Research Article

EFFICACY OF DULOXETINE IN THE TREATMENT OF GENERALIZED ANXIETY DISORDER IN PATIENTS WITH CLINICALLY SIGNIFICANT PAIN SYMPTOMS

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Anxiety disorders often are accompanied by painful physical symptoms. This report assessed the effectiveness of duloxetine in improving anxiety symptoms, pain severity, and patient functioning in adults diagnosed with generalized anxiety disorder (GAD), who presented with clinically significant pain symptoms. Data were pooled from two multicenter, randomized, double-blind, placebo-controlled clinical studies evaluating the efficacy of duloxetine 60–120 mg once daily compared with placebo in the treatment of GAD. The primary patient population for these analyses was patients with baseline Visual Analog Scale (VAS) overall pain severity score ≥ 30. Of the 798 randomized patients that had baseline VAS scores, approximately 44.4% of GAD patients were identified as having baseline VAS overall pain severity score ≥ 30 (duloxetine $N = 208$, placebo $N = 146$). Duloxetine-treated patients had significantly greater improvement compared with placebo-treated patients on anxiety symptoms (measured by Hamilton Anxiety Scale total score), on patient functioning (measured by the Sheehan Disability Scale Global Functional Impairment Score and across all Sheehan Disability Scale domains), and on all VAS pain items. Patients achieving remission at endpoint, and patients with lower scores on the Clinical Global Impression of Improvement and Patient Global Impression of Improvement scales had greater improvement in VAS pain severity scores. These results suggest that in patients with GAD who present with clinically significant pain symptoms, duloxetine is effective in reducing anxiety symptoms, pain severity, and in improving patient functioning. Depression and Anxiety 25:E1–E11, 2007.

Key words: *duloxetine; generalized anxiety disorder; pain; functioning; Visual Analog Scale*

INTRODUCTION

Generalized anxiety disorder (GAD) is associated with pervasive and excessive worry that is difficult to control [APA, 1994]. GAD affects approximately 3% of the population during a 12-month period, and the estimate of lifetime risk for GAD is approximately 8% [Kessler et al., 2005a,b]. The symptoms of GAD interfere with normal functioning and can impact

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quality of life (QOL). Patients with GAD miss more days of work, have decreased productivity, and need increased financial assistance [DuPont et al., 1996; Greenberg et al., 1999; Kessler et al., 1999; Marciniak et al., 2004; Mendlowicz and Stein, 2000]. In addition, patients experience impairments in functioning, including diminished social relationships and poorer well-being and life satisfaction [Mendlowicz and Stein, 2000]. These impairments are further compounded by the presence of comorbid disorders [Mogotsi et al., 2000].

Patients with GAD often present for treatment with a variety of somatic complaints rather than psychological symptoms [Kroenke et al., 2006; Schulz et al., 2005]. These patients have significantly more frequent and severe somatic symptoms associated with cardiovascular, headache, muscular, and gastrointestinal distress than matched controls [Hoehn-Saric, 1998]. Other comorbid pain symptoms that often accompany GAD are backache, chest pain, and joint pain [Carter and Maddock, 1992; Kirmayer et al., 1993; Krishnan et al., 1985; Kroenke and Price, 1993]. Studies investigating the prevalence of painful physical symptoms in patients with GAD have shown that painful physical symptoms are commonly comorbid with GAD [Graff-Guerrero et al., 2001; McWilliams et al., 2004]. To evaluate pain and Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) psychiatric diagnoses, Graff-Guerrero et al. [2001] surveyed 210 consecutive patients attending a psychiatric service for the first time. Twenty-three percent of patients had GAD (DSM-IV criteria); these patients had the highest number of pain complaints relative to individuals with other DSM-IV diagnoses.

A 2003 survey of 410 individuals screened for anxiety disorders found that 60% of respondents with undiagnosed medical conditions said that on days when they feel anxious or depressed, there is a moderate (41%) to severe (19%) change in their physical symptoms or aches and pains. These physical symptoms include backaches, vague aches and pains, headaches, digestive pain, and dizziness. The majority (88%) of respondents reported that they believe anxiety or depression can cause painful physical symptoms [Freedom from Fear, 2003]. Because this presentation may not be considered typical, patients may be subjected to unnecessary treatments, costly diagnostic tests, and referrals for specialty care [Lydiard, 2000; Schulz et al., 2005], which can result in the delay of effective treatment.

