Implications of Pain in Generalized Anxiety Disorder: Efficacy of Duloxetine

James T. Hartford, M.D.; Jean Endicott, Ph.D.; Susan G. Kornstein, M.D.; Christer Allgulander, M.D.; Madelaine M. Wohlreich, M.D.; James M. Russell, M.D.; David G. S. Perahia, M.D.; and Janelle S. Erickson, Ph.D.

Objective: To conduct a post hoc evaluation of the prevalence of clinically significant pain and the efficacy of duloxetine in patients with generalized anxiety disorder (GAD) and concurrent pain.

Method: Data from two 9- to 10-week double-blind, placebo-controlled, randomized clinical trials of duloxetine (60 to 120 mg) in DSM-IV–defined GAD were analyzed (study 1 was conducted from July 2004 to September 2005; study 2 was conducted from August 2004 to June 2005). Efficacy was assessed with the Hamilton Rating Scale for Anxiety (HAM-A), visual analog scales (VAS) for pain, the Hospital Anxiety Depression Scale (HADS), the Clinical Global Impressions-Improvement of Illness (CGI-I) scale, the Patient Global Impressions-Improvement (PGI-I) scale, and the Sheehan Disability Scale (SDS) global functional impairment scale.

Results: Of 840 patients randomly assigned to treatment, 61.3% (302 duloxetine, 213 placebo) had VAS scores ≥ 30 mm on at least 1 of the pain scales, indicating clinically significant pain. Among those patients with concurrent pain at baseline, change from baseline to endpoint in the HAM-A total score (42.9% change in mean scores for duloxetine, 31.4% for placebo), HADS anxiety scale (40.3% vs. 22.8%), HADS depression scale (36.1% vs. 20.5%), HAM-A psychic factor (45.9% vs. 29.9%), and SDS global functional improvement score (45.5% vs. 22.1%) was significantly (all p's < .001) greater for duloxetine compared with placebo. Improvement on the CGI-I ($p = .003$) and PGI-I ($p < .001$) was also significantly greater for duloxetine. Response (HAM-A total score decrease ≥ 50%) (49% vs. 29%) and remission (HAM-A total score ≤ 7 at endpoint) (29% vs. 18%) rates were significantly greater for duloxetine compared with placebo ($p < .001$ and $p = .041$, respectively). Duloxetine demonstrated statistically significantly greater reduction in pain on all 6 VAS pain scales (all p's < .001 except headaches with $p < .002$) (for duloxetine, percent change in means from baseline to endpoint ranged from 40.1% to 45.2% across the 6 VAS scales; for placebo, 22.0% to 26.3%).

Conclusion: Duloxetine, relative to placebo, improves anxiety symptoms, pain, and functional impairment among patients with GAD with concurrent clinically significant pain.

Trial Registration: clinicaltrials.gov Identifiers: NCT00122824 (study 1) and NCT00475969 (study 2)

(Prim Care Companion J Clin Psychiatry 2008;10:197–204)

Received Sept. 27, 2006; accepted Dec. 10, 2007. From Hartford Research Group, Cincinnati, Ohio (Dr. Hartford); Columbia University and New York State Psychiatric Institute, New York (Dr. Endicott); the Department of Psychiatry, Virginia Commonwealth University, Richmond (Dr. Kornstein); Karolinska Institutet, Stockholm, Sweden (Dr. Allgulander); Eli Lilly and Co., Indianapolis, Ind. (Drs. Wohlreich, Russell, and Erickson; Dr. Erickson is currently an employee of Orexigen Therapeutics, San Diego, Calif.); and Eli Lilly Research Center, Windlesham, Surrey and The Gordon Hospital, London, U.K. (Dr. Perahia).

The conduct of the 2 research studies included in this report, the analysis of the data, and the preparation of the manuscript were supported by Eli Lilly (Indianapolis, Ind.) and Boehringer Ingelheim, (Germany).

Acknowledgments appear at the end of the article.

Financial disclosure appears at the end of the article.

Corresponding author and reprints: James T. Hartford, M.D., Community Research, 4460 Red Bank Expressway, Suite 200, Cincinnati OH 45227 (e-mail: jhartford@communityresearch.com).

Generalized anxiety disorder (GAD) has been increasingly recognized as a common and disabling condition.[1] The most recent estimates of prevalence from large-scale epidemiologic studies are in the range of 4.1% to 5.7% for lifetime prevalence and 2.1% to 3.1% for 12-month prevalence.[2–4] The course of GAD is typically chronic, with less than half of patients in treatment settings achieving symptomatic remission over 8 years.[5] Community-based studies have shown that, among all mood, alcohol use, and anxiety disorders, GAD is ranked second (behind agoraphobia) in terms of total functional disability associated with the disorder, and the level of disability is equal to or greater than that observed with major physical disorders such as arthritis and heart disease.[6] In those individuals diagnosed with pure GAD (without any psychiatric comorbidities), functional role impairment is similar to that observed with major depressive disorder.[7]

Within primary care settings, GAD is especially common, with 12-month prevalence rates of approximately 4% and substantially higher rates when DSM-IV symptom criteria are used without a duration criterion.[8] Unlike in the general population, where major depressive disorder is more common than GAD, these 2 disorders are about equally as common in primary care settings.[8] The diagnosis of GAD is often missed in the primary care setting; less than half of patients with GAD receive the diagnosis.[8] Consequently, only about 20% of patients with

