The Effect of Duloxetine on Painful Physical Symptoms in Depressed Patients: Do Improvements in These Symptoms Result in Higher Remission Rates?

Maurizio Fava, M.D.; Craig H. Mallinckrodt, Ph.D.; Michael J. Detke, M.D., Ph.D.; John G. Watkin, D.Phil.; and Madelaine M. Wohlreich, M.D.

Background: Depression is a chronic disease consisting of emotional/psychological and physical symptoms. Emotional symptoms have been shown to respond to currently available antidepressants; however, physical symptoms may not be as responsive. It was hypothesized that resolution of both psychological and physical symptoms of depression would predict a higher percentage of patients achieving remission.

Method: Efficacy data were pooled from 2 identical, but independent, 9-week randomized, double-blind clinical trials of duloxetine 60 mg q.d. (N = 251) and placebo (N = 261). All patients met diagnostic criteria for DSM-IV major depressive disorder, which was confirmed by the Mini-International Neuropsychiatric Interview. Efficacy measures included the 17-item Hamilton Rating Scale for Depression (HAM-D-17) total score, the HAM-D-17 Maier subscale, the Clinical Global Impressions-Severity of Illness (CGI-S) scale, the Patient Global Impression of Improvement (PGI-I) scale, the Somatic Symptom Inventory, the Quality of Life in Depression Scale, and Visual Analog Scales (VAS) for pain (overall pain, headaches, back pain, shoulder pain, interference with daily activities, and time in pain while awake).

Results: Duloxetine-treated patients demonstrated significantly greater improvement in overall pain ($p = .016$), back pain ($p = .002$), and shoulder pain ($p = .021$) at week 9 compared with patients receiving placebo. When treatment effects were pooled over all visits, patients receiving duloxetine, 60 mg q.d., exhibited significantly greater improvement than placebo-treated patients in 5 of the 6 assessed VAS pain measures. Approximately 50% of the improvement in overall pain was independent of improvement in HAM-D-17 total score. Assuming the same level of improvement in core emotional symptoms of depression (Maier subscale), improvement in overall pain severity was associated with higher estimated probabilities of remission ($p < .001$). The week 9 means for VAS overall pain severity were 13.0 for remitters (last observed value for HAM-D-17 was ≤ 7) compared with 22.7 for nonremitters ($p < .001$), respectively, representing a greater than 3-fold improvement from baseline in remitters. The remission rate for pain responders (improvement in VAS overall pain from baseline to last observation $\geq 50\%$) was twice that observed for pain nonresponders (36.2% vs. 17.8%, $p < .001$). Greater improvements in pain outcomes were associated with more favorable endpoint outcomes on the CGI-S and PGI-I scales. In addition, early favorable responses in VAS overall pain severity were associated with favorable endpoint outcomes.

Conclusions: Treatment with duloxetine, 60 mg q.d., significantly reduced pain compared with placebo. Improvements in pain severity were attributable equally to the direct effect of duloxetine and to associated changes in depression severity. Improvement in painful physical symptoms was associated with higher remission rates even after accounting for improvement in core emotional symptoms.

(J Clin Psychiatry 2004;65:521–530)

Received March 24, 2003; accepted Jan. 8, 2004. *From the Department of Psychiatry, Massachusetts General Hospital, Boston (Dr. Fava); Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Ind. (Drs. Mallinckrodt, Detke, Watkin, and Wohlreich); Department of Psychiatry, Indiana University School of Medicine, Indianapolis (Dr. Detke); McLean Hospital, Belmont, and Harvard Medical School, Boston, Mass. (Dr. Detke).*

This work was sponsored by Eli Lilly and Company, Indianapolis, Ind. All authors accept full responsibility for the conduct of this trial, were given full access to all data from the trial, and participated in the decision to publish the data.

Dr. Fava has received research support and/or honoraria from Aspect Medical Systems, Abbott, Bayer AG, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest, GlaxoSmithKline, J & J Pharmaceuticals, Janssen, Knoll, Lichtwer Pharma GmbH, Lorex, Lundbeck, Novartis, Organon, Parke-Davis, Pfizer, Pharmacia & Upjohn, Pharmavite, Roche, Sanofi-Synthelabo, Solvay, Somerset, and Wyeth-Ayerst.

Corresponding author and reprints: Madelaine M. Wohlreich, M.D., Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (e-mail: mwmd@lilly.com).

Major depressive disorder (MDD) is a psychiatric disorder that encompasses a broad range of emotional/psychological, behavioral, and physical symptoms. Traditionally, the classification of MDD has focused primarily on psychological features, such as depressed mood, reduced interest/pleasure, feelings of worthlessness, and excessive guilt.[1] However, it is becoming increasingly recognized that physical symptoms represent the chief complaint for many depressed patients.[2] Up to 76% of patients with MDD also experience somatic/physical symptoms, including a range of painful complaints such as headaches; stomach pain; vague, poorly localized pain; and back pain.[3,4] Furthermore, a recent multinational survey found that 69% of depressed primary care patients reported only somatic symptoms as the reason for

  © Copyright 2004 Physicians Postgraduate Press, Inc.

visiting the physician.[5] These data not only reaffirm the proposal that physical ailments represent a major concern for depressed patients but also have implications for the timely recognition and appropriate treatment of MDD. Approximately half of all patients with a depressive disorder fail to receive an accurate diagnosis at the primary care level,[6] and the level of recognition of depressive illness has been found to decrease significantly when presentations involve primarily physical complaints.[7–11]

Standard measures of depression severity, such as the Hamilton Rating Scale for Depression (HAM-D)[12] and the Montgomery-Asberg Depression Rating Scale (MADRS),[13] emphasize the emotional/psychological symptoms of MDD. Only 3 questions on the 10-item MADRS address physical symptoms (decreased appetite, insomnia, and fatigue), whereas in the case of the HAM-D-17, only 18 points (32%) of the 56-point total score are utilized to assess physical ailments. Furthermore, physical symptoms involving pain receive even less emphasis in these standardized rating scales, with a single item on the HAM-D-17 (item 13) describing backaches, headaches, and muscle aches, and essentially no representation of painful symptoms within the MADRS. In addition, item 13 of the HAM-D-17 also measures lack of energy and fatigability, thereby confounding the assessment of pain.