GAD is associated with reduced QOL in the areas of interaction with friends, self-realization, subjective well-being [Cramer et al., 2005], and work [Schonfeld et al., 1997]. Maki et al. [2005] have shown that treating pain was predictive of patients obtaining subsequent remission from their GAD, thus highlighting the importance of recognizing and treating comorbid pain conditions in patients with GAD.

Duloxetine hydrochloride, hereafter referred to as duloxetine, is a selective serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor [Wong and Bymaster, 2002]. Treatment with duloxetine induced an anxiolytic effect in preclinical studies using animal models [Troelsen et al., 2005], and duloxetine was shown to reduce anxiety symptoms associated with depression [Dunner et al., 2003]. In two randomized, placebo-controlled, 9–10-week trials, duloxetine at doses of 60–120 mg per day was effective and safe in the treatment of GAD, and resulted in clinically significant improvement of anxiety symptom severity and overall impairment compared with placebo [Koponen et al., 2007; Rynn et al., 2007]. In clinical studies, duloxetine also has been shown to be safe and effective in the treatment of depression [Detke et al., 2002a,b; Goldstein et al., 2002, 2004a; Hudson et al., 2005; Mallinckrodt et al., 2003; Nemeroff et al., 2002], diabetic peripheral neuropathic pain [Goldstein et al., 2005; Raskin et al., 2005], and fibromyalgia [Arnold et al., 2004, 2005], and is associated with the reduction of painful physical symptoms in patients with major depressive disorder [MDD; Goldstein et al., 2004b].

This report presents a pooled analyses from two randomized, double-blind, placebo-controlled clinical studies evaluating the efficacy of duloxetine 60–120 mg once daily compared with placebo in the treatment of GAD. The primary patient population was those patients with baseline Visual Analog Scale (VAS) overall pain severity score ≥ 30. The objective was to examine whether duloxetine was effective in improving anxiety symptoms, pain severity, and patient functioning in adults diagnosed with DSM-IV-defined GAD, who presented with clinically significant pain symptoms.

METHODS

OVERVIEW

Data from two randomized, double-blind, multicenter, placebo-controlled studies examining the efficacy, tolerability, and safety of duloxetine for the treatment of adults with GAD were included in the analysis. The ethical review boards provided approval of the study protocols in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent after the study was explained and before the performance of any protocol procedures and administration of the study drug.

Potential investigators were rigorously trained in the use of key diagnostic tools and rating scales before the start of studies. Raters underwent training in the Structured Interview Guide for Hamilton Anxiety Scale (HAMA) [Shear et al., 2001] and were evaluated for their interview skills using a modified version of the Rater Applied Performance scale [Lipsitz et al., 2004] that measures dimensions of rater performance. In mock HAMA interviews, raters were assessed for interview style (question clarification and follow-up, rapport), standardization (adherence, neutrality), and inter-rater scoring reliability. Those unable to

demonstrate satisfactory rating ability were not permitted to participate as raters. For both studies, analyses of inter-rater reliability included a detailed analysis of rater bias, dispersion, and inter-rater agreement using weighted kappa scores, Kendall's coefficient of concordance and intraclass correlation coefficients. The rater qualification, training and certification procedures, and the inter-rater reliability results predict with a reasonable level of certainty that Structured Interview Guide for HAMA raters in these studies provided consistent and accurate ratings of study patients throughout the course of the study.

ENTRY CRITERIA

Patients had to be ≥ 18 years of age and have a primary diagnosis of DSM-IV-defined GAD. Diagnosis was determined based on the Mini International Neuropsychiatric Interview for the DSM-IV [Sheehan et al., 1998] and was confirmed by study psychiatrists. Each patient's GAD severity had to be of at least moderate intensity as defined by a Hospital Anxiety and Depression Scale anxiety subscale score ≥ 10 and a Covi Anxiety Scale total score ≥ 9, the Covi Anxiety Scale total score had to be greater than the Raskin Depression Scale total score, and no item on the Raskin Depression Scale could be rated > 3. In addition, the patient should have had a rating of at least 4 (moderate) on the Clinical Global Impressions-Severity Scale (CGI-S). Patients were required to be healthy as determined by a physical exam, electrocardiogram, and laboratory results. Females of potential childbearing status were required to use a reliable method of birth control.

