloxetine relative to venlafaxine. Indeed, at lower doses (below 150 mg daily), venlafaxine's activity is confined to 5-HT reuptake inhibition; doses above this range, perhaps as high as 375 mg daily, are required for significant NE reuptake blockade.[11,15,16] Venlafaxine appears to be more effective than the SSRIs and to have a faster onset of therapeutic action, but these benefits may be more pronounced at higher dosages, when there is presumed dual reuptake inhibition.[12,17,18] Studies in which no advantage was shown for a dual reuptake inhibitor like venlafaxine relative to SSRIs may have been due to inadequate dosing of the latter.[19] The likelihood of adverse effects with venlafaxine treatment also increases with dose. Higher doses (generally above 225 mg/day) yield effects consistent with NE potentiation, in particular, blood pressure elevation, necessitating regular monitoring.[20] At lower doses, adverse effects are similar to those of the SSRIs, although some of these, such as nausea, may initially be more pronounced with venlafaxine therapy.[21] These effects may be managed by slow titration.[15]

In contrast, duloxetine's balanced effects on the NE and 5-HT systems suggest a broader spectrum of therapeutic efficacy even at low doses, with the possibility of a near-immediate onset of therapeutic effects. In addition to potent reuptake blockade in these systems, duloxetine is also a weak inhibitor of dopamine reuptake.[22] It has little affinity for muscarinic cholinergic, H_1, α_1, β_1, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, D_2, and opioid receptors.[23] Its pharmacokinetics have been shown to be linear in an escalating multiple-dose study, in which healthy male subjects were administered a starting dose of 20 mg twice daily, which was increased to 30 mg twice daily and then 40 mg twice daily, at weekly intervals. Duloxetine was associated with small but statistically significant increases in both systolic and diastolic recumbent blood pressure, although there was no clear dose-response relationship. A slight decrease in recumbent heart rate and a nonsignificant increase in standing heart rate were also observed. Adverse effects, consisting largely of somnolence, nausea, and dry mouth, were mild and transient.[22]

DEFINING RESPONSE AND REMISSION IN CLINICAL STUDIES OF DEPRESSION

The importance of clearly specified acceptable outcomes in evaluating antidepressant clinical trials is increasingly appreciated because of the developing consensus that the explicit goal of antidepressant therapy should be complete symptom remission rather than partial response.[24] Many patients are treated only to less stringent criteria, and several recent investigations point to the presence of residual symptoms as a predictor of relapse. Such symptoms constitute not only an inconvenience to the patient but also a continuation of the depressive episode, which may easily regain its former severity.[2,3] Paykel and colleagues[3] found that patients who met remission criteria but nonetheless had residual symptoms were 3 times more likely to relapse (76% relapse rate) than patients whose recovery was complete (25% relapse rate). Relapse to another major depressive episode occurred 3 times faster when residual symptoms were present than when recovery was complete.[2] Only the presence of lingering symptoms, and not their severity, predicted relapse. Future treatment responsiveness may also be affected when full recovery is not achieved.[10] Accordingly, it is extremely important to specify what criteria constitute remission so that effective treatment decisions may be made.

Response is generally defined as a decrease in pretreatment depression score, typically measured by the 17-item version of the Hamilton Rating Scale for Depression (HAM-D-17), of 50% or more. One problem with this definition is that a patient with a high baseline score may have significant residual symptomatology.[25] A patient who improves only to this level after several weeks of treatment requires a change of regimen.[26]

Full remission suggests a return to premorbid functioning, but this outcome must be further quantified. A criterion often selected in evaluating new therapies is a HAM-D-17 score equal to or less than 7. Again, even with this measure, residual symptoms may be present, including symptoms that are not generally considered to be core features of depression such as irritability or pain and thus

are not tracked.[25] In addition, the period of minimal or no symptoms must be maintained for a significant length of time before it can be considered to signify recovery. A period of as much as 8 weeks has been proposed as an appropriate interval to maintain remission following an initial episode of depression and is commonly selected as an outcome measure in clinical trials.[25] Other authors suggest that remission should be maintained for 6 months before a patient can be considered recovered and that pharmacotherapy should be continued throughout this period, or longer.[27,28]