GAD seen by primary care physicians or other general medical providers receive even a minimally adequate course of treatment.[9]

Perhaps the major reason why GAD is underdiagnosed and undertreated in primary care settings is that such patients typically present with other complaints besides anxiety. In fact, only 13% of patients with a diagnosis of GAD present with a chief complaint of anxiety.[8] The most common presenting complaints of GAD patients in primary care include somatic symptoms (48%), pain (35%), sleep disturbance (33%), and depression (16%).[8] The pain symptoms common in GAD include nonspecific pain (lower back, unexplained causes) and specific pain conditions such as migraine. The association between GAD and pain symptoms such as migraine and arthritis is as strong or stronger than that seen for depression.[10,11] Adequate treatment of painful symptoms in GAD appears particularly important in a primary care setting where many patients are seeking treatment based upon these symptoms,[8,12] and successful treatment of painful symptoms associated with GAD would therefore likely reduce health care utilization and costs and improve patient functioning.

In contrast to the selective serotonin reuptake inhibitors (SSRIs), the dual-acting serotonin-norepinephrine reuptake inhibitors venlafaxine and duloxetine have demonstrated efficacy in the treatment of several specific pain symptoms.[13] In particular, venlafaxine has shown efficacy in the treatment of migraine and neuropathic pain.[14,15] Duloxetine has shown safety and efficacy in the treatment of pain associated with fibromyalgia in women and diabetic peripheral neuropathy.[16–19] Duloxetine has also shown efficacy in reducing painful symptoms associated with major depressive disorder.[20,21]

This article reports on the efficacy of duloxetine in the treatment of GAD with associated pain. Pooling data from 2 randomized, placebo-controlled trials of duloxetine for GAD, the following questions are addressed. (1) How prevalent is clinically significant pain among patients with GAD? (2) Among patients with clinically significant pain at baseline, does duloxetine improve anxiety and depressive symptoms and functional impairment compared with placebo? (3) Does duloxetine improve pain symptoms in GAD compared with placebo?

METHOD

Overview

Data from 2 randomized, placebo-controlled trials of duloxetine for GAD were pooled for these analyses. Patients were initially selected for inclusion in the analyses based on having clinically significant pain. Within this subsample, change from baseline was evaluated on measures of anxiety symptoms, depressive symptoms, disability, and pain.

Design and Procedures

All patients participated in 1 of 2 randomized, placebo-controlled studies of duloxetine for GAD.[22,23] Both studies were acute treatment trials consisting of a single-blind placebo lead-in period (5–9 days for the first study and 1 week in duration for the second), followed by 9 or 10 weeks of acute double-blind treatment with duloxetine or placebo, and ending with a 2-week drug discontinuation phase.

A total of 840 adult patients (men and women aged ≥ 18 years) with a diagnosis of GAD as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) were recruited by referral and advertisements and then randomly assigned to treatment across the 2 studies. Diagnosis of GAD and other psychiatric diagnoses were established using the Mini-International Neuropsychiatric Interview (MINI).[24] Experienced interviewers (generally the physician investigators) participated in a training session at study startup and were approved by the sponsor for participation in the study after review of their clinical skills in conducting interviews. In addition to a GAD diagnosis, inclusion criteria in both studies consisted of (1) a GAD disease severity of at least moderate intensity as defined by a Hospital Anxiety Depression Scale[25] (HADS) anxiety subscale score ≥ 10 and a Covi Anxiety Scale[26] (CAS) score ≥ 9, (2) no item on the Raskin Depression Scale[27] (RDS) > 3, (3) a CAS score greater than the RDS score, and (4) a Clinical Global Impressions-Severity of Illness scale[28] score > 4 at the screening visit and again prior to the placebo lead-in phase. In addition, to be included within the subsample of patients analyzed in the current report, patients must have had a visual analog scale (VAS) for pain[29] score ≥ 30 on any of the 6 pain scales (see below).

In both studies, patients were excluded if they had any of the following diagnoses: any current and primary DSM-IV Axis I diagnosis other than GAD; major depressive disorder in the past 6 months; panic disorder, posttraumatic stress disorder, or an eating disorder within the past year; obsessive-compulsive disorder, bipolar disorder, psychosis, factitious disorder, or somatoform disorders during their lifetime; or history of alcohol or any psychoactive substance abuse or dependence within the past 6 months (or screened positive for any substances of abuse at the screening visit). Patients were also excluded if, prior to enrollment in the placebo lead-in period, they had used a benzodiazepine within 14 days, received a monoamine oxidase inhibitor or fluoxetine within 30 days, received any experimental medication within 30 days, had been previously treated with duloxetine, used caffeine excessively, or began (or changed the intensity of) psychotherapy or other nondrug therapy within 6 weeks. Additional exclusion criteria consisted of any serious medical illness or any clinically significant laboratory abnormality. Patients judged clinically to be at

serious suicidal risk or patients who, in the opinion of the investigator, were poor medical or psychiatric risks for study completion were also excluded. Patients who reported a lack of response of the current episode of GAD to 2 or more adequate trials of antidepressants, benzodiazepines, or other anxiolytics at a clinically appropriate dose for a minimum of 4 weeks were excluded. Women who were pregnant or breastfeeding were also excluded.

Study 1[22] was conducted at 41 study sites in 7 countries (Finland, France, Germany, South Africa, Spain, Sweden, and the United States) from July 2004 to September 2005. Study 2[23] was conducted at 28 study sites in the United States from August 2004 to June 2005.