Patients were excluded if they had a recent (past 6 months) diagnosis of MDD or substance abuse/dependence; a past year history of panic disorder, posttraumatic stress disorder, or eating disorder; or a lifetime history of obsessive-compulsive disorder, bipolar affective disorder, psychosis, factitious disorder, or somatoform disorders. Patients were required to not take excluded medications at least 2 weeks before randomization. Exclusion criteria also included any medical condition that would contraindicate the use of duloxetine, and a lack of response of the patient's GAD to two or more adequate trials of antidepressant and/or benzodiazepine treatments. For a more detailed description of exclusion criteria, see Koponen et al. [2007] and Rynn et al. [2007].

STUDY DESIGN AND TREATMENTS

Study 1 was a multicenter (41 study sites located in seven countries [Finland, France, Germany, South Africa, Spain, Sweden, and United States]), randomized, double-blind, fixed-dose, placebo-controlled, phase 3 study, with a 1-week, single-blind placebo lead-in; a 9-week, double-blind continuation phase; and a 2-week, double-blind drug-tapering phase. Patients were randomly assigned to duloxetine 60 mg once daily, duloxetine 120 mg once daily or placebo. The methods for this study are described in detail in Koponen et al. [2007]. Patients randomly assigned to either duloxetine treatment group started treatment with duloxetine 60 mg once daily at baseline. If 60 mg once daily could not be tolerated, the dose for patients randomly assigned to duloxetine 120 mg once daily could be reduced to 30 mg once daily until week 1, followed by 60 mg once daily until week 2. For patients randomly assigned to duloxetine 60 mg once daily, the dose could be reduced to 30 mg once daily until week 2. At week 2, patients must have been able to tolerate their randomly assigned dose.

Study 2 was a multicenter (28 study sites in the United States), randomized, double-blind, flexible-dose, placebo-controlled, phase 3 study, with a 1-week, single-blind placebo lead-in; 10-week, double-blind acute therapy phase; and a 2-week, double-blind drug-tapering phase. The methods for this study are described in detail in Rynn et al. [2007]. The starting dose of duloxetine was 60 mg once daily; however, a dose decrease to 30 mg once daily was allowed for the first 1–2 weeks to allow patients to adjust to the medication, followed by doses of 60 mg once daily, and subsequent dose increases of 30 mg once daily to a maximum dose of 120 mg once daily. Dose increases to maximize efficacy were allowed based on investigator judgment; however, the protocol required the dose be increased if a patient's CGI-Improvement (CGI-I) scale score was 3 or higher (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 two downward dose adjustments for tolerability concerns were allowed, with a minimum allowable dose of duloxetine 60 mg/day.

OUTCOMES MEASURES

The primary efficacy measure was the Hamilton Anxiety Scale (HAMA) [Hamilton, 1959] total score which was administered at each visit. The HAMA is a clinician-administered rating scale used to assess the severity of anxiety, its improvement during the course of treatment, and the timing of such improvement [Riskind et al., 1987]. The scale consists of 14 items, which provide an overall measure of general anxiety. Each item is rated on a 5-point scale of 0 (not present) to 4 (very severe). The HAMA total score is the sum of the 14 items and ranges from 0 to 56. Higher total scores indicate a greater degree of symptom severity and impairment.

Disability was assessed using the Sheehan Disability Scale (SDS) [Sheehan, 1983a,b]. This is a patient-rated 3-item measure (0–10 scale) that rates impairment in the life domains of work/school, social life/leisure activities, and family/home management/responsibilities. The global functional impairment score is comprised of the sum of the three items and ranges from 0

(unimpaired) to 30 (highly impaired). Higher scores are associated with greater functional impairment.