RESPONSE AND REMISSION RATES IN TRIALS OF ANTIDEPRESSANT EFFICACY

Issues of outcome definition and instrument selection comprise only one set of factors complicating the interpretation of response and remission rates across studies of antidepressant efficacy. Characteristics of the patient population under study also influence outcomes, as does study design. Nonetheless, attempts have been made to estimate the relative effectiveness of different antidepressant classes. A very recent attempt to establish overall placebo response rates in antidepressant trials examined data from trials carried out since 1981.[29] Response was defined using the criterion of a greater than or equal to 50% symptom reduction on the HAM-D. Rate of response to placebo was approximately 30% overall; rate of response to any active antidepressant was approximately 50%, with similar rates reported for TCAs (46.9%) and SSRIs (48.9%).[29]

Response and remission rates may be higher relative to placebo with dual reuptake inhibitors such as venlafaxine. A meta-analysis of remission rates in 8 controlled studies comparing venlafaxine, an SSRI, and placebo revealed rates of 45%, 35%, and 25%, respectively. Rates of remission, defined as a HAM-D-17 score of less than or equal to 7, were all significantly different from each other ($p < .001$).[12]

It is worthwhile to underscore the point that these rates are meaningful only insofar as the instruments used to assess depressive symptomatology actually track relevant symptoms. Since physical symptoms are not extensively queried on inventories of depressive symptoms, changes in these symptoms may not be adequately reflected in published response and remission rates.

CLINICAL STUDIES OF DULOXETINE

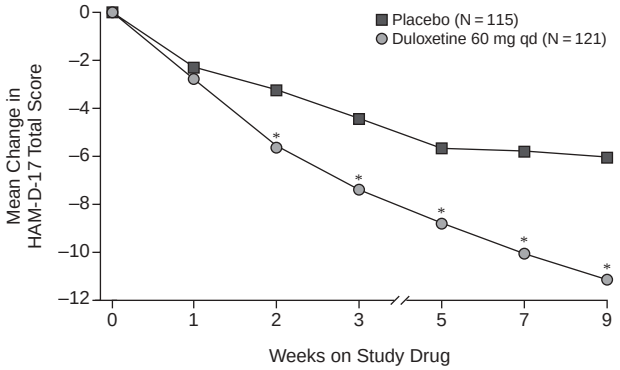
Three multicenter, double-blind, controlled studies of the efficacy, safety, and tolerability of duloxetine in patients with MDD have been reported. In a phase II proof-of-concept, 8-week, parallel-group study, patients with HAM-D-17 scores of at least 15 received duloxetine administered on a twice-daily dosing schedule (N = 70), fluoxetine 20 mg daily (N = 33), or placebo (N = 70). The underpowered fluoxetine arm of the study was included for purposes of qualitative comparison.[23] The starting dose of duloxetine was 20 mg twice daily; the daily dosage was titrated in 40-mg increments at intervals of no less than 1 week, to the target dose of 120 mg daily (administered as 60 mg twice daily). The primary efficacy measure was the HAM-D-17; secondary measures included the Montgomery-Asberg Depression Rating Scale, the Clinical Global Impressions-Severity of Illness scale (CGI-S), the Patient Global Impressions-Improvement scale (PGI), and the Hamilton Rating Scale for Anxiety (HAM-A).