Patients were screened for the study at a clinic visit occurring between 3 and 30 days prior to beginning the 1-week, single-blind, placebo, lead-in period. After the lead-in period, patients were randomly assigned to treatment. In study 1, patients were randomly assigned to placebo, duloxetine 60 mg q.d., or duloxetine 120 mg q.d. Patients randomly assigned to either duloxetine treatment group started treatment with duloxetine 60 mg q.d. at baseline. If 60 mg q.d. could not be tolerated, the dose for patients randomly assigned to duloxetine 120 mg q.d. could be reduced to 30 mg q.d. until the end of week 1, followed by 60 mg q.d. until the end of week 2. For patients randomly assigned to duloxetine 60 mg q.d., the dose could be reduced to 30 mg q.d. until the end of week 2. At the end of week 2, patients had to be able to tolerate their randomly assigned dose or else they discontinued the study.

In study 2, patients were randomly assigned to either placebo or duloxetine 60 to 120 mg/day. The starting dose of duloxetine was 60 mg q.d.; however, a dose decrease to 30 mg q.d. was allowed for the first 1 to 2 weeks so that patients could adjust to the medication, followed by a dose increase to 60 mg q.d. and subsequent dose increases of 30 mg q.d. up to a maximum dose of 120 mg q.d. Dose increases to maximize efficacy were allowed based on investigator judgment; however, the protocol required that the dose be increased if a patient's Clinical Global Impressions-Improvement of Illness (CGI-I) scale[28] score was 3 (minimal improvement, no change, or worse) during the first 4 weeks of treatment, unless the patient was unable to tolerate an increased dose. A total of 2 downward-dose adjustments for tolerability concerns were allowed, with a minimum allowable dose of 60 mg/day of duloxetine.

The protocols were approved by the respective institutional review boards or ethics committees at the participating clinical sites. All patients gave written informed consent to participate in the research studies.

Assessments

Assessment instruments were the same in both studies. Anxiety symptoms were measured using the clinician-administered Hamilton Rating Scale for Anxiety[30] (HAM-A). The HAM-A consists of 14 items, each rated on a 5-point scale of 0 (not present) to 4 (very severe). The HAM-A total score is the sum of the 14 items and ranges from 0 to 56, with higher scores indicating a greater degree of symptom severity. In addition to the HAM-A total score, the widely used psychic and somatic factors from this scale were also examined. Clinical response was defined as a 50% or greater decrease in the HAM-A total score from baseline to endpoint. Whether or not each patient sustained a clinical improvement was also examined and was defined as achieving a ≥ 30% decrease in the HAM-A total score from baseline to the first postbaseline assessment visit that this criterion was met, and then maintaining or exceeding this improvement at all subsequent assessment visits. Remission was defined as a HAM-A total score ≤ 7 at endpoint.[31]

Pain was assessed using the self-reported VAS for pain. The VAS is a line of 100-mm length, with 0 at one end representing "no pain" and 100 at the other end representing "pain as severe as I can imagine." Patients mark their perceived level of pain intensity during the past week by indicating a point on the line, and the examiner scores the instrument by measuring the distance in millimeters from the zero anchor to the mark that the patient identified as his or her level of pain. Separate VAS ratings were obtained for overall pain, headache, backache, and shoulder pain. Two additional ratings of proportion of day while awake with pain (ranging from "none of the time" to "all of the time") and daily interference due to pain (ranging from "not at all" to "complete disability") are also made on a 0 to 100 scale. The VAS ratings were obtained at each study visit (baseline and weeks 1, 2, 4, 6, and 9 in study 1; baseline and weeks 1, 2, 4, 7, and 10 in study 2).

Patients who had a VAS score ≥ 30 on any of the pain scales were identified as having clinically significant pain and are the focus of the current report (the same sample was used for all analyses, provided measures were not missing). The criterion of ≥ 30 was based on previous research indicating that baseline VAS scores in excess of 30 correspond to a verbal report of at least moderate pain.[32] Clinically significant change on these VAS pain scales was examined by calculating response on each scale, defined as a 50% or greater change from baseline to endpoint. Studies have demonstrated that a reduction of approximately 30% in pain scales such as the 11-point pain intensity numerical rating scale represents a clinically important difference.[33] However, for the purposes of these analyses, a higher hurdle of a 50% reduction in pain symptoms was chosen.

Additional efficacy variables included the anxiety and depression subscale scores of the HADS and the Sheehan Disability Scale (SDS) global functional impairment score.[34] Global improvement was measured with the

clinician-rated CGI-I and the patient-rated Patient Global Impressions-Improvement (PGI-I) scale,[28] each of which is scored from 1 (very much improved) to 7 (very much worse).

In study 1, assessment visits were conducted at baseline and weeks 1, 2, 4, 6, and 9; in study 2, visits were conducted at baseline and weeks 1, 2, 4, 7, and 10. The HAM-A, CGI-I, and PGI-I were administered at each of these visits; the HADS and SDS were given at baseline and endpoint only.

