Annals of Clinical Psychiatry, 20[4]:187–193, 2008

ISSN: 1040-1237 print / 1547-3325 online
DOI: 10.1080/10401230802435609

informa
healthcare

The Effect of Pain on Outcomes in a Trial of Duloxetine Treatment of Major Depressive Disorder

LESLEY M. ARNOLD, MD
Women's Health Research Program, Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, OH, USA

ADAM L. MEYERS, MS
Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA

PRABHA SUNDERAJAN, MD
Depression and Anxiety Disorders Program, Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, USA

C. BRENDAN MONTANO, MD
Internal Medicine Practice, Cromwell, CT, USA

ETHAN KASS DO, MBA
CNS Clinical Research Group, Coral Springs, , FL, USA

MADHUKAR TRIVEDI, MD
Mood Disorders Research Program and Clinic, Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, USA

MADELAINE M. WOHLREICH, MD
Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA

Background. *Patients with major depressive disorder (MDD) frequently report one or more pain symptoms. To explore the relationship between improvement in pain symptoms and MDD treatment outcomes, we conducted a secondary analysis of an approximately 12-week, open label trial of duloxetine in MDD. The primary objective was to test the hypothesis that a greater reduction in pain was associated with a higher probability of MDD remission.*
Methods. *Adults with DSM-IV MDD were enrolled in the study if they had a Hamilton Depression Scale (HAMD-17) total score of 15 or more and a Clinical Global Impression of Severity (CGI-S) score of 4 or more. The duloxetine dose of patients could be titrated on the basis of the degree of response within the range from 60 to 120 mg given QD, with 90 mg QD as an intermediate dose. Remission of major depressive disorder was defined as a HAMD-17 total score of ≤ 7. Core emotional symptoms of depression were determined by the HAMD-17 Maier subscale. Pain was assessed using a 100 mm visual analog scale (VAS) of overall pain severity over the last week (0 = no pain, 100 = pain as severe as I can imagine). For the primary analysis, mean change in VAS overall pain score over time was compared between remitters and non-remitters at endpoint using a mixed model repeated measures approach.*
Results. *Two hundred forty nine patients were included in the analysis. A greater reduction in pain was associated with a significantly higher probability of remission of MDD, after accounting for changes in the core emotional symptoms. Greater pain reduction was associated with significant improvement in MDD core emotional symptoms. A greater improvement in pain was also associated with improvements in patient and clinician-rated global assessments.*

Address correspondence to Lesley M. Arnold, M.D., University of Cincinnati Medical Arts Building, 222 Piedmont Avenue, Suite 8200, Cincinnati, Ohio 45219. E-mail: Lesley.Arnold@uc.edu

Conclusions. *The effective treatment of pain symptoms in patients with major depressive disorder was associated with higher remission rates. The results underscore the importance of effectively treating painful symptoms associated with depression.*

Keywords Depression, Pain, Duloxetine, Clinical Trial

INTRODUCTION

Major depressive disorder is a common psychiatric disorder that is characterized by multiple symptom domains, including emotional symptoms like depressed mood and anhedonia and physical symptoms such as fatigue, sleep disturbances, and appetite changes. Although there has been less emphasis on pain as one of the physical symptoms of depression, on average, 65% of patients with depression report one or more pain symptoms (1). Furthermore, a general population survey found that 43.4 % of individuals with major depressive disorder had at least one chronic pain condition (e.g., limb pain, backache, joint or articular conditions, gastrointestinal disease, headache) (2).

The presence of pain in depressed patients has a substantial impact on depression outcomes. For example, increased pain severity in depressed patients has been associated with more severe depression, more functional limitations, worse self-reported health, and higher unemployment, more frequent use of opiates, and more pain-related doctor visits (1,3). The presence of a chronic pain condition in depressed patients increases the frequency and severity of several depressive symptoms (4). Depressed patients with comorbid pain experience more severe psychological distress and make about 20% more visits to medical providers than depressed patients without pain (5). Finally, the economic burden of depression is magnified when depression is accompanied by pain symptoms (6).