The HAM-D-17 scores in duloxetine-treated patients declined significantly more across the 8-week period than did the scores in placebo-treated patients ($p < .009$); a significant difference between these groups was apparent by week 4 ($p < .049$). The duloxetine-treated group showed significant improvement versus placebo on all secondary measures as well, except for the HAM-A total score and the sleep subscale of the HAM-D-17. However, duloxetine-treated patients showed significant improvement relative to placebo on all other HAM-D-17 subscales, including the anxiety subscale. Estimated response rates after 8 weeks of treatment were 48%, 64%, and 52% for placebo, duloxetine, and fluoxetine, respectively, and did not differ significantly. Estimated probability of remission was significantly greater for duloxetine (56%) than for placebo (32%) and fluoxetine (30%). Discontinuation rates were nearly identical for all 3 groups; there were no significant differences between rates of discontinuation due to adverse events. However, significantly more patients taking placebo than duloxetine discontinued due to lack of efficacy. Among reported adverse events, only insomnia and asthenia were significantly more frequent with duloxetine than placebo.

Duloxetine had small, clinically insignificant effects on vital signs and body weight. Three measurements differed significantly from placebo: recumbent heart rate was 3.49 beats per minute greater in duloxetine-treated patients ($p = .042$); standing diastolic blood pressure was 2.80 mm Hg greater in duloxetine-treated patients ($p = .041$); and body weight decreased by 0.59 kg (1.31 lb) in duloxetine-treated patients ($p = .005$).

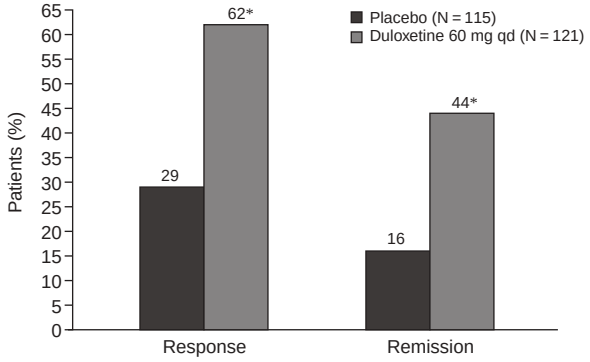
This preliminary controlled investigation clearly suggested efficacy of duloxetine in the treatment of depression and demonstrated the favorable cardiovascular profile of duloxetine. The small effects noted on blood pressure and heart rate are consistent with NE potentiation but are clinically insignificant. Several points are worth underscoring. First, the estimated response and remission rates (64% and 56%) for duloxetine were higher than those noted in many antidepressant trials and were numerically superior to fluoxetine. However, it is difficult to interpret the fluoxetine data in light of the small sample size of this patient group and dose used. Furthermore, response and remission rates were surprisingly high for placebo (48% and 32%) and, in fact, differed little from those for fluoxetine.

Figure 1. Mean Changes in HAM-D-17 Total Scores for Patients Treated With Once-Daily Duloxetine or Placebo[a]



[a]Adapted with permission from Detke et al.[32] HAM-D-17 scores of patients treated with duloxetine were significantly lower than those of placebo-treated patients by week 2.
*Duloxetine vs. placebo ($p < .001$).
Abbreviation: HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

Figure 2. Response and Remission Rates in Patients Treated With Once-Daily Duloxetine or Placebo[a]



[a]Data from Detke et al.[32] Based on mixed-effects model repeated-measures analysis. Estimated probability of response determined by last-observation-carried-forward analysis: placebo (23%) and duloxetine, 60 mg q.d. (45%; $p \leq .001$ vs. placebo). Estimated probability of remission: placebo (15%), duloxetine, 60 mg q.d. (31%; $p \leq .001$ vs. placebo).
*Duloxetine vs. placebo ($p \leq .001$).