Statistical Analyses

The primary patient population for this post hoc efficacy analysis was those patients with clinically significant pain at baseline (any VAS scale score ≥ 30). For entry into the studies, patients were not required to meet a minimum threshold at baseline for pain. Within the subsample that had any VAS scale score ≥ 30, patients who had a baseline measurement on a given efficacy measure, and at least 1 postbaseline measurement on that efficacy measure, were included in the efficacy analyses of that measure. Across both studies, patients treated with either 60 mg or 120 mg of duloxetine were combined to form 1 treatment group and compared with placebo-treated patients. Treatment group comparisons on baseline clinical and demographic variables were conducted using χ^2 statistics for categorical variables and analysis of variance (with treatment and study as terms in the model) for continuous variables.

For continuous efficacy variables, with the exception of CGI-I and PGI-I scores, treatment group differences were examined using an analysis of covariance model with treatment and study as main effects and the baseline score as the covariate (last observation carried forward, LOCF). The CGI-I and PGI-I endpoint scores were analyzed using an analysis of variance model with treatment and study as fixed effects. Comparisons between treatment groups on response, sustained improvement, and remission outcomes were conducted using a Cochran-Mantel-Haenszel χ^2 analysis with study as the stratifying factor.

Changes in pain symptoms (each VAS scale separately) were examined between the treatment groups with mixed-effects repeated-measures (MMRM) analysis using data from all postbaseline assessments (also referred to as main effect of treatment). The model included the fixed categorical effects of treatment, site, visit, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline score and baseline-by-visit interaction. The analysis compared the treatment groups on the adjusted-for-baseline estimated VAS scale means across all postbaseline visits (i.e., not the slope across visits). An unstructured covariance matrix was specified to model the within-patient errors. The Kenward-Roger method was used to estimate denominator degrees of freedom.

Analyses were implemented using SAS (version 8.0, SAS Institute Inc., Cary, N.C.). Mean refers to the least-squares mean, which is the model-adjusted mean for the respective analysis. Statistical significance was declared at a α level of .05 (2 tailed).

Table 1. Baseline Clinical and Demographic Characteristics of Patients[a]

Characteristic	Duloxetine (N = 302)	Placebo (N = 213)
Female, N (%)	207 (68.5)	138 (64.8)
Age, mean ± SD, y	42.2 ± 12.6	43.1 ± 13.7
Race, N (%)		
White	283 (93.7)	194 (91.1)
African American	8 (2.7)	9 (4.2)
Other	11 (3.6)	10 (4.7)
HAM-A total score, mean ± SD	25.7 ± 7.1	26.0 ± 7.9
CGI-S score, mean ± SD	4.7 ± 0.6	4.8 ± 0.6
HADS anxiety subscale score, mean ± SD	13.6 ± 3.4	13.4 ± 3.8
HADS depression subscale score, mean ± SD	8.4 ± 3.9	8.8 ± 4.0
SDS global functional impairment score, mean ± SD	16.2 ± 6.6	15.9 ± 7.1
Visual analog pain scales, mean ± SD (%)[b]		
Overall pain severity	43.5 ± 23.5 (68.9)	41.7 ± 23.2 (68.5)
Headaches	34.9 ± 27.5 (52.0)	30.9 ± 25.4 (49.3)
Back pain	34.7 ± 27.5 (52.7)	32.9 ± 27.0 (47.4)
Shoulder pain	31.7 ± 28.8 (47.2)	30.6 ± 29.0 (46.5)
Interference in daily activities	34.4 ± 25.5 (51.5)	36.4 ± 24.7 (57.8)
Pain while awake	48.7 ± 27.7 (72.1)	48.4 ± 27.0 (76.5)

[a]There were no significant differences between the treatment groups on any baseline measure. All patients with a score ≥ 30 on any of the visual analog pain scales at baseline were included here.
[b]Percentage with score ≥ 30.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HADS = Hospital Anxiety Depression Scale, HAM-A = Hamilton Rating Scale for Anxiety, SDS = Sheehan Disability Scale.

RESULTS

Baseline Clinical and Demographic Characteristics

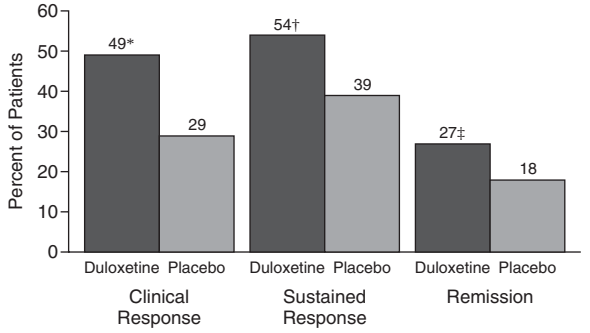
Of the 840 patients who were randomly assigned in the 2 studies, 515 (61.3%) (302 duloxetine, 213 placebo) had a VAS score ≥ 30 on at least 1 of the pain scales, indicating clinically significant pain. Of these, 506 (294 duloxetine, 212 placebo) received study medication and had at least 1 postbaseline assessment. Demographic and clinical characteristics of the 515 patients with VAS scores ≥ 30 are given in Table 1. Among the patients, 67.0% (345/515) were women, 92.6% (477/515) were white, and the mean ± SD age was 42.6 ± 13.1 years. The mean ± SD baseline HAM-A total scores were 25.7 ± 7.1 and 26.0 ± 7.9 for duloxetine and placebo, respectively. The mean ± SD overall pain rating on the VAS was 42.73 ± 23.39 (0–100 scale). There were no statistically significant differences between the treatment groups on any of these

Table 2. Results for Efficacy Measures at Endpoint During 9 to 10 Weeks of Double-Blind Treatment[a]