Such an emphasis on nonsomatic symptoms has led to a lack of information concerning the effect of antidepressants on physical and somatic symptoms associated with MDD. It is clear from the literature that psychological symptoms respond well to antidepressant treatment.[14] However, physical symptoms may be less responsive to traditional medications, as they frequently represent residual symptoms among patients who have shown otherwise good response to antidepressant treatment.[15] Thus, even patients meeting standard criteria for remission of depressive symptoms (HAM-D-17 total score ≤ 7) may continue to suffer from somatic/physical symptoms that are not adequately tracked by the rating scale. Given the fact that residual symptoms of any nature, including somatic/physical symptoms, can be strong predictors of poor outcome in the long-term,[16] clinicians need to be proactive and aggressive in targeting such residual symptoms.

Within the domain of physical symptoms of depression, emphasis has traditionally been placed on items such as fatigue, sleep problems, and appetite changes. However, physical symptoms involving pain (e.g., headache, neck and back pain, abdominal pain, diffuse musculoskeletal pain) are particularly common[17] and may be as prevalent in depressed patients as anxiety symptoms.[18] Approximately 60% of depressed patients presenting to primary care facilities report at least 1 pain complaint,[19–25] whereas the prevalence of painful symptoms among inpatients may be even higher. In one study,[3] 92% of a group of 150 depressed inpatients reported 1 or more symptoms involving pain.

Evidence suggests that medications that inhibit the reuptake of both serotonin (5-HT) and norepinephrine, for example, some tricyclic antidepressants (TCAs), may possess superior analgesic efficacy to those acting upon a single neurotransmitter.[26–28] These observations are consistent with experimental data that indicate that both 5-HT and norepinephrine exert analgesic effects via descending pain pathways.[29–31] Thus, antidepressants exhibiting dual reuptake inhibition may be useful in the treatment of physical symptoms associated with depression, especially those involving pain. In one open-label study,[32] patients who had failed to respond to selective serotonin reuptake inhibitor (SSRI) therapy showed a significant improvement in the somatic scale of the Symptom Questionnaire following treatment with mirtazapine, a dual action medication that facilitates presynaptic release of 5-HT and norepinephrine.

Duloxetine is a potent dual reuptake inhibitor of both 5-HT and norepinephrine.[33] Previous studies have established the efficacy of duloxetine in the treatment of MDD,[34–37] with estimated probabilities of remission ranging from 43% to 57% being observed in clinical trials of 8 to 9 weeks' duration. In addition, duloxetine has been shown to be efficacious in the alleviation of painful physical symptoms[34,35] and in the treatment of the pain associated with diabetic neuropathy.[38]

Agents demonstrating dual reuptake inhibition of 5-HT and norepinephrine have been associated with higher rates of remission when compared with SSRIs.[39] However, whether or not the alleviation of painful physical symptoms is associated with higher remission rates has not been investigated. The primary objective of the current study was to assess the relationship between alleviation of painful physical symptoms and remission rate—independent of changes in the core emotional symptoms of depression. Data from 2 double-blind, placebo-controlled clinical trials of duloxetine at the same dose (60 mg q.d.) were pooled to investigate this hypothesis.

METHOD

Data

Data were pooled from 2 identical, but independent, randomized, double-blind studies of duloxetine, 60 mg q.d., in the treatment of MDD.

Selection of Patients

Study participants were men and women at least 18 years of age, all of whom provided written informed consent prior to study procedures or administration of study drug, in accordance with the Declaration of Helsinki. All patients met diagnostic criteria for MDD defined in the *Diagnostic and Statistical Manual of Mental Disorders*,

Fourth Edition (DSM-IV).[1] The diagnosis was confirmed by the Mini-International Neuropsychiatric Interview (MINI),[40] a standardized diagnostic interview based on DSM-IV criteria. Baseline disease severity was defined by patients' scores on the HAM-D-17[12] and the Clinical Global Impressions-Severity of Illness scale (CGI-S).[41] All patients were required to have a score ≥ 15 on the HAM-D-17 and ≥ 4 on the CGI-S, indicating at least moderate illness, at the screening and second study visits.

Patients were excluded for the following reasons: current and primary Axis I disorder (other than MDD), anxiety disorder as a primary diagnosis within a year of study entry, an Axis II disorder that could interfere with adherence to the study protocol, lack of response of the current depression episode to 2 or more adequate courses of antidepressant therapy or treatment-resistant depression (that is, depression deemed to be refractory to treatment by the study clinician), serious medical illness, initiating or stopping psychotherapy within 6 weeks prior to enrollment or initiating psychotherapy at any time during the study, and a history of substance abuse or dependence within a year of study entry or a positive urine drug screen.

Study Design

These 2 trials were randomized, double-blind, parallel-group, placebo-controlled studies of duloxetine in patients with MDD, conducted at 39 centers in the United States. The protocol was reviewed and approved by an institutional review board prior to commencement of the study. The study design incorporated double-blind, variable-duration placebo lead-in and lead-out periods to blind patients and investigators to the start and end of active therapy. Qualified patients were randomly assigned (1:1 ratio) to placebo or duloxetine, 60 mg q.d., for up to 9 weeks. The studies were designed to have 80% power to detect a difference of 2.73 points on the HAM-D-17 total score. Patients were not required to meet a minimum threshold at baseline for pain, and the studies were not specifically powered for pain outcomes.

Study drug consisted of 3 capsules (either placebo or 20 mg of duloxetine in each capsule) taken once daily in the morning. If necessary, the dose could be reduced to 2 capsules (2 capsules of placebo or duloxetine, 40 mg q.d.) but had to be escalated back to 3 capsules after 3 weeks on study drug and remain so for the remainder of the study. Concomitant medications with primarily central nervous system activity were not allowed, with the exception of chloral hydrate (up to 1000 mg) or zolpidem (up to 10 mg) for insomnia on no more than 6 total nights during the study. Chronic use of prescription pain medications was not allowed, although episodic use was permitted (with the exception of narcotics). Antihypertensive medications were not allowed unless the patient had been taking a stable dose for at least 3 months prior to study entry.