In another controlled study, the effects of 80 mg daily of duloxetine (administered as 40 mg twice daily) were compared with 40 mg/day of duloxetine (administered as 20 mg twice daily), paroxetine at 20 mg/day, and placebo. Both dosages of duloxetine and paroxetine separated from placebo in efficacy. The higher dose was also significantly more effective than paroxetine.[30] Estimated rates of remission in this study were 57% for duloxetine-treated patients—a figure nearly identical to that obtained in the previous study[23]—again suggesting considerable antidepressant efficacy for duloxetine, even at a dose one third less than that previously investigated. Other findings were consistent with those of the previous study, with duloxetine-treated patients demonstrating superior improvement relative to placebo on a number of outcome measures, including the PGI and CGI. Of particular interest is the finding that duloxetine was associated with significant reductions in painful physical symptoms as measured by item 13 of the HAM-D-17. This finding is intriguing because of the frequency with which pain and other physical symptoms are reported by depressed patients. It is also in keeping with findings indicating that antidepressants with effects on more than one monoamine system, for example, serotonergic-noradrenergic tricyclics such as amitriptyline and imipramine, are more effective analgesics than are agents with more purely serotonergic or noradrenergic effects.[31] Finally, the side effect profile of duloxetine was similar to that noted in the previous study, with nausea as the most frequently reported adverse event. Consistent but small decreases in body weight were also observed in this study. Most importantly, there were no clinically significant cardiovascular effects associated with duloxetine.

The study that to date best demonstrates the therapeutic promise of duloxetine has been recently reported by Detke and colleagues.[32] This study was designed to test the efficacy of once-daily dosing—a regimen preferable to divided dosing, since simpler regimens tend to enhance patient compliance.[33] Another rationale for such a dosing schedule is the fact that duloxetine, like other drugs that penetrate the blood-brain barrier, may persist in central nervous system tissues longer than would be suggested by its 12-hour half-life in plasma.[34,35] Another extremely important feature of the study design was the addition of visual analogue scales (VAS) for pain to the protocol as a secondary efficacy measurement to investigate the effects of duloxetine on the physical symptoms of depression.

Patients diagnosed with MDD according to DSM-IV criteria were randomly assigned to receive placebo (N = 122) or duloxetine 60 mg once daily (N = 123) for 9 weeks. For patients on active medication, starting dosage was 60 mg; it could be reduced to 40 mg if necessary but had to be escalated back to 60 mg within 3 weeks. The primary efficacy measure was the HAM-D-17; secondary measures included the CGI, PGI, and Quality of Life in Depression Scale, as well as the VAS.

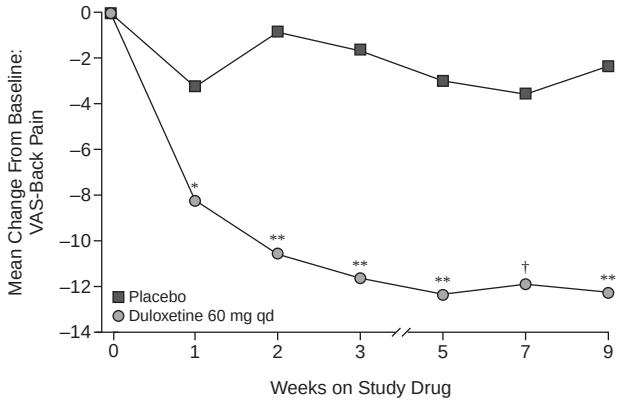
The duloxetine-treated group demonstrated a robust antidepressant effect relative to placebo. The HAM-D-17 scores of these patients were significantly lower than those of placebo-treated patients by the end of the second week following randomization ($p < .001$)—a difference that was maintained throughout the remainder of the measurement period. Figure 1 depicts the effects of placebo and duloxetine over time. Antidepressant effects were obtained regardless of baseline symptom severity, as illustrated in Figure 2. Estimated probabilities of response and remis-

Table 1. Estimated Probability of Response and Remission for Duloxetine, an SSRI, and Placebo in 3 Studies