	Duloxetine (N = 291)		Placebo (N = 211)		
Efficacy Measure	Endpoint, Mean (SD)	Least-Squares Change, Mean (SE)	Endpoint, Mean (SD)	Least-Squares Change, Mean (SE)	p Value
HAM-A total score	14.7 (9.9)	–10.7 (0.57)	17.8 (10.5)	–8.0 (0.64)	.002
HAM-A psychic score	7.8 (5.5)	–6.4 (0.32)	10.2 (5.9)	–4.3 (0.36)	< .001
HAM-A somatic score	6.9 (5.1)	–4.3 (0.29)	7.7 (5.4)	–3.8 (0.33)	.195
HADS anxiety score	8.1 (4.7)	–5.2 (0.28)	10.3 (4.8)	–3.1 (0.31)	< .001
HADS depression score	5.3 (4.1)	–3.1 (0.25)	7.0 (4.5)	–1.7 (0.28)	< .001
SDS global functional impairment score	8.9 (8.1)	–7.2 (0.49)	12.4 (8.5)	–3.6 (0.54)	< .001
CGI-I score	2.6 (1.3)	NA	3.0 (1.3)	NA	.003
PGI-I score	2.7 (1.6)	NA	3.2 (1.4)	NA	< .001

[a]A greater decrease on the HAM-A, HADS, and SDS indicates more improvement. A lower mean score on the CGI-I and PGI-I indicates greater improvement. All patients with a score ≥ 30 on any of the visual analog scales at baseline and at least 1 postbaseline score on the listed efficacy measures were included here.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement of Illness scale, HADS = Hospital Anxiety Depression Scale, HAM-A = Hamilton Rating Scale for Anxiety, NA = not applicable, PGI-I = Patient Global Impressions-Improvement scale, SDS = Sheehan Disability Scale.

Figure 1. Response, Sustained Improvement, and Remission Rates for Duloxetine (N = 294) and Placebo (N = 212) Among Patients With Clinically Significant Pain at Baseline[a]



[a]Clinical response = HAM-A total score change ≥ 50% from baseline to endpoint. Sustained improvement = HAM-A total score change ≥ 30% from baseline at first postrandomization visit that is maintained or exceeded at all subsequent visits. Remission = HAM-A total score ≤ 7 at endpoint.
*p < .001.
†p = .005.
‡p = .041.
Abbreviation: HAM-A = Hamilton Rating Scale for Anxiety.

baseline demographic or clinical characteristics. For the 515 patients included here, there was no significant difference between the proportion of patients completing treatment (70.4% [150/213] for placebo, 64.9% [196/302] for duloxetine).

Improvement in Symptoms and Functioning

Among patients with clinically significant pain at baseline, change from baseline to endpoint in the HAM-A total score was significantly (p = .002) greater for duloxetine compared with placebo (Table 2). Duloxetine was also significantly (p < .001) superior to placebo on the HADS anxiety scale, HADS depression scale, and HAM-A psychic factor. Improvement in functioning was also significantly greater (p < .001) for duloxetine compared with placebo, as measured by the SDS global functional impairment scale. Overall improvement, as reflected in the clinician-rated CGI-I (p = .003) and the patient-rated PGI-I (p < .001) scales, also demonstrated significantly greater improvement for duloxetine-treated patients compared with placebo-treated patients. The only efficacy measure that was not statistically significantly different between the treatment groups was the HAM-A somatic factor.

There was a clinically meaningful and statistically significant (p < .001) difference in response rates (duloxetine: 49%, placebo: 29%) between the 2 treatment groups. Duloxetine-treated patients were also significantly more likely to achieve a sustained improvement (p = .005) across the acute treatment period and were more likely (p = .041) to achieve symptomatic remission at endpoint compared with placebo-treated patients (Figure 1).

Change in Pain Symptoms

When treatment effects were pooled over all visits (MMRM, main effect of treatment), duloxetine-treated patients demonstrated significantly greater reductions in pain compared with placebo-treated patients (all p values < .001 except headaches with p < .002) for all 6 VAS pain scales (Table 3). The mean change in VAS scores from baseline to endpoint expressed as percentages for improvement in painful symptoms in duloxetine-treated patients ranged across the 6 VAS scales from 40.1% to 45.2%, compared with 22.0% to 26.3% in placebo-treated patients. The duloxetine group had significantly higher response (defined as a ≥ 50% change from baseline to endpoint) rates (ranging from 51% to 59% of patients) for all 6 of the VAS pain items compared with the placebo group (ranging from 38% to 45% of patients), with p values ranging from .041 to .005 (Figure 2).

DISCUSSION

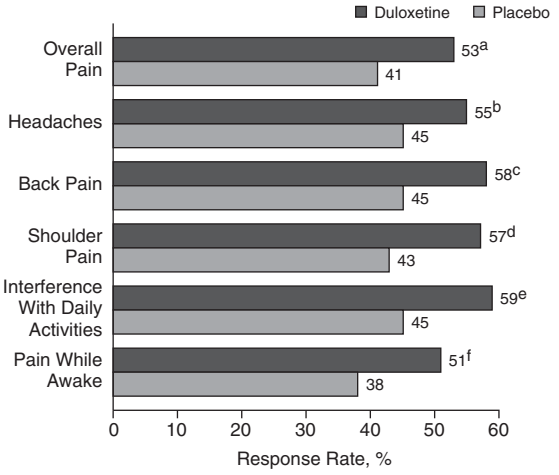
There were 3 major findings from this post hoc analysis. The first was that a substantial number of