Efficacy Measures

The primary efficacy measure was the HAM-D-17 total score, recorded at every study visit. The HAM-D-17 was administered only by site personnel who underwent training on the use of the instrument and met predetermined criteria for interviewing skills and HAM-D scoring. These criteria were evaluated during rater training sessions at the investigator startup meeting. Secondary measures recorded at every visit included the clinician-assessed CGI-S,[41] the Somatic Symptom Inventory (SSI),[42] and Visual Analog Scales (VAS)[43] for pain assessed on 6 separate items: overall pain, headaches, back pain, shoulder pain, interference with daily activities, and time in pain while awake. VAS pain assessments require patients to describe their pain intensity by placing a mark on a 100-mm line anchored by "no pain" at 0 mm and "pain as bad as you can imagine" at 100 mm. The Patient Global Impression of Improvement scale (PGI-I)[41] was also a secondary efficacy measure collected at every post-baseline visit. In addition, the Quality of Life in Depression Scale (QLDS)[44] was collected at baseline and after 9 weeks of treatment.

Statistical Methods

All randomized patients with at least 1 postbaseline assessment were included in the analyses. The primary analysis as described in the original protocols was used to assess treatment group differences in mean changes from baseline in VAS pain outcomes (see results in Table 2 and Figures 1 and 2). This analysis was a likelihood-based mixed-effects model repeated measures (MMRM) approach. The MMRM model included the fixed, categorical effects of treatment, investigator, visit, and treatment-by-visit interaction, as well as the fixed, continuous covariates of baseline and baseline-by-visit interaction.

Path analysis was used to estimate the percentage of duloxetine's total effect on pain that was due to a direct effect versus the percentage arising from indirect effects that occurred secondarily as a result of improvement in depression (as measured by the HAM-D-17 total score). Full details of path analysis are provided by Retherford and Choe.[45] The procedure involved 2 regression analyses of pain outcomes. The first included HAM-D-17 total score as a covariate whereas the second did not. The direct versus indirect effect of duloxetine was determined by comparing the magnitude of the treatment effect with and without adjusting for change in HAM-D-17 total score.

The primary hypothesis of the current investigation was assessed using a categorical repeated measures analysis of remission. Specifically, the influence of VAS pain outcomes over time (overall pain and back pain) on visit-wise remission rates was assessed using a categorical MMRM approach. This analysis included a probit link function and a binomial error distribution along with the fixed, categorical effects of treatment, time, and treat-

ment-by-time interaction, and the fixed, continuous covariates of baseline HAM-D-17 score and postbaseline VAS pain score (overall pain or back pain included in separate analyses) as a fixed, continuous covariate. In this analysis, significance of the pain outcomes would suggest that postbaseline changes in pain outcomes influenced visitwise remission rates. A second replicate of this analysis was conducted including postbaseline outcomes on the Maier subscale[46] of the HAM-D-17. This analysis addressed the primary objective of the study—the association between painful physical symptoms and remission independent of improvements in core emotional symptoms of depression. Significance of pain outcomes in this analysis would suggest that postbaseline changes in pain outcomes influenced visitwise remission rates after accounting for changes in the core emotional symptoms of depression.

The association between pain and remission was also investigated using several secondary analyses. Mean changes from baseline in VAS pain outcomes were compared for remitters (endpoint HAM-D-17 ≤ 7) versus nonremitters (see results in Figure 4 and Table 4) using the same MMRM approach, with remission status replacing treatment in the model.

Analysis of variance (ANOVA) was used to compare endpoint means for VAS pain outcomes across endpoint CGI and PGI categories (see results in Tables 5 and 6). The ANOVA model included the fixed, categorical effects of group (defined by endpoint CGI or PGI score), investigator, and baseline VAS pain score as a covariate. Remission status at endpoint was also cross-tabulated with early and endpoint pain response status. Patients were defined as early pain responders if they had a reduction from baseline of 50% or greater in VAS overall pain in week 1 or week 2. Patients were defined as endpoint responders if they met this criterion at endpoint. Fisher exact test was used to assess the significance of the difference. Separate analyses were conducted for all patients, duloxetine-treated patients only, and placebo-treated patients only.

Associations between responses in pain outcomes, depression outcomes, and quality of life were assessed using Pearson's correlations. The term *significant* in this report indicates statistical significance ($p \leq .05$).

RESULTS

Patient Characteristics

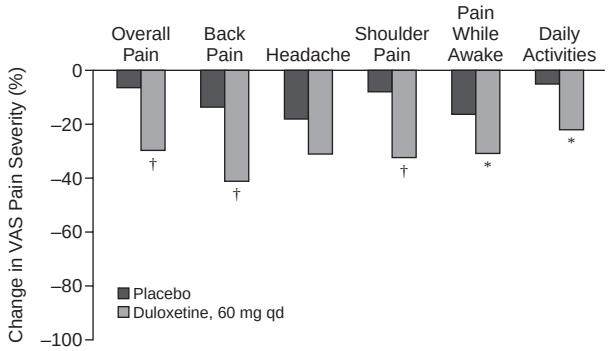
A total of 708 patients entered the screening phase of the 2 studies. Of these patients, 196 failed to meet entry criteria or declined to participate. The remaining 512 patients were randomly assigned to placebo (N = 261) or duloxetine, 60 mg q.d. (N = 251). A total of 495 patients had at least 1 postrandomization visit and were thus included in the efficacy analysis (placebo, N = 251; duloxetine, N = 244). Demographic characteristics of the randomized patients are summarized in Table 1. No significant differences were observed between treatment groups in baseline demographics or psychiatric history.

Table 1. Baseline Patient Demographics and Psychiatric History

Characteristic	Placebo (N = 261)	Duloxetine, 60 mg qd (N = 251)
Gender, N (%)		
Female	182 (69.7)	165 (65.7)
Age, y, mean	41.6	41.6
Age, y, range	18–82	18–75
Ethnicity, N (%)		
White	212 (81.2)	207 (82.5)
Hispanic	31 (11.9)	20 (8.0)
African descent	16 (6.1)	16 (6.4)
Other	2 (0.8)	8 (3.2)
Psychiatric profile score, mean		
HAM-D-17 total	20.78	20.86
CGI-S	4.28	4.27
VAS overall pain	27.11	27.19

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, VAS = Visual Analog Scales.