Recent studies have begun to address the impact of pain symptoms on the response to treatment of major depressive disorder. A naturalistic, randomized trial designed to compare the effectiveness of three SSRIs (fluoxetine, paroxetine, sertraline) in 573 depressed primary care patients, found that there was a strong relationship between increasing pain severity and worse depression and poorer health-related quality of life. Furthermore, increased pain severity at baseline and less improvement in pain over a period of 3 months were strongly associated with worse depression treatment outcomes (7). In another study of 64 patients with major depressive disorder who were treated with antidepressants, 19 (32%) had residual symptoms, of whom 94% had mild to moderate physical symptoms, including pain. These residual symptoms were very strong predictors of subsequent early relapse (8). Therefore, the continued presence of pain symptoms after treatment of depression may increase the risk of depression relapse. Finally, improvement in pain symptoms may be associated with higher remission rates as demonstrated in a recent study in which the remission rate for depressed patients who had a ≥ 50% improvement in pain symptoms was nearly twice that of depressed patients who had < 50% improvement in pain (9).

Duloxetine hydrochloride (Cymbalta), a selective serotonin and norepinephrine reuptake inhibitor, is a safe and effective antidepressant (10–12) that also significantly reduces pain symptoms associated with major depressive disorder (13). In a post-hoc analysis of two identical but independent 9-week randomized, controlled trials in outpatients with major depressive disorder comparing duloxetine with placebo, approximately 50% of duloxetine's total effect on overall pain was independent of changes in depression, suggesting an independent analgesic effect of duloxetine that has also been demonstrated in clinical trials of diabetic peripheral neuropathic pain (14,15) and fibromyalgia (16,17). Furthermore, the study provided evidence that reduction in pain was associated with a greater probability of remission, independent of change in the core emotional symptoms of depression (9).

In order to explore further the possible relationship between improvement in pain symptoms and depression treatment outcomes, we conducted a secondary analysis of an approximately 12-week, open label trial of duloxetine that was primarily designed to assess the effects of duloxetine for the treatment of major depressive disorder in patients initiating duloxetine therapy compared with patients switching to duloxetine from selective serotonin reuptake inhibitors or venlafaxine (18). Consistent with previous trials of duloxetine in the treatment of major depressive disorder, overall pain severity decreased with duloxetine treatment in both groups of patients, as measured by the mean changes in the 100 mm visual analog scale (VAS) (0 = no pain, 100 = pain as severe as I can imagine) for overall pain severity. The primary objective of the present study was to test the hypothesis that a greater reduction in pain was associated with a higher probability of depression remission.

METHODS

Patient Selection

Full details of patient selection and assessment are presented in Wohlreich et al., (2005) (18). Briefly, we recruited women or men age ≥ 18 years who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (19) criteria for major depressive disorder. They were required to have a 17-item Hamilton Rating Scale for Depression (HAMD-17) (20) score of ≥ 15 and a Clinical Global Impression of Severity (CGI-S) (21) score of ≥ 4 at 2 consecutive screening visits. Patients were excluded if they had bipolar disorder, schizophrenia or other psychotic disorder; a personality disorder that would interfere with compliance with the study

protocol; clinically significant or unstable medical conditions; serious suicide risk; treatment with fluoxetine within 30 days before visit 1; lack of response of the current episode to 2 or more adequate courses of antidepressant therapy at a clinically appropriate dose for a minimum of 4 weeks, or in the judgment of investigator, meeting criteria for treatment-resistant depression; any anxiety disorder as a primary diagnosis with the past 6 months; a history of substance dependence with the past 6 months; or a positive urine drug screen. Concomitant medications with primarily central nervous system activity were not allowed, with the exception of episodic use of chloral hydrate or zolpidem.

Study Design

The 12-week, open-label, multicenter trial of duloxetine for the treatment of major depressive disorder was conducted at 27 study centers in the US. The study protocol was reviewed and approved by the ethical review board at each site, and all patients provided written informed consent before the administration of any study procedure or study drug.