Pain was evaluated by the VAS for pain [DeLoach et al., 1998]. This is a self-reported measurement and is commonly used to rate pain intensity [Carlsson, 1983; Williams et al., 2000]. 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 bad as it could be. Patients are asked to mark their perceived level of pain intensity by indicating a point on the line (Fig. 1), and the examiner scores the instrument by measuring the distance, in millimeters, from the zero anchor to the mark that the patient identified as their level of pain. Separate VAS ratings were obtained for overall pain, headache, backache, shoulder pain, proportion of day while awake with pain, and daily interference due to pain.

In addition, the CGI-I and the Patient Global Impression of Improvement (PGI-I) scales (Guy, 1976) also were assessed at all post-randomization visits. The CGI-I scale [Guy, 1976] is a clinician-rated instrument used to measure the degree of the patient's improvement since taking study drug. It is a 7-point scale where 1 = very much improved, 4 = no change, and 7 = very much worse. The PGI-I scale is completed by the patient and measures the degree of improvement since taking study drug. The score ranges from 1 (very much better) to 7 (very much worse).

STATISTICAL ANALYSES

The data were pooled from two randomized, double-blind studies in which all duloxetine treatment arms were pooled together to create one treatment arm and all placebo treatment arms were pooled together. The primary patient population for this post hoc efficacy analyses were those patients with baseline VAS overall pain severity score ≥ 30. The value of 30 was chosen for VAS-Overall Pain score because it was considered to be a point that distinguished patients with little or mild bodily pain from those with moderate or notable bodily pain. Baseline VAS scores in excess of 30 correspond with a verbal report of at least moderate pain [Collins et al., 1997]. Patients were not required to meet a minimum threshold at baseline for pain, and the studies were not powered for pain outcomes. Patients who had a baseline measurement and at least one post-baseline measurement were included in the efficacy analyses.

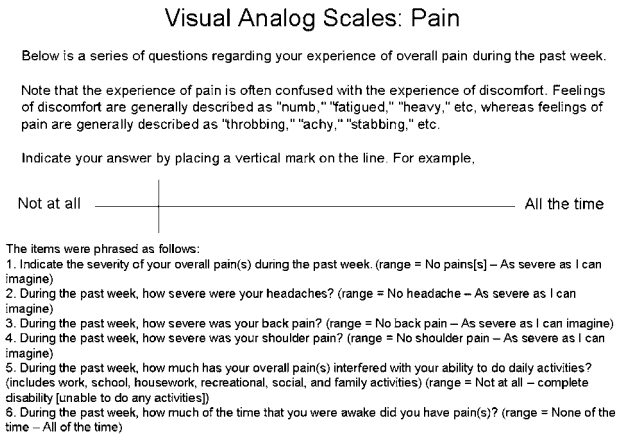

Figure 1. Visual Analog Scale for pain.

The primary analysis described in the protocol was used to assess treatment group differences in mean change from baseline to endpoint (endpoint for study 1 was 9 weeks and for study 2 was 10 weeks) using an analysis of covariance (ANCOVA) model with baseline value as a covariate and factors for study and treatment. For the analysis of the VAS pain items, a mixed-effects model repeated measures approach also was performed (also referred to as main effect of treatment). The main effect of treatment analysis estimates the treatment effects pooled across all patient visits and is similar to an area under the curve analysis. The mixed-effects model repeated measures model included the fixed categorical effects of treatment, investigator, visit, treatment-by-visit interaction, as well as the continuous fixed 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 anxiety symptoms. It was implemented using a regression model on change in pain measure with the regressors of treatment and change in measure for anxiety (HAMA total score). The direct effect versus indirect effect was determined by comparing the magnitude of treatment effect with and without adjusting for change in HAMA total score.

The association between pain and remission was also investigated. Remission was defined as a HAMA total score ≤ 7 at endpoint. Mean changes from baseline to endpoint on the VAS pain items were compared for remitters and non-remitters, using the ANCOVA model with baseline value as a covariate and factors for study and remission status.

The association between pain and patient improvement as measured by the CGI-I and PGI-I also was investigated. Mean changes from baseline to endpoint on the VAS pain items were compared for the fixed categorical effects of improvement (as defined by endpoint CGI-I and PGI-I scores), using the ANCOVA model with baseline value as a covariate and factors for study and improvement status.