Figure 1. Percentage Change in VAS Pain Severity From Baseline to Endpoint (pooled over all visits) for Duloxetine (N = 241) and Placebo (N = 248)

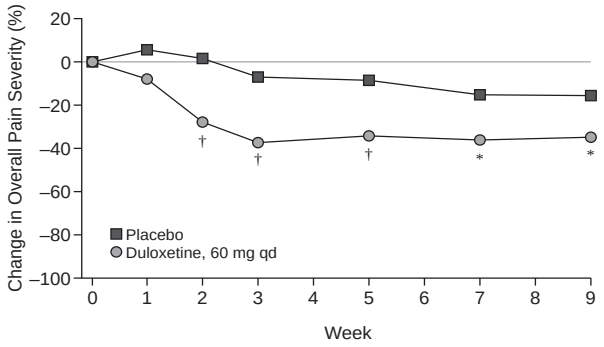


*$p \leq .05$ vs. placebo.
†$p \leq .005$ vs. placebo.
Abbreviation: VAS = Visual Analog Scales.

Efficacy

When treatment effects were pooled over all visits, duloxetine-treated patients demonstrated significantly greater reductions in mean VAS pain scores compared with placebo on 5 of the 6 assessed measures (overall pain, back pain, shoulder pain, pain while awake, interference with daily activities; Figure 1). When expressing the mean changes as percentages, improvements from baseline in pain severity for duloxetine-treated patients ranged from 22.1% to 41.0%, compared with 5.2% to 18.1% improvements for patients receiving placebo. A visitwise plot of percentage change in VAS overall pain severity is shown in Figure 2, and results for other VAS items

Figure 2. Visitwise Percentage Change in VAS Overall Pain Severity for Duloxetine (N = 241) and Placebo (N = 247)



*p ≤ .05 vs. placebo.
†p ≤ .005 vs. placebo.
Abbreviation: VAS = Visual Analog Scales.

are summarized in Table 2. Significantly greater improvements in VAS pain severity at week 9 were observed for duloxetine over placebo in overall pain (p = .016), back pain (p = .002), and shoulder pain (p = .021). In the case of back pain and shoulder pain, significant improvements for duloxetine-treated patients were observed after 1 week of treatment.

In the path analysis, 50.6% of duloxetine's total effect on overall pain was independent of changes in depression, whereas 49.4% was an indirect effect mediated through change in the HAM-D-17 total score.

In the primary analysis that simultaneously assessed the links between pain, core emotional symptoms, and remission, greater improvement in pain scores (as measured by VAS) was associated with a higher estimated probability of remission, after accounting for changes in the core emotional symptoms of depression (as measured by the HAM-D-17 Maier subscale) (p < .001). This primary analysis provides, theoretically, the most meaningful assessment of the influence of pain on remission rates independent of changes in core emotional symptoms. Its interpretation is, however, somewhat complicated. Therefore, we offer several additional means of interpreting this key result. At the same level of improvement in core emotional symptoms of depression (e.g., depressed mood, guilt, psychic anxiety, etc.), alleviation of painful physical symptoms was associated with a greater likelihood of remission. As core emotional symptoms improved, the likelihood of remission increased, but this increase was greater for patients who also showed improvements in pain severity. This synergistic relationship between improvements in painful physical symptoms and core emotional symptoms is depicted in Figure 3.

This same general approach was repeated using remission at last observation carried forward (LOCF) rather than the repeated measures approach. Again, improvement in VAS overall pain had a significant influence on remission rate independent of improvement in core emotional symptoms (p = .001). In the LOCF analysis, with the same magnitude of improvement in core emotional symptoms, the estimated probability of remission for patients with an endpoint VAS overall pain severity score of 10 was approximately 8% greater than for patients with an endpoint VAS overall score of 25.

Another method for assessing the effect of overall pain severity on improvements in depressive symptoms is to compare correlations over time. Rochon[47] noted that if a secondary outcome (VAS pain in the present investigation) had a synergistic effect with the outcome variable of interest (HAM-D-17 total score in the present investigation), then the pattern of correlations over time for the 2 variables would be relatively symmetrical. In other words, correlations of early changes in pain with subsequent HAM-D-17 scores would have approximately the same magnitude as correlations of early changes in HAM-D-17 scores with subsequent changes in pain. However, if changes in pain severity were merely an artifact of overall improvement in depression, then early changes in HAM-D-17 scores would be correlated with subsequent changes in pain, but early changes in pain would not be correlated with subsequent changes in HAM-D-17 scores. Visitwise correlations between VAS overall pain and HAM-D-17 total score are summarized in Table 3.

Correlations of early changes in pain with subsequent changes in HAM-D-17 total scores were of approximately the same magnitude as correlations of early changes in HAM-D-17 total scores with subsequent changes in pain. Such a pattern of correlation suggests a synergistic effect between the 2 outcomes, rather than a situation in which one outcome drives changes in the other.[47]

The results presented thus far have focused on assessing (1) the effects of duloxetine on pain, (2) the independence of changes in pain and depression, and (3) the effect of changes in pain on remission independent of changes in core emotional symptoms. These results are, therefore, the most useful in assessing the primary hypotheses of the present investigation. Subsequent results are presented to reinforce the previous results using perhaps less rigorous but more intuitive approaches.

Pooled across both treatment groups, the remission rate (HAM-D-17 total score ≤ 7) for pain responders (improvement in VAS overall pain from baseline to last observation of 50% or greater) was twice that observed for pain nonresponders (36.2% vs. 17.8%, p < .001). Within the duloxetine treatment group, remission rates were 38.8% versus 24.8% (p = .027) for pain responders and nonresponders, respectively, whereas remission rates within the placebo group were 32.6% for pain responders versus 12.3% for pain nonresponders (p < .001).