As reviewed in Wohlreich et al. (18), the study included 2 participant groups: a group of patients who were not currently receiving antidepressants or were treatment-naïve, and a group who were switched from their current antidepressant due to poor tolerability or suboptimal response. Patients in the untreated group who had previously received an antidepressant (other than fluoxetine) were required to have discontinued the antidepressant at least 21 days before study participation. The currently untreated or treatment-naïve patients were randomized in a 1:1 ratio to receive duloxetine 30 mg or 60 mg once daily (QD) for the first week. The group of patients who were switched from their current antidepressant therapy included patients receiving citalopram ≤ 40 mg/d, escitalopram ≤ 20 mg/d, fluvoxamine ≤ 150 mg/d, paroxetine ≤ 40 mg/d, sertraline ≤ 150 mg/d, or venlafaxine ≤ 150 mg/d. These patients were directly switched to duloxetine 60 mg QD for the first week with no intermediate tapering or titration. After the first week, the duloxetine doses in both groups of patients could be titrated for up to 12 weeks on the basis of the degree of response within the range from 60 to 120 mg given QD, with 90 mg QD as an intermediate dose. To mimic clinical practice, intervals between study visits during the dose stabilization phase (up to 12 weeks) of the study were flexible.

Efficacy Measures

Included among several outcome measures in the trial (18), were the 17-item Hamilton Rating Scale for Depression (HAMD-17) total score and a 100 mm visual analog scale (VAS) of overall pain severity over the last week (0 = no pain, 100 = pain as severe as I can imagine). Remission of major depressive disorder was defined as a HAMD-17 total score of 7 or less; response was defined as a ≥ 50% reduction in the baseline HAMD-17 total score. Clinically important pain reduction was defined as a reduction in VAS overall pain severity score by ≥ 10 mm and ≥ 30% of the baseline VAS score (22). Therefore, only the group of patients with at least a score of 10 mm on the 0–100 mm VAS for pain at baseline could potentially show a clinically important reduction in pain. Core emotional symptoms of depression were assessed using the HAMD-17 Maier subscale, which includes the items for depressed mood, feelings of guilt, suicide, work and activities, psychomotor retardation and psychomotor agitation, and psychic anxiety. Global assessment of improvement was measured using the Clinical Global Impression of Severity (CGI-S) score, ranging from 1 (*normal, not at all ill*) to 7 (*among the most extremely ill patients*) and the Patient Global Impression of Improvement scores (PGI-I) for emotional and physical symptoms, ranging from 1 (*very much better*) to 7 (*very much worse*).

Statistical Analysis

Patients who entered the study not currently receiving antidepressants and patients who were switched from their current antidepressant were compared using a mixed model repeated measures approach (MMRM). The analysis included the fixed, categorical effects of status of antidepressant use at study entrance, investigator, number of days on therapy, and a two-way interaction between status and number of days on therapy. No differences were observed in mean change on the HAMD-17 total score or the VAS overall pain score between these patient groups. For all subsequent analyses, all patients were pooled.

Baseline characteristics for continuous variables were assessed using an analysis of variance (ANOVA) including a term for investigator. The percentage of patients who had at least a score of 10 mm on the 0–100 mm VAS for pain at baseline and were therefore eligible for a clinically important reduction in pain was summarized. In addition, the rates of depression response and remission and clinically important reduction in pain at trial endpoint were summarized.

For the primary analysis, a categorical MMRM analysis was conducted in all patients without regard to baseline pain severity to determine if probability of remission was associated with reduction in pain scores independent of improvement in the core emotional symptoms of depression. The analysis included the effects of baseline HAMD-17 Maier subscale score, mean change in HAMD-17 Maier subscale score, mean change in VAS overall pain score, number of days on therapy, and a quadratic term of number of days on therapy. Also, mean change in VAS overall pain score over time was compared between remitters and non-remitters at endpoint using an MMRM approach. The analysis included effects of remission status, investigator, number of days on therapy, and a two-way interaction between remission status and number of days on therapy.