Table 3. Change in Visual Analog Scale Pain Scores From Baseline to Postbaseline (pooled over all visits)[a]

	Duloxetine (N = 291)		Placebo (N = 211)		Duloxetine vs Placebo	
Visual Analog Scale Rating	Least-Squares Mean	SE	Least-Squares Mean	SE	Difference	p Value
Overall pain	–18.22	1.15	–10.66	1.25	–7.56	< .001
Headaches	–13.85	1.10	–8.83	1.20	–5.02	< .002
Back pain	–14.51	1.08	–8.59	1.19	–5.92	< .001
Shoulder pain	–13.51	1.04	–8.01	1.13	–5.50	< .001
Interference with daily activities	–14.51	1.15	–8.11	1.26	–6.40	< .001
Pain while awake	–19.47	1.39	–11.87	1.52	–7.60	< .001

[a]Means are average during treatment (weeks 1–9 or 10) scores estimated from mixed-model analysis with treatment, visit, treatment by visit, baseline, and baseline by visit as terms. All patients with a score ≥ 30 on any of the visual analog scales at baseline and at least 1 postbaseline score on the listed efficacy measures were included here.

Figure 2. Response Rates (≥ 50% decrease to endpoint) on VAS Pain Scales for Duloxetine (N = 294) and Placebo (N = 212) Among Patients With Clinically Significant Pain at Baseline



[a]p = .007.
[b]p = .041.
[c]p = .017.
[d]p = .009.
[e]p = .005.
[f]p = .008.
Abbreviation: VAS = visual analog scale.

treatment-seeking patients with GAD report clinically significant pain: over 60% of the sample had a score ≥ 30 at baseline on 1 or more of the VAS pain scales. The second finding was that, among these GAD patients with pain symptoms, duloxetine was clinically and statistically superior to placebo in reducing anxiety and depressive symptoms and in improving functioning. The third finding was that duloxetine improved pain symptoms to a greater degree than placebo. The overall amount of change in pain symptoms was also clinically meaningful, with percent improvement from baseline ranging from 40.1% to 45.2% across scales in the duloxetine group (compared with 22.0% to 26.3% in placebo-treated patients).

The high rate of pain symptoms found in this treatment-seeking patient sample is generally consistent with previous studies using both community and clinical samples. While the exact rates of clinically significant pain symptoms in community samples of GAD patients have not been published, high rates of GAD have been observed for individuals with specific pain conditions (arthritis, migraine, back pain).[35] Although 35% of patients with GAD seeking treatment in primary care settings report pain as a presenting complaint,[8] this is likely to be an underestimate. Many GAD patients with pain may not mention the pain symptom as a presenting complaint because of its chronic nature. Thus, studies that systematically assess pain, rather than relying on spontaneous reports of presenting complaints, will expectedly yield higher rates of pain. Among GAD patients with pain in the current study, the average overall pain rating is comparable to that found previously for patients with major depressive disorder.[20]

The nature of the connection between pain and GAD is poorly understood. There are several mechanisms through which persistent pain can arise, including disease states, metabolic changes, trauma, and chronic inflammation. Descending serotonergic and noradrenergic neural pathways are implicated in chronic inflammatory pain.[36] These same serotonergic and noradrenergic pathways also send ascending signals to areas of the brain that are implicated in depression and anxiety.[37] It is possible that impaired functioning of these pathways may lead to the high co-occurrence of pain symptoms with psychiatric syndromes like depression and anxiety.[38] Consistent with this explanation is the effect of duloxetine—a potent and balanced inhibitor of the reuptake of both serotonin and norepinephrine—on improving both pain and anxiety/depression.

Regardless of the reasons for the co-occurrence of pain symptoms in GAD patients, the current study suggests that duloxetine demonstrates clinically meaningful efficacy in treating GAD patients who have pain symptoms. This is noteworthy for 2 reasons. The first is that, as mentioned, pain symptoms are common in GAD patients. Second, SSRIs commonly prescribed in primary care for a wide range of patients with anxiety and depressive disorders have shown inconsistent efficacy in regard to pain.[39,40] Animal studies of pain suggest that the combined reuptake blockade of serotonin and norepinephrine is more effective than blockade of serotonin reuptake

alone,[41] and clinical studies in patients with pain support the use of dual-action antidepressants.[16–19] In this study, duloxetine improved both the anxiety symptoms and the pain symptoms of those GAD patients with clinically significant pain.

The current study has several limitations. One is that the sample was a selected subgroup from a larger sample of GAD patients. As such, it would be useful to confirm these findings with a prospectively selected group of patients with pain and GAD. A second limitation is that the report of pain symptoms in the context of GAD may be influenced by the worry and high focus on physical sensations and symptoms inherent in the GAD syndrome. Because of this issue, it is difficult to know for certain from this study alone if duloxetine is acting directly on pain or simply reducing the worrying about symptoms more generally. However, previous studies demonstrating the efficacy of duloxetine within pain populations, as well as animal studies of duloxetine and pain, have indicated that duloxetine does act directly on pain.[16–19,37,42] A third limitation is that little is known about the specific pain experienced by patients in the study since the VAS scales are limited in their assessment of pain syndromes. Confounding factors, such as painful side effects (e.g., headaches) from duloxetine, cannot be separated from pain originating from other sources. Such side effects, however, would work against obtaining differences in improvement on pain measures between duloxetine and placebo. A final limitation, inherent in most clinical trials, is the nature of the inclusion/exclusion criteria and the consequential restriction on the generalizability of the findings. In particular, patients with serious medical illness or comorbid medical and psychiatric conditions were excluded, and, thus, the patient population may not be fully representative of those seen in all practice settings. Whether duloxetine improves pain in the context of patients with GAD and concurrent medical illnesses remains a topic for further research.