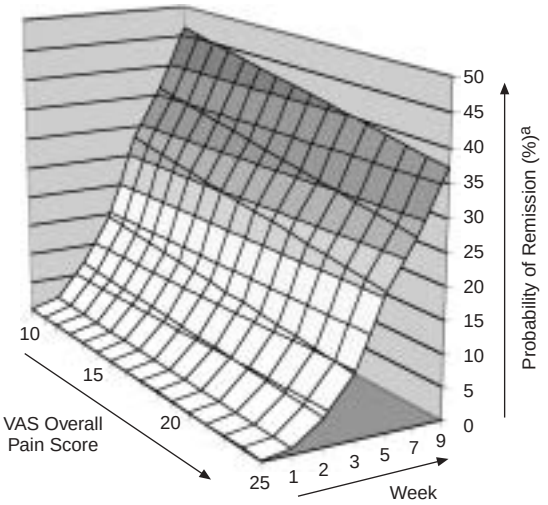
Significant differences were found in mean VAS pain severity scores between patients achieving remission at

Table 2. Postbaseline Visitwise Percentage Change in Visual Analog Scales (VAS) Pain Severity Scores for Placebo- and Duloxetine-Treated Patients[a]

VAS Pain Item	Treatment	Week 1	Week 2	Week 3	Week 5	Week 7	Week 9
Headache	Placebo	–3.5	–8.5	–17.5	–21.9	–34.3	–22.7
	Duloxetine	–6.5	–27.1*	–36.1*	–33.4	–42.3	–41.1
Back pain	Placebo	–9.0	–7.0	–12.6	–19.6	–16.9	–18.3
	Duloxetine	–32.1†	–38.4†	–44.9†	–46.4†	–40.6†	–43.4†
Shoulder pain	Placebo	–1.1	5.2	–5.7	–22.6	–13.3	–12.5
	Duloxetine	–25.8†	–31.2†	–31.2*	–33.2	–36.0*	–37.1*
Pain while awake	Placebo	–8.2	–5.7	–14.3	–23.0	–24.2	–24.2
	Duloxetine	–17.6	–29.2†	–32.0*	–35.2	–37.6	–33.1
Daily activities	Placebo	3.3	3.0	0.9	–7.3	–15.5	–15.6
	Duloxetine	–7.4	–18.1*	–25.3†	–26.3*	–30.3	–25.3

[a]Duloxetine dose = 60 mg q.d.
*p ≤ .05 vs. placebo.
†p ≤ .005 vs. placebo.

Figure 3. Visitwise Probabilities of Remission for Patients With Postbaseline VAS Overall Pain Scores From 10 to 25



[a]17-item Hamilton Rating Scale for Depression score ≤ 7.
Abbreviation: VAS = Visual Analog Scales.

Table 3. Postbaseline Visitwise Correlations Between VAS Overall Pain Severity and HAM-D-17 Total Score[a]

HAM-D-17 Total Score Week	VAS Overall Pain Week 1	Week 2	Week 3	Week 5	Week 7	Week 9
1	**.191**	.093	.136	.149	.138	.145
2	.171	**.193**	.169	.151	.182	.163
3	.141	.115	**.226**	.169	.184	.145
5	.101	.087	.203	**.242**	.210	.144
7	.144	.127	.193	.213	**.275**	.199
9	.125	.096	.190	.195	.169	**.207**

[a]Bolded correlations, on the diagonal, are correlations between the 2 outcomes at the same timepoint. Correlations above the diagonal are correlations of early changes in HAM-D-17 total score with subsequent changes in pain. Correlations below the diagonal are correlations of early changes in pain with subsequent changes in HAM-D-17 total score.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, VAS = Visual Analog Scales.

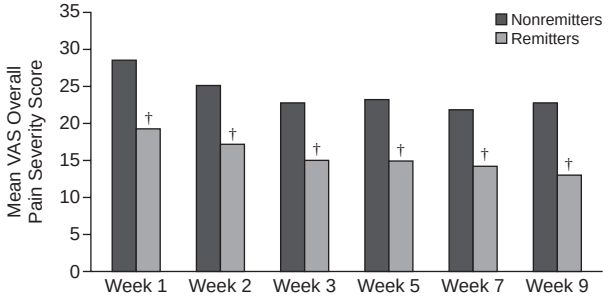
endpoint and those failing to achieve remission. In the case of VAS overall pain (Figure 4), endpoint remitters had significantly lower mean VAS scores compared with nonremitters at week 1 and at every subsequent visit (all p ≤ .005). At week 9, the mean overall VAS pain score was 22.7 among nonremitters compared with 13.0 for remitters (p < .001). Given that the baseline VAS overall pain score was 27.2 for duloxetine-treated patients, this represents a greater than 3-fold improvement in VAS overall pain among remitters. In each of the other 5 assessed VAS pain measures, endpoint remitters had significantly lower mean VAS scores at endpoint compared with nonremitters (Table 4). In the case of back pain, pain while awake, and interference with daily activities, differences in mean VAS scores between remitters and nonremitters were significant at week 1 and at every subsequent visit.

A similar result was observed for mean scores on the SSI. Starting at week 1, and for each subsequent visit, endpoint remitters demonstrated significantly lower mean SSI scores than nonremitters (p < .001 at each visit).

Early pain response (50% or greater improvement in VAS overall pain severity from baseline) among all patients was associated with significantly higher probability of remission (HAM-D-17 total score ≤ 7) at endpoint. Patients demonstrating pain response within 2 weeks of initiating therapy had an estimated probability of achieving depressive symptom remission of 35.4%, compared with 20.9% among those patients not showing early pain response. The probability of remission for early pain responders remained significantly higher than that for nonresponders even after accounting for changes in HAM-D-17 total score during the first 2 weeks of therapy (p = .009).

Comparisons of CGI-S score at endpoint and mean VAS pain severity at endpoint revealed a consistent trend in which higher endpoint CGI-S scores were associated with higher endpoint pain scores (Table 5). Thus, patients with a week 9 CGI-S score of 1 ("normal, not at all depressed") demonstrated a mean endpoint VAS overall

Figure 4. Postbaseline Visitwise Means for VAS Overall Pain Scores in Patients Achieving Remission Versus Those Not Achieving Remission at Endpoint[a]



[a]Remission is defined as a HAM-D-17 total score ≤ 7.
†p ≤ .005.
Abbreviation: VAS = Visual Analog Scales.

pain score of 11.5, compared with a VAS overall pain score of 24.2 among patients with a final CGI-S score of 4 ("moderately depressed"; $p < .001$), and 42.5 for those with an endpoint CGI-S score of 6 ("severely depressed"; $p = .003$). Similar trends were observed across all 5 other assessed VAS pain measures (Table 5). Significant differences were also found in mean endpoint SSI scores among patients with differing CGI-S outcomes.