Study	Duloxetine Dose	Duloxetine		SSRI		Placebo	
		Response (%)	Remission (%)	Response (%)	Remission (%)	Response (%)	Remission (%)
Detke et al[32a]	60 mg qd	62[b]	44[b]	…	…	29	6
Goldstein et al[23c]	60 mg bid	64	56[d]	52	30	48	32
Goldstein et al[30e]	40 mg bid	59	57	51	34	30	25

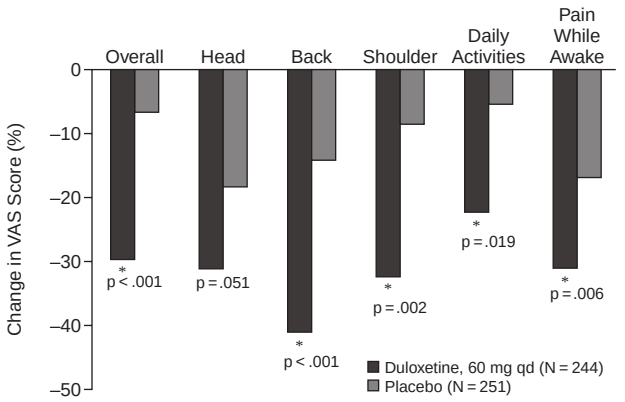
[a]No SSRI comparator drug.
[b]$p < .001$ for duloxetine vs. placebo.
[c]SSRI, fluoxetine, 20 mg q.d.
[d]$p = .02$ for duloxetine vs. placebo.
[e]SSRI, paroxetine, 20 mg q.d.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Figure 3. Mean Change From Baseline in VAS-Back Pain Scores in Patients Treated With Duloxetine vs. Placebo[a]



[a]Adapted with permission from Detke et al.[32]
*Duloxetine vs. placebo ($p = .013$).
**Duloxetine vs. placebo ($p < .001$).
†Duloxetine vs. placebo ($p = .002$).
Abbreviation: VAS = visual analogue scale.

Figure 4. Comparison of Changes in Visual Analogue Scale (VAS) Score in Patients With Painful Physical Symptoms[a]



[a]Data from Detke et al.[32,36] Data reflect percent mean changes from baseline; main effect of treatment (pooling all visits).
*Duloxetine vs. placebo ($p < .05$).

sion at 9 weeks were 62% and 44%, respectively, for duloxetine, and 29% and 16% for placebo ($p < .001$). Detke et al.[32] also reported that the remission rates using the last-observation-carried-forward method were 31% and 15% for duloxetine and placebo, respectively. These rates represent a very large relative benefit for duloxetine (more than 100% over placebo). In contrast, relative benefit computation using data from pooled analyses shows that the benefit rate for venlafaxine was 80% over placebo and for the SSRIs was 40%.[12] Response and remission rates for all 3 controlled duloxetine studies are summarized in Table 1.

Secondary outcome measures yielded similar results. The duloxetine-treated group showed significantly greater improvement on all 5 subscales of the HAM-D-17 (anxiety, core, retardation, Maier, and sleep). Significant anxiety subscore change was noted by the end of the second week of treatment. Global improvement and quality-of-life scores also improved significantly ($p \leq .001$). Significant improvement as indexed by the CGI was rapid, evident by the end of the first week of treatment. Of particular interest are the results of the pain measures: duloxetine-treated patients exhibited a significant reduction in physical symptoms (e.g., back, head, and muscle pain or ache), as measured by item 13 of the HAM-D-17, relative to placebo ($p = .013$). The VAS data extended this finding: pain scores were significantly lower at 1 or more measurement points throughout the treatment period for duloxetine-treated patients on 5 of 6 items (overall pain, back pain, shoulder pain, degree of interference of pain with daily activities, and time in pain while awake); only head pain scores were not significantly reduced with duloxetine treatment. A reduction in back pain was the largest and most persistent of these changes and is illustrated in Figure 3. On each of these items, significant differences were apparent by the end of the second week of treatment. Analgesic efficacy was independent of baseline pain severity.