In the secondary analysis, patients who had at least a score of 10 mm on the 0–100 mm VAS for pain at baseline were evaluated based on whether they had a clinically important reduction in pain. Remission rates for patients experiencing a clinically important reduction in pain versus those who did not were compared using Fisher's exact test and probability of remission was compared for patients experiencing a clinically important reduction in pain from baseline to week 1 or 2 versus those who did not using a logistic regression model with predictors for pain response status, investigator, baseline HAMD-17 total score, and greatest change from baseline at weeks 1 or 2 in HAMD-17 total score. The effects of sex, age, sex by pain reduction status, and age by pain reduction status were analyzed by adding these terms to a logistic regression model. In eligible patients, a similar categorical MMRM analysis was run to determine if probability of remission was associated with a clinically important reduction of pain (using a categorical predictor variable).

An MMRM analysis was also run to determine if mean change on the HAMD-17 Maier subscale was associated with mean changes in VAS overall pain score over time. The analysis included the effects of baseline HAMD-17 Maier subscale score, change in VAS overall pain score, number of days on therapy, and a quadratic term of number of days on therapy. Also, an MMRM analysis was run to compare mean change on the HAMD-17 Maier subscale across time between patients with and without a clinically important reduction in pain. The analysis included the effects of pain reduction status, investigator, baseline HAMD-17 Maier subscale score, number of days on therapy, and a two-way interaction between pain reduction status and number of days on therapy.

A last observation carried forward (LOCF) approach was used to compare mean change at endpoint in VAS overall pain score between patients who had a 50% reduction in HAMD-17 total score at weeks 1 or 2 versus those who did not. The analysis of covariance (ANCOVA) was conducted using a model with terms for investigator, baseline VAS overall pain score, and early HAMD-17 reduction status. Mean change in VAS overall pain score was also compared between endpoint CGI and PGI score groups using an LOCF approach. Time to a clinically important pain reduction and a 50% reduction in HAMD-17 total score were analyzed using Kaplan-Meier estimation.

RESULTS

Patients

Two hundred forty nine patients (112 who were switched directly from an SSRI or venlafaxine therapy and 137 who were currently untreated) were included in the analysis. Table 1 summarizes the baseline clinical and demographic characteristics of the patients. Seventy-one percent (177/249) of patients completed the trial, and of those with a baseline measure, 68% (167/245) of patients had at least a score of 10 mm on the 0–100 mm VAS for pain and were eligible to achieve a clinically important reduction in pain.

Table 1 Baseline Demographic and Clinical Characteristics of Patients

Baseline Characteristics	Total (n = 249)
Age (y), mean (SD)	43.2 (11.9)
Sex, n (%) women	169 (67.9)
Ethnicity, n (%)	
African American	16 (6.4)
Asian	1 (0.4)
White	213 (85.5)
East Asian	2 (0.8)
Hispanic	17 (6.8)
HAMD-17 total, mean (SD)	20.8 (3.8)
VAS overall pain, mean (SD)	27.3 (24.1)
CGI-Severity, mean (SD)	4.4 (0.5)

HAMD-17, 17-item Hamilton Rating Scale for Depression (HAMD-17): VAS, visual analog scale of overall pain severity over the last week (0 = no pain, 100 = pain as severe as I can imagine).
CGI-S, Clinical Global Impression of Severity score, ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill patients).

Efficacy

The proportion of patients achieving response and remission in the symptoms of depression at endpoint was 67% (161/242) and 53% (128/242), respectively. Eighty percent (133/167) of eligible patients achieved a clinically important reduction in pain at endpoint after open-label treatment with duloxetine.

In all patients without regard to baseline pain severity, greater reduction in pain scores as measured by the VAS overall was associated with a higher estimated probability of remission, after accounting for changes in the core emotional symptoms of depression (as measured by the Maier subscale) ($p < .001$) and these improvements were significantly different between patients achieving versus not achieving remission at each week ($p < .001$) (Figure 1). Greater reduction in pain scores was also associated with greater improvement in the core emotional symptoms of depression ($p < .001$).