RESULTS

Approximately 44.4% of GAD patients in the intent-to-treat population were identified as having baseline VAS score ≥ 30 (duloxetine $N = 208$, placebo $N = 146$). There were no significant differences among treatment groups in any of the patient

demographics including origin, age, gender, and weight (Table 1). The majority of patients were female (69.8%) and Caucasian (92.1%). The mean patient age was 42.7 years.

The baseline HAMA total score and the SDS scores of the GAD patient population identified as having baseline VAS score ≥ 30 were consistently higher on all the domains compared with patients with VAS score <30. There were significant differences at baseline between the population identified as having baseline VAS score ≥ 30 compared with patients with VAS score <30 on all the SDS scales rating global functional impairment, impairment in work/school, social life, and family/home management (Table 2). There were also significant differences on the HAMA total score at baseline between patients with VAS score ≥ 30 compared with those with VAS score <30 (Table 2).

In the primary patient population, duloxetine-treated patients had significantly greater improvement compared with placebo-treated patients on anxiety symptoms as measured by the HAMA total score ($P = .017$) (Fig. 2). The mean decrease in the HAMA total scores was -11.08 for duloxetine (41.9% improvement from baseline) compared with -8.83 (31.9% improvement from baseline) in the placebo group.

Duloxetine-treated patients also experienced significantly greater improvements in their functioning, as shown by changes from baseline to endpoint in the SDS global improvement score and across each specific role domain (work, social life, and family/home management) compared with placebo-treated patients ($P \leq .001$; Fig. 3).

When treatment effects were pooled over all visits (main effect of treatment analysis, Fig. 4), duloxetine-treated patients demonstrated significantly greater improvements compared with placebo-treated patients on all of the six VAS pain items: overall pain ($P < .001$), headache ($P = .009$), back pain ($P = .003$), shoulder pain ($P < .001$), daily interference due to pain ($P < .001$), and the proportion of day while awake with pain ($P < .001$). Consistent results were seen in the intent-to-treat population. When expressing mean changes as percentages, improvement from baseline in pain severity ranged from 42 to 48.7% for duloxetine-treated patients compared with 26 to 31.3% for placebo-treated patients.

TABLE 1. Patient demographics

	Duloxetine		Placebo	
	VAS <30 ($N = 272$)	VAS ≥ 30 ($N = 208$)	VAS <30 ($N = 172$)	VAS ≥ 30 ($N = 146$)
Age: years, mean (*SD*)	44.0 (13.5)	42.1 (12.7)	42.0 (13.7)	43.6 (13.9)
Gender: *n* (%)				
Female	161 (59.20)	154 (74.0)	110 (64.0)	93 (63.7)
Racial origin: *n* (%)				
Caucasian	246 (90.4)	194 (93.3)	149 (86.6)	132 (90.4)
African	18 (6.6)	4 (1.9)	15 (8.7)	7 (4.8)
East Asian	3 (1.1)	2 (1.0)	0 (0.0)	0 (0.0)
Hispanic	2 (0.7)	5 (2.4)	6 (3.5)	7 (4.8)
West Asian	3 (1.1)	3 (1.4)	2 (1.2)	0 (0.0)
Weight: Kg, mean (*SD*)	74.7 (17.9)	74.0 (19.3)	76.5 (18.3)	77.9 (18.0)

VAS, Visual Analog Scale.