The combined effects of 60-mg duloxetine therapy for various painful physical symptoms (as measured by changes in VAS scores) are presented in Figure 4.[32,36]

Duloxetine treatment proved tolerable and safe in this study, as in earlier investigations. The rate of discontinuation due to adverse events was 13.8% in the active treatment group compared with 2.5% in the placebo group. This compares favorably with discontinuation rates re-

Table 2. Pooled Data on Duloxetine: Effect on Blood Pressure[a]

Treatment	Total N	Development of Hypertension[b] N (%)
Duloxetine, mg/d		
40	174	0 (0)
60	244	2 (0.8)
80	168	2 (1.2)
120	149	1 (0.7)
Total duloxetine	735	5 (0.7)
Placebo	565	2 (0.4)

[a]Data on file, Eli Lilly and Company, Indianapolis, Ind. No statistically significant differences among the groups.
[b]Hypertension defined as 3 consecutive assessments of either systolic blood pressure ≥ 140 mm Hg and ≥ 10 mm Hg increase from baseline or diastolic blood pressure ≥ 90 mm Hg and ≥ 10 mm Hg increase from baseline.

ported in trials of TCAs and SSRIs; one meta-analysis reported rates of 19% and 14.9% for these 2 antidepressant classes.[37] The single most frequent treatment-emergent adverse event was nausea, reported by 46.3% and 9% of duloxetine-treated and placebo-treated patients, respectively, and was generally judged to be mild to moderate and transient. (This rate is considerably higher than the average rate of 21.8% that has been observed in other controlled studies of duloxetine; data on file, Eli Lilly and Company, Indianapolis, Ind.) Only 1 patient discontinued treatment for this reason. Other adverse events reported at a frequency significantly greater than placebo included various other gastrointestinal complaints, dry mouth, somnolence, and dizziness, a symptom experienced particularly during the placebo lead-out period. Finally, the small but significant decrease in body weight noted in other studies of duloxetine was observed here as well (0.76 kg [1.69 lb]).

Cardiovascular monitoring revealed similarities to effects observed in previous studies of duloxetine, such as a clinically insignificant increase in heart rate of 0.97 beats per minute. Systolic blood pressure actually declined slightly with duloxetine treatment, although the decline was significantly less than that observed in the placebo group. Diastolic blood pressure did not differ between the 2 groups. Treatment-emergent sustained hypertension developed in only 1 patient in the duloxetine group (0.8%) compared with none in the placebo group (p = NS).

CONCLUSIONS

In summary, the results of the study by Detke et al.[32] provide particularly clear evidence of the safety and efficacy of duloxetine in treating the symptoms of major depression, including physical symptoms such as pain that are often inadequately acknowledged in diagnosis and treatment and that may correlate with greater severity of depression.[38] Somatic symptoms are common residual symptoms in patients who do not achieve complete remission. Paykel and colleagues[3] noted that physical symptoms persisted in 94% of patients with residual symptoms, a large majority of whom later relapsed. Given that the presence of residual symptoms is a strong predictor of relapse, the eradication of such symptoms must be a primary goal of treatment. Longer-term studies are required to determine whether successful treatment of such symptoms with duloxetine does in fact prevent relapse.

One of the most promising aspects of these results is the fact that these patients were not selected for prominent pain symptomatology; in fact, their baseline VAS scores were quite low overall, affording little room for a treatment effect. Nonetheless, significant reductions in pain symptomatology were achieved. An obvious extension of this research is to test the efficacy of duloxetine in treating patients whose depressive symptoms consist predominantly of pain and other physical symptoms. The need for such an investigation is pressing given that many depressed patients report only such symptoms.[39]

The findings of Goldstein et al.[23] and Detke et al.[32] also support the relatively well-established idea that antidepressants that affect neurotransmission in both the noradrenergic and serotonergic descending pain pathways, such as the TCAs, are more effective in alleviating pain symptoms than are highly selective agents such as the SSRIs.[40–42] An SNRI such as duloxetine, with potent and balanced enhancement of both NE and 5-HT, may have analgesic efficacy equal to that of the TCAs. This issue requires further empirical clarification, but the preliminary findings are extremely encouraging.