In summary, the present study suggests that pain symptoms are common in GAD patients and that duloxetine shows clinical efficacy, relative to placebo, in treating the symptoms and impaired functioning of such patients with pain and GAD. Moreover, the pain symptoms themselves improve significantly more with duloxetine compared with placebo. Increasing the awareness of the association between painful physical symptoms and anxiety may help in the detection of GAD, which is often unrecognized in primary care settings. Duloxetine may be a useful treatment option for GAD patients in general, including those with pain symptoms.

Drug names: duloxetine (Cymbalta), fluoxetine (Prozac and others), norepinephrine (Levophed and others), venlafaxine (Effexor and others).

Acknowledgments: The authors acknowledge Paul Crits-Christoph, Ph.D., for assistance in preparing the manuscript; Deborah N. D'Souza, Ph.D., M.B.A., for review of the manuscript; and Wenqi You, M.S., Huifang Chen, M.S., and Steve Gelwicks, M.S., for statistical programming support. Dr. Crits-Christoph is an employee of the University of Pennsylvania and has served as a consultant to Eli Lilly, Pfizer, Alkermes, Cephalon, and Bristol-Myers Squibb. Dr. D'Souza and Mr. Gelwicks are employees of and stock shareholders in Eli Lilly. Ms. You is an employee of Eli Lilly. Ms. Chen works as a contractor for Eli Lilly via MedFocus.

Financial disclosure: **Dr. Hartford** has received grant research support from AstraZeneca International Pharmaceuticals, Avera, Boehringer Ingelheim, Bristol-Myers Squibb, Cephalon, Cyberonics, DOV, Eli Lilly, Fabre-Kramer, Forest, GlaxoSmithKline, J & J, Janssen, Kyowa, MediciNova, Merck, Merck KGaA, Mitsubishi Chemical, Neurocrine Biosciences, Neuronetics, Organon, Otsuka America, Pfizer, Sanofi-Aventis, Sepracor, Shire, Solvay, Somerset, Sumitomo, Takeda, Targacept, and Wyeth-Ayerst. **Dr. Endicott** has received grant/research support from Abbott, Bristol-Myers Squibb, Cyberonics, Interneuron, Merck, Parke-Davis, Pfizer, UpJohn, and Wyeth-Ayerst and has served as a consultant to or on the advisory boards for Abbott, AstraZeneca, Berlex, Bristol-Myers Squibb, Cyberonics, Eli Lilly, GlaxoSmithKline, Novartis, Otsuka, Janssen, Parke-Davis, Pfizer, Sanofi-Synthelabo Research, and Wyeth-Ayerst. **Dr. Kornstein** has received grant/research support from Department of Health and Human Services, National Institute of Mental Health, Pfizer, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Mitsubishi-Tokyo, Merck, Biovail, Wyeth, Berlex, Novartis, Sepracor, Boehringer Ingelheim, Sanofi-Synthelabo, and Astra-Zeneca; has served on the advisory boards of or received honoraria from Pfizer, Wyeth, Eli Lilly, Bristol-Myers Squibb, Warner-Chilcott, Biovail, Berlex, and Forest; and has received book royalties from Guilford Press. **Dr. Allgulander** has served as a consultant to or on the speakers or advisory boards of Eli Lilly. **Drs. Wohlreich**, **Russell**, and **Perahia** are employees of and stock shareholders in Eli Lilly. **Dr. Erickson** is a former employee of Eli Lilly and a current employee of Orexigen Therapeutics.

REFERENCES

1. Wittchen HU. Generalized anxiety disorder: prevalence, burden and cost to society. Depress Anxiety 2002;16:162–171
2. Grant BF, Hasin DS, Stinson FS, et al. Prevalence, correlates, comorbidity, and comparative disability of DSM-IV generalized anxiety disorder in the USA: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Psychol Med 2005;35:1747–1759
3. Kessler RC, Berglund PA, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:593–602
4. Kessler RC, Chiu WT, Demler O, et al. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:617–627
5. Yonkers KA, Bruce SE, Dyck IR, et al. Chronicity, relapse, and illness—course of panic disorder, social phobia, and generalized anxiety disorder: findings in men and women from 8 years of follow-up. Depress Anxiety 2003;17:173–179
6. Buist-Bouwman MA, De Graaf R, Vollebergh WAM, et al. Functional disability of mental disorders and comparison with physical disorders: a study among the general population of 6 European countries. Acta Psychiatr Scand 2006;113:492–500
7. Kessler RC, Dupont RL, Berglund P, et al. Impairment in pure and comorbid generalized anxiety disorder and major depression at 12 months in 2 national surveys. Am J Psychiatry 1999;156:1915–1923
8. Wittchen HU, Kessler RC, Beesdo K, et al. Generalized anxiety and depression in primary care: prevalence, recognition, and management. J Clin Psychiatry 2002;63(suppl 8):24–34
9. Wang PS, Bohn RL, Glynn RJ, et al. Hazardous benzodiazepine regimens in the elderly: effects of half life, dosage, and duration on risk of hip fracture. Am J Psychiatry 2001;158:892–898
10. McWilliams LA, Cox BJ, Enns MW. Mood and anxiety disorders associated with chronic pain: an examination in a nationally representative sample. Pain 2003;106:127–133
11. Merikangas KR, Angst J, Isler H. Migraine and psychopathology: results