In patients with a VAS overall pain score ≥10 at baseline, a clinically important reduction of pain at any time over the course of the study was associated with a trend toward significantly higher probability of remission, after accounting for improvement in core emotional symptoms ($p = 0.052$). Furthermore, patients with clinically important reduction in pain had significantly greater improvement in the core mood symptoms as measured by mean change in the HAMD-17 Maier subscale than those without a clinically important reduction in pain (–7.98 vs. –5.87, $p < .001$) (Figure 2).

In an evaluation of the relationship between pain reduction and improvement in mood over time, patients who achieved

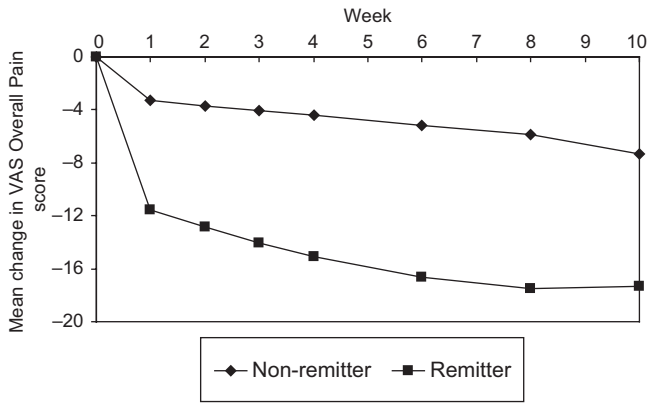

Figure 1 Mean change in visual analog scale (VAS) overall pain score by remission status at endpoint. Remission is defined as an endpoint 17-item Hamilton Rating Scale for Depression (HAMD-17) score ≤ 7.

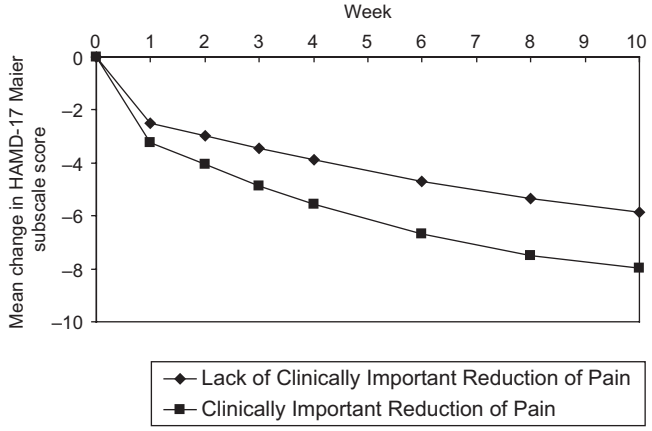

Figure 2 Mean change in 17-item Hamilton Rating Scale for Depression (HAMD-17) Maier subscale score by clinically important reduction of pain status. Clinically important reduction of pain is defined as a 10-unit and 30% or greater reduction in visual analog scale (VAS) overall pain score from baseline.

remission at endpoint had significantly lower mean pain scores at each visit and had significantly greater mean decrease and percent decrease in pain scores over time than patients who did not remit ($p < .001$). In addition, patients who experienced clinically important pain reduction in the first week of duloxetine treatment were significantly more likely than the patients without this pain reduction to reach remission of depression at endpoint (64.0% vs. 35.6%, $p < .001$). Furthermore, controlling for early depression response, patients who had a clinically important pain reduction from baseline to week 1 or 2 were more likely to achieve depression remission than those who did not have the pain reduction (54% vs. 28%, $p = .026$).

Similarly, changes in the HAMD-17 total scores were associated with subsequent changes in pain. Patients who had a depression response (≥ 50% improvement in the HAMD-17 total score) by week 1 or 2 had a greater improvement in pain over time as measured by mean change in the pain score from baseline to endpoint (–20.8 vs –6.2, $p < .001$).