The safety and tolerability profile of duloxetine as demonstrated in these studies appears to be favorable. Rates of discontinuation due to adverse events are similar to those noted in meta-analyses of SSRI discontinuation and significantly less than those reported for the TCAs. Despite its potentiation of NE, duloxetine was not associated with dose-dependent sustained hypertension, as Table 2 illustrates (data on file, Eli Lilly and Company, Indianapolis, Ind.). In contrast, a meta-analysis has demonstrated such an association with venlafaxine at higher doses (≥ 300 mg daily), which are frequently necessary to achieve clinical effectiveness.[20] Measurements of the QTc interval as well indicate a benign cardiovascular profile for duloxetine; there is no effect on this interval with duloxetine (data on file, Eli Lilly and Company, Indianapolis, Ind.), whereas a 4.7-msec QTc increase has been associated with venlafaxine, relative to a 1.9-msec decrease with placebo.[43]

The data of Goldstein and colleagues[23] indicate little adverse effect of duloxetine on sexual functioning. This is a welcome finding, given the sexual dysfunction associated with many other antidepressants. A recent study assessing rates of sexual dysfunction among newer antidepressants using the Changes in Sexual Functioning Questionnaire found similarly high rates (approximately 30%) for various SSRIs, particularly citalopram, and for venlafaxine, even among patients without risk factors for

sexual problems.[44] Open-label trials with duloxetine indicate much lower rates of spontaneously reported dysfunction (< 4%).[37] Clearly, direct query is preferable to spontaneous report, but these data in tandem with the questionnaire results of Goldstein et al.[23] suggest that duloxetine may exert fewer disruptive effects on sexual functioning than do agents with primarily serotonergic affinity.

A great advantage of duloxetine over other antidepressant medications would appear to be the rapid onset of therapeutic effects following initiation of therapy. This is particularly striking in the Detke et al.[32] study, in which patients began therapy with the target dose of 60 mg daily. Eighty-five percent of duloxetine-treated patients tolerated this dose without a temporary reduction, and significant improvements in mood and physical symptoms were apparent after 2 weeks of treatment. These benefits appeared earlier in treatment than when duloxetine was initiated at a lower dose (40 mg) for a minimum of 1 week and titrated upward.[23]

The extent to which there is a relationship between dose of duloxetine and therapeutic response remains to be determined. High rates of response and remission were noted for duloxetine with a dosing regimen of 60 mg twice daily,[23] but placebo response was unusually high in this study as well. A similar remission rate was noted with 40-mg twice-daily dosing.[30] With a regimen of 60 mg once daily, response and remission rates were lower in absolute terms; however, they were higher relative to placebo. Some evidence from a 6-week open-label study indicates efficacy at a dose as low as 20 mg daily; response and remission rates of 78% and 60%, respectively, were reported for a group of 79 patients with unipolar MDD.[45] However, in the absence of a placebo control group, these results must be viewed with caution. In any case, while 60 mg daily appears to be an optimal dose, duloxetine is tolerable and effective across a range of dosing options.

If further clinical trials support and extend these findings, duloxetine will offer important advantages in the treatment of MDD. In particular, the elusive goals of rapid treatment response and sustained improvement through more complete symptom remission may be achievable with duloxetine therapy.

Drug names: amitriptyline (Elavil and others), citalopram (Celexa), clomipramine (Anafranil and others), fluoxetine (Prozac and others), imipramine (Tofranil, Surmontil, and others), nefazodone (Serzone), paroxetine (Paxil), venlafaxine (Effexor).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, duloxetine and milnacipran have not been approved by the U.S. Food and Drug Administration for treatment of major depressive disorder.

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