 © Copyright 2008 Physicians Postgraduate Press, Inc.

of the Zurich cohort study of young adults. Arch Gen Psychiatry 1990; 47:849–853
12. Roy-Byrne PP. Generalized anxiety and mixed anxiety-depression: association with disability and health care utilization. J Clin Psychiatry 1996; 57(suppl 7):86–91
13. Briley M. Clinical experience with dual action antidepressants in different chronic pain syndromes. Hum Psychopharmacology 2004;19 (suppl 1):S21–S25
14. Ozyalcin SN, Talu GK, Kiziltan E, et al. The efficacy and safety of venlafaxine in the prophylaxis of migraine. Headache 2005;45:144–152
15. Rowbotham MC, Goli V, Kunz NR, et al. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. Pain 2004;110:697–706
16. Arnold LM, Lu Y, Crofford LJ, et al. A double-blind, multicenter trial comparing duloxetine to 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, et al. 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. Goldstein DJ, Lu Y, Detke MJ, et al. Duloxetine vs placebo in patients with painful diabetic neuropathy. Pain 2005;116:109–118
19. Wernicke J, Lu Y, D'Souza DN, et al. Antidepressants: duloxetine at doses of 60 mg qd and 60 mg bid is effective in treatment of diabetic neuropathic pain (DNP). J Pain 2004;5(3 suppl 1):S48
20. Brannan SK, Mallinckrodt CH, Brown EB, et al. Duloxetine 60 mg once daily in the treatment of painful physical symptoms in patients with major depressive disorder. J Psychiatr Res 2005;39:43–53
21. Goldstein DJ, Lu Y, Detke MJ, et al. Effects of duloxetine on painful physical symptoms associated with depression. Psychosomatics 2004; 45:17–28
22. Koponen H, Allgulander C, Pritchett Y, et al. A fixed-dose study of the efficacy and safety of duloxetine for the treatment of generalized anxiety disorder. Presented at Anxiety Disorders Association of America; March 23–26, 2006; Miami, Fla
23. Rynn M, Russell J, Erickson J, et al. Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: a flexible-dose, progressive-titration, placebo-controlled trial. Presented at Anxiety Disorders Association of America; March 23–26, 2006; Miami, Fla
24. 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
25. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67:361–370
26. Lipman RS, Covi L. Outpatient treatment of neurotic depression: medication and group psychotherapy. In: Spitzer R, Klein D, eds. Evaluation of Psychological Therapies. Baltimore, Md: John Hopkins University Press; 1976:178–218
27. Raskin A, Schulterbrandt J, Reating N, et al. Replication of factors of psychopathology in interview, ward behavior and self-report ratings of hospitalized depressives. J Nerv Ment Dis 1969;148:87–98
28. Guy W. Clinical Global Impressions. In: ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education and Welfare publication (ADM) 76-338. Washington, DC: National Institute of Mental Health; 1976:218–222
29. 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
30. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
31. Ballenger JC. Clinical guidelines for establishing remission in patients with depression and anxiety. J Clin Psychiatry 1999;60(suppl 22):29–34
32. Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres? Pain 1997;72:95–97
33. Farrar JT, Young JP Jr, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149–158
34. Sheehan DV. Sheehan Disability Scale. In: American Psychiatric Association. Handbook of Psychiatric Measures. Washington, DC: American Psychiatric Association; 1983:113–115
35. McWilliams LA, Goodwin RD, Cox BJ. Depression and anxiety associated with 3 pain conditions: results from a nationally representative sample. Pain 2004;111:77–83
36. Traub RJ. Spinal modulation of the induction of central sensitization. Brain Res 1997;778:34–42
37. Max MB. Antidepressant drugs as treatments for chronic pain: efficacy and mechanisms. In: Bromm B, Desmedt JE, eds. Pain and the Brain: From Nociception to Cognition: Advances in Pain Research and Therapy, vol 22. New York, NY: Raven Press, Ltd; 1995:501–514
38. Jones CK, Peters SC, Shannon HE. Efficacy of duloxetine, a potent and balanced serotonergic and noradrenergic reuptake inhibitor, in inflammatory and acute pain models in rodents. J Pharmacol Exp Ther 2005;312: 726–732
39. Bair MJ, Robinson RL, Eckert GJ, et al. Impact of pain on depression treatment response in primary care. Psychosom Med 2004;66:17–22
40. Maizels M, McCarberg B. Antidepressants and antiepileptic drugs for chronic noncancer pain. Am Fam Physician 2005;71:483–490
41. Pedersen LH, Nielsen AN, Blackburn-Munro G. Antinociception is selectively enhanced by parallel inhibition of multiple subtypes of monoamine transporters in rat models of persistent and neuropathic pain. Psychopharmacology 2005;182:551–561
42. Perahia DG, Pritchett YL, Desaiah D, et al. Efficacy of duloxetine in painful symptoms: an analgesic or antidepressant effect? Int Clin Psychopharmacol 2006;21:311–317