Table 2 Mean Change from Baseline in Visual Analog Scale (VAS) Overall Pain Score* by Endpoint Clinical Global Impression of Severity (CGI-S) and Patient Global Impression of Improvement (PGI-I) Score Categories**

	Endpoint Measure Category (n, Mean Change in VAS)						
Measure	1	2	3	4	5	6	7
CGI-Severity	n = 84	n = 59	n = 41	n = 38	n = 9	n = 5	N/A
	–23.0	–14.2	–9.3	–1.5	15.9	26.9	
PGI-I	n = 55	n = 88	n = 39	n = 35	n = 8	n = 6	n = 2
Emotional	–19.9	–12.5	–12.2	–8.2	1.3	26.8	1.6
PGI-I	n = 42	n = 84	n = 48	n = 36	n = 12	n = 8	n = 3
Physical	–23.8	–14.7	–11.6	–6.8	3.9	12.8	45.7

*VAS overall pain score ranged from 0 (no pain) to 100 (pain as severe as I can imagine).
**CGI-S scores range from 1 (normal, not at all ill) to 7 (among the most extremely ill patients); PGI-I scores range from 1 (very much better) to 7 (very much worse).

When comparing the median time to response between the pain score and the HAMD-17 total score, it took 14 days (95% CI: 10 to 17 days) for patients to achieve a clinically important reduction in pain, and 28 days (95% CI: 27 to 35 days) for patients to have a depression response (≥ 50% reduction in the HAMD-17 total score). To provide further context, median time to a ≥ 50% reduction in pain score was 16 days (95% CI: 14 to 22 days).

Evaluating global measures of improvement, patients with an endpoint CGI-S score of 1 ("normal") had the most pain improvement while those with an endpoint score of 6 ("severe") had the most pain worsening. Similarly, patients with lower endpoint PGI-I scores had greater pain improvement (Table 2).

There were no significant differences in pain reduction among age groups (< 40, 40–50, > 50 years of age). Although women had a greater reduction in overall pain, the sex difference was not significant. Neither sex x pain reduction nor age x pain reduction was a significant predictor of remission.

DISCUSSION

In this 12-week, open-label trial of duloxetine 60 mg QD to 120 QD in 249 patients with major depressive disorder, a greater reduction in pain was associated with a higher probability of remission of depression, after accounting for changes in the core emotional symptoms of depression. Furthermore, greater pain reduction was associated with improvement in the core emotional symptoms of depression. A greater improvement in pain was also associated with improvements in patient and clinician-rated global assessments.

In addition to evaluating overall change in pain scores, we also evaluated the impact of a clinically important reduction in pain (defined as ≥ 30% reduction and ≥ 10 mm reduction in the VAS for overall pain) on depression outcomes. Notably, treatment with duloxetine resulted in a clinically important reduction in pain in 80% of the 167 patients who had at least a score of 10 mm on the

baseline VAS for overall pain. Patients with clinically important reduction in pain at any time in the study compared to those who did not have this reduction in pain had significantly greater improvement in the core emotional symptoms and an increased probability of remission, after accounting for improvement in core emotional symptoms, which approached significance.

When evaluating the relationships of improvement in pain and mood over time, we found a similar magnitude of association between early reduction in pain and subsequent remission of depression and between an early depression response and subsequent pain reduction. This suggests a synergistic effect between relief of pain and improvement in depressive illness severity, similar to what has been found in previous studies of duloxetine in major depressive disorder (9). The time to reach a clinically important reduction in pain, using the 30% or 50% reduction criteria, occurred earlier than the depression response. Taken together, these results suggest that the reduction in pain severity with duloxetine treatment is not simply an effect of improvement in overall mood. Indeed, studies of duloxetine in chronic pain disorders like fibromyalgia and diabetic peripheral neuropathic pain have consistently demonstrated an independent analgesic effect of duloxetine (14–17).

The results of this study are consistent with previous studies of the effect of duloxetine on painful symptoms in depressed patients (9,13). The dual reuptake inhibition of both serotonin and norepinephrine is believed to be the mechanism by which duloxetine improves mood and alleviates pain. Both serotonin and norepinephrine are key neurotransmitters in descending pain inhibitory pathways in the brain and spinal cord (23). Increasing the availability of serotonin and norepinephrine through treatment with duloxetine may promote pain inhibition centrally.