Similar trends were found in patient-rated assessments of global improvement (PGI-I scale). Patients with a week 9 PGI-I score of 1 ("very much better/improved") demonstrated a mean VAS overall pain score at endpoint of 11.6, compared with an endpoint VAS overall pain score of 24.5 among patients with a final PGI-I score of 4 ("no change"; $p = .003$), and 54.5 for those with a final PGI-I score of 7 ("very much worse"; $p < .001$). Associations between lower endpoint pain scores and more favorable PGI-I outcomes were found across the other 5 assessed VAS pain measures (Table 6), as well as in endpoint mean SSI score.

Improvements in measures of psychological symptoms from baseline to endpoint were found to be strongly correlated with improvements in quality of life, as measured by the QLDS. Thus, the correlation coefficient of QLDS score with HAM-D-17 Maier subscale was 0.71 ($p < .001$), whereas that between QLDS and HAM-D-17 item 10 (psychic anxiety) was 0.53 ($p < .001$). Significant correlations also existed between baseline-to-endpoint change in QLDS score and changes in each VAS pain severity measure. Coefficients ranged from 0.27 ($p < .001$) for the correlation of QLDS with VAS pain while awake to 0.34 ($p < .001$) for the correlation between QLDS and VAS headache severity.

DISCUSSION

In the present analyses of pooled data, duloxetine was significantly superior to placebo in reducing the severity of painful physical symptoms in depressed patients. Similar findings were reported from the individual studies included in the pooled analyses.[37] Data were pooled to provide the most reliable estimates for both the magnitude of the treatment effect and the proportion of the treatment outcome that were due to a direct effect on pain versus secondary effects resulting from improvements in depression.

Improvements from baseline in pain severity for duloxetine-treated patients ranged from 22.1% to 41.0% compared with 5.2% to 18.1% improvement for patients receiving placebo. As evidenced by the path analysis, approximately half of duloxetine's total effect on pain was a direct effect and approximately half was an indirect effect attributable to improvement in depression (as measured by HAM-D-17 total score). Previous studies of duloxetine in the treatment of painful conditions in nondepressed patients have also demonstrated robust efficacy.[38]

The primary hypothesis of the present investigation was that alleviation of painful physical symptoms was associated with higher remission rates. Although it is difficult to address this question with a prospectively defined study, these post hoc analyses provide compelling evidence that, independent of changes in the core emotional symptoms of depression, alleviation of painful symptoms was associated with greater probabilities of remission. The importance of treating painful physical symptoms was further established via demonstration of strong links between improvements in pain outcomes and improvements in clinician- and patient-rated global outcomes and quality of life. Our findings suggest a strong relationship between changes in pain severity and changes in depressive illness severity, but cannot elucidate whether such a relationship is more or less specific than the one between changes in depression severity and changes in other symptoms, such as sleep disturbances or anxiety.

It has been suggested that antidepressants that inhibit the reuptake of both 5-HT and norepinephrine demonstrate greater efficacy than those acting upon a single neurotransmitter on the basis of several clinical trials in which dual reuptake medications, or combinations of selective 5-HT and norepinephrine inhibitors, demonstrated efficacy superior to that of SSRI comparators.[48,49] Furthermore, pooled remission rates for venlafaxine, which also achieves dual 5-HT/norepinephrine reuptake inhibition at high doses, have been reported to be higher than those observed for SSRIs.[39] In addition, antidepressant medications that influence the reuptake of multiple neurotransmitters (for example, certain TCAs) have been proposed to exhibit greater efficacy in relieving pain than SSRIs[27] and to have perhaps a broader spectrum of action.[50] In previous studies of duloxetine, the estimated probabilities of remission ranged from 43% to 57%.[37] It has been postulated that duloxetine's dual reuptake mechanism of action may be responsible for its ability to address

Table 4. Postbaseline Visitwise Mean VAS Pain Severity Scores in Patients Achieving Remission Versus Those Not Achieving Remission at Endpoint[a]

VAS Pain Item	Patients	Week 1	Week 2	Week 3	Week 5	Week 7	Week 9
Headache	Nonremitters	21.1	19.2	18.2	18.1	15.0	17.2
	Remitters	20.0	14.7	10.7†	10.4†	9.9*	9.7†
Back pain	Nonremitters	20.3	19.9	18.7	17.9	18.9	19.2
	Remitters	14.4†	13.7†	12.0†	10.6†	11.9†	9.8†
Shoulder pain	Nonremitters	15.6	16.0	15.4	13.9	13.6	14.3
	Remitters	12.3	11.6*	10.0†	8.3†	10.5	9.1*
Pain while awake	Nonremitters	31.5	29.9	28.2	26.8	25.9	27.7
	Remitters	22.8†	21.8†	19.5†	16.4†	16.4†	15.2†
Daily activities	Nonremitters	20.4	19.1	18.6	17.9	17.4	18.2
	Remitters	12.7†	13.0*	11.3†	10.2†	8.1†	7.7†

[a]Remission defined as HAM-D-17 total score ≤ 7.
*$p \leq .05$ vs. nonremitters.
†$p \leq .005$ vs. nonremitters.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, VAS = Visual Analog Scales.

Table 5. Relationship of Mean VAS Pain Severity Scores at Endpoint to Final CGI-S Scores

	Final CGI-S Score[a]					
VAS Pain Item	1	2	3	4	5	6
Overall pain	11.5	14.5	17.8	24.2	32.8	42.5
Headache	8.6	13.0	11.8	19.8	29.7	34.8
Back pain	5.6	11.8	13.4	20.5	25.4	41.7
Shoulder pain	5.8	10.7	10.5	15.5	21.8	24.3
Pain while awake	13.6	18.1	21.0	30.9	34.8	54.7
Daily activities	7.2	11.8	11.7	19.4	27.6	45.8

[a]CGI-S scale range: 1 = "normal, not at all depressed" to 6 = "severely depressed."
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, VAS = Visual Analog Scales.

Table 6. Relationship of Mean VAS Pain Severity Scores at Endpoint to Final PGI-I Scores

	Final PGI-I Score[a]						
VAS Pain Item	1	2	3	4	5	6	7
Overall pain	11.6	14.3	20.8	24.5	27.2	28.0	54.5
Headache	7.6	12.8	13.8	18.9	29.3	22.7	57.5
Back pain	7.3	12.1	14.7	21.7	23.0	22.5	49.0
Shoulder pain	4.1	10.5	12.6	16.7	19.6	14.5	49.5
Pain while awake	11.0	19.9	23.4	31.2	36.0	32.4	50.0
Daily activities	5.0	11.5	15.2	19.3	23.7	24.2	71.0

[a]PGI-I scale range: 1 = "very much better/improved" to 7 = "very much worse."
Abbreviations: PGI-I = Patient Global Impression of Improvement, VAS = Visual Analog Scales.

both emotional and physical symptoms of depression and thereby achieve high rates of remission.[34] The current results underscore the importance of effectively addressing the painful symptoms frequently associated with MDD and support the notion that treatment of both psychological ("core") and somatic/physical aspects of MDD may be associated with higher rates of remission.