Several limitations of this study should be considered. This was an open-label study, and in the absence of a placebo group, the efficacy results should be interpreted with caution. In addition, patients with some comorbid psychiatric and medical disorders were excluded and the results may not generalize to all patients with major depressive disorder. The results comparing the time to response for pain and depression should be interpreted with caution, because the response definitions are different for each. While 30% or 50% reduction of pain and 50% reduction of HAM-D scores are clinically important, there is little evidence that these are equivalent. Furthermore, this study is a secondary analysis of another study in which the demonstration of the relationship between pain relief and depression outcomes was not the primary objective. Therefore the patient population varied with regard to the presence of pain and many patients lacked pain at baseline. Studies specifically designed to assess the relationship between pain relief and depression outcomes will be required to confirm the results of this study.

CONCLUSIONS

The results of this study suggest that effective treatment of pain symptoms in patients with major depressive disorder may be associated with higher remission rates. The results underscore the importance of effectively treating painful symptoms associated with depression.

ACKNOWLEDGMENTS

This work was sponsored by Eli Lilly and Company, Indianapolis, Indiana. Lesley Arnold has received consulting fees from Eli Lilly and Company, Pfizer Inc, Cypress Biosciences Inc, Wyeth Pharmaceuticals, Sanofi-Aventis, Boehringer Ingelheim, Sepracor, Forest Laboratories Inc, Allergan, and Vivus Inc; has received research support from Eli Lilly and Company, Pfizer Inc, Cypress Biosciences Inc, Wyeth Pharmaceuticals, Sanofi-Aventis, Boehringer Ingelheim, Allergan, and Forest; and is on the Speakers Bureau for Eli Lilly and Company and Pfizer Inc. Adam Meyers and Madelaine Wohlreich are stock shareholders and full-time employees of Eli Lilly and Company. Prabha Sunderajan receives grant support from Eli Lilly and Company. C. Brendan Montano has received research support from AstraZeneca, Forest/Cypess, Eli Lilly and Company, Novartis, Predix, and Sanofi-Aventis; and has been on the Speakers Bureau for AstraZeneca, Eli Lilly and Company, GlaxoSmithKline, and Takeda. Ethan Kass is on the Speakers Bureau for GlaxoSmithKline, Sanofi-Aventis, Wyeth Pharmaceuticals, and AstraZeneca; has been on the Speakers Bureau for Eli Lilly and Company and Pfizer Inc; and has received research support from Eli Lilly and Company, Wyeth Pharmaceuticals, Novartis, GlaxoSmithKline, Pfizer Inc, Organon Pharmaceuticals, Sepracor, Merck, Bristol-Myers Squibb, and AstraZeneca. Madhukar Trivedi has received research support from Bristol-Myers Squibb, Cephalon Inc, Corcept Therapeutics Inc, Cyberonics Inc, Eli Lilly and Company, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica, Merck, National Institute of Mental Health, National Alliance for Research in Schizophrenia and Depression, Novartis, Pfizer Inc, Pharmacia & Upjohn, Predix Pharmaceuticals, Solvay Pharmaceuticals Inc, and Wyeth-Ayerst Laboratories; has received consulting fees from Abbott Laboratories Inc, Akzo (Organon Pharmaceuticals Inc), AstraZeneca, Bayer, Bristol-Myers Squibb, Cephalon Inc, Cyberonics Inc, Eli Lilly and Company, Fabre-Kramer Pharmaceuticals Inc, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica Products LP, Johnson & Johnson PRD, Meade Johnson, Neuronetics, Parke-Davis Pharmaceuticals Inc, Pfizer Inc, Pharmacia & Upjohn, Sepracor, Solvay Pharmaceuticals Inc, VantagePoint, and Wyeth-Ayerst Laboratories; and is on the Speakers Bureau for Abdi Brahim, Akzo (Organon Pharmaceuticals Inc), Bristol-Myers Squibb, Cephalon Inc, Cyberonics Inc, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica Products LP, Eli Lilly and Company, Pharmacia & Upjohn, Solvay Pharmaceuticals Inc, and Wyeth-Ayerst Laboratories.

REFERENCES

1. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity. A literature review. *Arch Intern Med* 2003;1′63: 2433–2445.
2. Ohayon MM, Schatzberg AF. Using chronic pain to predict depressive morbidity in the general population. *Arch Gen Psychiatry* 2003;60:39–47.

3. Von Korff M, Ormel J, Katon W, Lin EHB. Disability and depression among high utilizers of health care. A longitudinal analysis. *Arch Gen Psychiatry* 1992;49:91–100.
4. Ohayon MM. Specific characteristics of the pain/depression association in the general population. *J Clin Psychiatry* 2004;65 [suppl 12]:5–9.
5. Boa Y, Sturm R, Croghan TW. A national study of the effect of chronic pain on the use of health care by depressed persons. *Psychiatr Serv* 2003;54:693–697.
6. Greenberg PE, Leong SA, Birnbaum HG, Robinson RL. The economic burden of depression with painful symptoms. *J Clin Psychiatry* 2003;64[suppl 7]:17–23.
7. Bair MJ, Robinson RL, Eckert GJ, Stang PE, Croghan TW, Kroenke K. Impact of pain on depression treatment response in primary care. *Psychosom Med* 2004;66:17–22.
8. Paykel ES, Ramana R, Cooper Z, Hayhurst H, Kerr J, Barocka A. Residual symptoms after partial remission: an important outcome in depression. *Psychol Med* 1995;25:1171–1180.
9. Fava M, Mallinckrodt CH, Detke MJ, Watkin JG, Wohlreich MM. The effect of duloxetine on painful physical symptoms in depressed patients: do improvements in these symptoms results in higher remission rates? *J Clin Psychiatry* 2004;65:521–530.
10. Goldstein DJ, Mallinckrodt C, Lu Y, Demitrack MA. Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. *J Clin Psychiatry* 2002;63:225–231.
11. Detke MJ, Goldstein DJ, Hayes JR, Demitrack MA. Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. *J Clin Psychiatry* 2002;63: 308–315.
12. Detke MJ, Lu Y, Goldstein DJ, McNamara RK, Demitrack MA. Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression. *J Psychiatr Res* 2002;36:383–390.
13. Goldstein DJ, Lu Y, Detke MJ, Hudson J, Iyengar S, Demitrack MA. Effects of duloxetine on painful physical symptoms associated with depression. *Psychosomatics* 2004;45:17–28.
14. Raskin J, Pritchett YL, Wang F, D'Souza DN, Waninger Al, Iyengar S, Wernicke JF. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. *Pain Med* 2005;6:346–356.
15. Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S. Duloxetine vs. placebo in patients with painful diabetic neuropathy. *Pain* 2005; 116:109–118.
16. Arnold LM, Lu Y, Crofford LJ, Wohlreich M, Detke MJ, Iyengar S, Goldstein DJ. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. *Arthritis Rheum* 2004; 50:2974–2984.
17. Arnold LM, Rosen A, Pritchett YL, D'Souza DN, Goldstein DJ, Iyengar S, Wernicke JF. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. *Pain* 2005;119:5–15.
18. Wohlreich MM, Martinez JM, Mallinckrodt CH, Prakash A, Watkin JG, Fava M. An open-label study of duloxetine for the treatment of major depressive disorder. *J Clin Psychopharmacol* 2005;25:552–560.
19. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
20. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; 23:56–62.
21. Guy W. *ECDEU Assessment Manual for Psychopharmacology*, Revised. US Department of Health, Education, and Welfare publication (ADM). Rockville, MD: National Institute of Mental Health, 1976: 76–338.
22. Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001;94:149–158.
23. Millan MJ. Descending control of pain. *Prog Neurobiol* 2002; 66:355–474.