Lower endpoint pain severity was associated not only with a reduced total burden of depressive symptoms (as measured by the HAM-D-17), but also with enhanced clinician- and patient-rated global improvement (CGI-S and PGI-I scales) and improved quality of life (QLDS). The fact that the alleviation of painful physical symptoms appears to be linked to more favorable outcomes in such a wide range of functional measures emphasizes the importance of effective treatment of the painful symptoms associated with MDD.

On some VAS pain measures (back pain, shoulder pain), duloxetine-treated patients exhibited significantly greater reductions in pain severity, compared with placebo, after only 1 week of treatment, while overall pain severity showed significant improvement over placebo at week 2 and maintained this advantage to endpoint. Furthermore, early overall pain response (50% or greater improvement in pain severity at week 1 or 2) was associated with a significantly higher probability of remission at endpoint. Such rapid improvement in pain severity, occurring on a timescale shorter than that normally associated with onset of antidepressant action, has been used as evidence in support of an antidepressant medication having a direct effect on pain, independent of its efficacy in depression. However, previous studies have shown that duloxetine also exhibits efficacy in emotional/psychological symptoms of depression within 1 to 2 weeks of treatment initiation,[37] suggesting that improvements in both emotional and physical symptom domains may follow rapid time courses.

Given the intimate relationship between pain and depression[51,52] and the role played by the 5-HT and norepinephrine systems in both conditions,[53] the results of the present analysis may appear somewhat intuitive in that an improvement in one of these conditions may be expected to lead to a corresponding improvement in the other. However, extremely limited data are available from adequately controlled, double-blind clinical trials to support the hypothesis that treatment of unexplained painful symptoms associated with depression may be linked to higher overall rates of remission. This lack of data is especially noteworthy since achievement of remission is considered to be the primary goal of depression treatment. Thus, despite the post hoc nature of the results presented here, they may serve as a catalyst for future studies of the

interrelationship between painful physical symptoms and depression treatment outcomes.

Limitations of these studies include uncertainty with regard to the generalizability of the results, in that patients with many comorbid medical and psychiatric conditions were excluded and thus the patient population may not be fully representative of those seen in all practice settings. In addition, the Visual Analog Scales utilized to assess pain severity are not as well established as standardized questionnaires such as the Symptom Questionnaire (with its associated somatic subscale)[54] and the 90-item Hopkins Symptom Checklist.[55] Furthermore, data were obtained from 2 clinical trials that employed fixed-dose design and may not, therefore, be truly representative of clinical practice. However, the ability to conduct dose adjustment to achieve optimal responses in individual patients may result in larger treatment effects being observed in actual clinical settings.

One strength of the study was that the patient population was not prescreened for the presence of painful physical symptoms, and thus the study contained depressed patients displaying a spectrum of pain symptom severity (mean baseline overall pain severity was 27 out of a possible score of 100, whereas individual patient baseline scores ranged from 0 to 97). The fact that such widespread associations were found between pain severity improvement and depressive symptom improvement, using a variety of analytic techniques, even within this population of relatively low baseline pain severity, is noteworthy and may spur further research in populations with higher baseline levels of pain.

CONCLUSIONS

The results presented here further establish the efficacy of duloxetine as a treatment for both the psychological/emotional symptoms of depression and the painful physical symptoms associated with MDD. Significant improvements for duloxetine-treated patients over placebo were observed in 5 of the 6 assessed VAS pain measures, with initial advantages being observed after only 1 week of treatment in some cases. Duloxetine's pharmacologic mechanism of action, involving dual reuptake inhibition of both 5-HT and norepinephrine, is postulated to underlie its broad spectrum of efficacy across both emotional and physical symptom domains.

Furthermore, the current analyses also demonstrated that 50% of the improvement in pain was independent of improvements in depression, and that the improvements in pain severity were associated with more favorable depression treatment outcomes, including higher rates of remission, improved quality of life, and improved clinician- and patient-rated global outcomes. Although further investigations are needed to confirm these findings, the present results emphasize the importance of adequately treating the painful physical symptoms associated with MDD and the potential role such treatment may play in achieving higher overall rates of depressive symptom remission.

Drug names: mirtazapine (Remeron), venlafaxine (Effexor), zolpidem (Ambien).

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
2. Fava M. Somatic symptoms, depression, and antidepressant treatment [commentary]. J Clin Psychiatry 2002;63:305–307
3. Corruble E, Guelfi JD. Pain complaints in depressed inpatients. Psychopathology 2000;33:307–309
4. Kroenke K, Price RK. Symptoms in the community: prevalence, classification, and psychiatric comorbidity. Arch Intern Med 1993;153:2474–2480
5. Simon GE, Von Korff M, Piccinelli M, et al. An international study of the relation between somatic symptoms and depression. N Engl J Med 1999;341:1329–1335
6. Von Korff M, Shapiro S, Burke JD, et al. Anxiety and depression in a primary care clinic: comparison of Diagnostic Interview Schedule, General Health Questionnaire, and practitioner assessments. Arch Gen Psychiatry 1987;44:152–156
7. Docherty JP. Barriers to the diagnosis of depression in primary care. J Clin Psychiatry 1997;58(suppl 1):5–10
8. Gerber PD, Barrett J, Barrett J, et al. Recognition of depression by internists in primary care: a comparison of internist and "gold standard" psychiatric assessments. J Gen Intern Med 1989;4:7–13
9. Katon W. Depression: relationship to somatization and chronic medical illness. J Clin Psychiatry 1984;45(3, sec 2):4–12
10. Posse M, Hallstrom T. Depressive disorders among somatizing patients in primary health care. Acta Psychiatr Scand 1998;98:187–192
11. Kirmayer LJ, Robbins JM, Dworkind M, et al. Somatization and the recognition of depression and anxiety in primary care. Am J Psychiatry 1993;150:734–741
12. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
13. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
14. Worthington J, Fava M, Davidson K, et al. Patterns of improvement in depressive symptoms with fluoxetine treatment. Psychopharmacol Bull 1995;31:223–226
15. Denninger JW, Mahal Y, Merens W, et al. The relationship between somatic symptoms and depression. Presented at the 155th annual meeting of the American Psychiatric Association; May 18–23, 2002; Philadelphia, Pa
16. Paykel ES, Ramana R, Cooper Z, et al. Residual symptoms after partial remission: an important outcome in depression. Psychol Med 1995;25: 1171–1180
17. von Knorring L, Perris C, Eisemann M, et al. Pain as a symptom in depressive disorders, pt 2: relationship to personality traits as assessed by means of KSP. Pain 1983;17:377–384
18. Silverstein B. Gender difference in the prevalence of clinical depression: the role played by depression associated with somatic symptoms. Am J Psychiatry 1999;156:480–482
19. von Knorring L. The experience of pain in depressed patients: a clinical and experimental study. Neuropsychobiology 1975;1:155–165
20. Lindsay PG, Wyckoff M. The depression-pain syndrome and its response to antidepressants. Psychosomatics 1981;22:571–577
21. Hollifield M, Katon W, Morojele N. Anxiety and depression in an outpatient clinic in Lesotho, Africa. Int J Psychiatry Med 1994;24:179–188
22. Pelz M, Merskey H, Brant CC, et al. A note on the occurrence of pain in psychiatric patients from a Canadian Indian and Inuit population. Pain 1981;10:75–78
23. Marchesi C, De Ferri A, Petrolini N, et al. Prevalence of migraine and muscle tension headache in depressive disorders. J Affect Disord 1989; 16:33–36

24. Magni G, Schifano F, De Leo D. Pain as a symptom in elderly depressed patients: relationship to diagnostic subgroups. Eur Arch Psychiatry Neurol Sci 1985;235:143–145
25. Baker JW, Merskey H. Pain in general practice. J Psychosom Res 1967;10:383–387
26. Lynch ME. Antidepressants as analgesics: a review of randomized controlled trials. J Psychiatry Neurosci 2001;26:30–36
27. O'Malley PG, Jackson JL, Santoro J, et al. Antidepressant therapy for unexplained symptoms and symptom syndromes. J Fam Pract 1999; 48:980–990
28. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. Pain 1999;83:389–400
29. Jones SL. Descending noradrenergic influences on pain. Prog Brain Res 1991;88:381–394
30. Richardson BP. Serotonin and nociception. Ann N Y Acad Sci 1990; 600:511–519
31. Willis WD, Westlund KN. Neuroanatomy of the pain system and of the pathways that modulate pain. J Clin Neurophysiol 1997;14:2–31
32. Fava M, Dunner DL, Greist JH, et al. Efficacy and safety of mirtazapine in major depressive disorder patients after SSRI treatment failure: an open-label trial. J Clin Psychiatry 2001;62:413–420
33. Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, et al. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. Neuropsychopharmacology 2001;25:871–880
34. Detke MJ, Lu Y, Goldstein DJ, et al. Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. J Clin Psychiatry 2002;63:308–315
35. Detke MJ, Lu Y, Goldstein DJ, et al. Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression. J Psychiatr Res 2002;36:383–390
36. Goldstein DJ, Mallinckrodt C, Lu Y, et al. Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. J Clin Psychiatry 2002;63:225–231
37. Nemeroff CB, Schatzberg AF, Goldstein DJ, et al. Duloxetine for the treatment of major depressive disorder. Psychopharmacol Bull 2002;36: 106–132
38. Goldstein DJ, Lu Y, Iyengar S, et al. Duloxetine in the treatment of the pain associated with diabetic neuropathy. Presented at the 156th annual meeting of the American Psychiatric Association; May 17–22, 2003; San Francisco, Calif
39. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. Br J Psychiatry 2001;178:234–241
40. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(suppl 20):22–33
41. Guy W. ECDEU Assessment Manual for Psychopharmacology, Revised. US Dept Health, Education, and Welfare publication (ADM)76-338. Rockville, Md: National Institute of Mental Health; 1976
42. Barsky AJ, Wyshak G, Klerman GL. Hypochondriasis: an evaluation of the DSM-III criteria in medical outpatients. Arch Gen Psychiatry 1986; 43:493–500
43. DeLoach LJ, Higgins MS, Caplan AB, et al. The Visual Analog Scale in the immediate postoperative period: intrasubject variability and correlation with a numeric scale. Anesth Analg 1998;86:102–106
44. Hunt SM, McKenna SP. The QLDS: a scale for the measurement of quality of life in depression. Health Policy 1992;22:307–319
45. Retherford RD, Choe MK. Statistical Models for Causal Analysis. New York, NY: John Wiley & Sons, Inc; 1993
46. Maier W, Philipp M. Improving the assessment of severity of depressive states: a reduction of the Hamilton Depression Scale. Pharmacopsychiatry 1985;18:114–115
47. Rochon J. Using a serial marker to predict a repeated measures outcome in a cohort study. J Biopharm Stat 2003;13:283–300
48. Danish University Antidepressant Group. Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. J Affect Disord 1990;18:289–299
49. Nelson JC, Mazure CM, Bowers MB Jr, et al. A preliminary, open study of the combination of fluoxetine and desipramine for rapid treatment of major depression. Arch Gen Psychiatry 1991;48:303–307
50. Nelson JC. Synergistic benefits of serotonin and noradrenaline reuptake inhibition. Depress Anxiety 1998;7(suppl 1):5–6
51. Romano JM, Turner JA. Chronic pain and depression: does the evidence support a relationship? Psychol Bull 1985;97:18–34
52. Von Korff M, Simon G. The relationship between pain and depression. Br J Psychiatry 1996;168(suppl 30):101–108
53. Stahl SM. The psychopharmacology of painful physical symptoms in depression [Brainstorms]. J Clin Psychiatry 2002;63:382–383
54. Kellner R. A symptom questionnaire. J Clin Psychiatry 1987;48:268–274
55. Derogatis LR, Lipman RS, Rickels K, et al. The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. Behav Sci 1974;19:1–15