TABLE 2. Clinical characteristics at baseline

	Duloxetine				Placebo			
	VAS <30		VAS ≥ 30		VAS <30		VAS ≥ 30	
	N	Mean (*SD*)	*N*	Mean (*SD*)	*N*	Mean (*SD*)	*N*	Mean (*SD*)
HAMA total score*	264	22.3 (7.1)	205	26.4 (7.1)	169	21.9 (6.9)	146	27.7 (7.9)
SDS Scales								
Global Functional Impairment*	246	13.3 (7.5)	189	16.7 (6.7)	157	12.5 (7.6)	132	17.4 (6.5)
Work/school**	201	4.4 (2.9)	160	5.4 (2.7)	130	4.1 (2.8)	107	5.4 (2.6)
Social life*	246	4.5 (2.8)	189	5.8 (2.6)	157	4.3 (2.8)	132	5.9 (2.5)
Family/home management**	246	4.4 (2.7)	189	5.5 (2.5)	157	4.2 (2.8)	132	6.0 (2.4)
VAS Pain Scales								
Overall	263	11.7 (9.2)	202	55.4 (17.8)	170	11.9 (9.3)	145	53.4 (17.9)
Headache*	263	13.1 (18.2)	202	39.2 (28.2)	170	13.9 (16.4)	145	34.0 (27.0)
Back	263	11.0 (14.5)	202	41.1 (28.6)	170	12.4 (16.7)	145	37.8 (27.8)
Shoulder	262	10.4 (16.8)	202	36.9 (29.9)	170	10.4 (14.8)	145	36.5 (30.9)
Daily activities	262	9.5 (11.7)	202	41.9 (26.3)	170	9.9 (13.2)	145	44.6 (23.6)
Pain while awake	262	16.1 (18.2)	202	56.4 (27.0)	170	17.2 (19.1)	145	55.8 (25.8)

*$P < .05$, **$P \leq .01$ versus patients with VAS <30.

VAS, Visual Analog Scale; SDS, Sheehan Disability Scale; HAMA, Hamilton Anxiety Scale.

N = Number of patients with baseline and at least one non-missing post-baseline data.

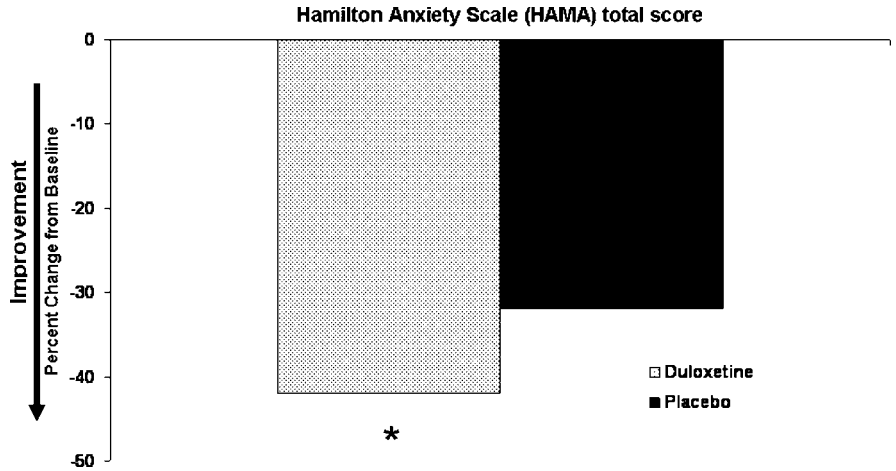

Figure 2. Percentage change from baseline to endpoint on the Hamilton Anxiety Scale (HAMA) total score in patients with baseline Visual Analog Scale overall pain ≥30. *P<.05 duloxetine versus placebo.

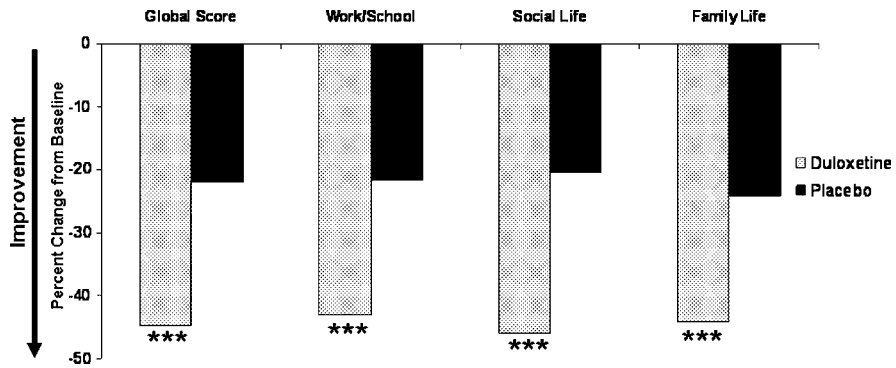

Figure 3. Percentage change from baseline to endpoint on the Sheehan Disability Scale global functional impairment and specific domain scores in patients with baseline Visual Analog Scale overall pain ≥30. ***P≤.001 duloxetine versus placebo.

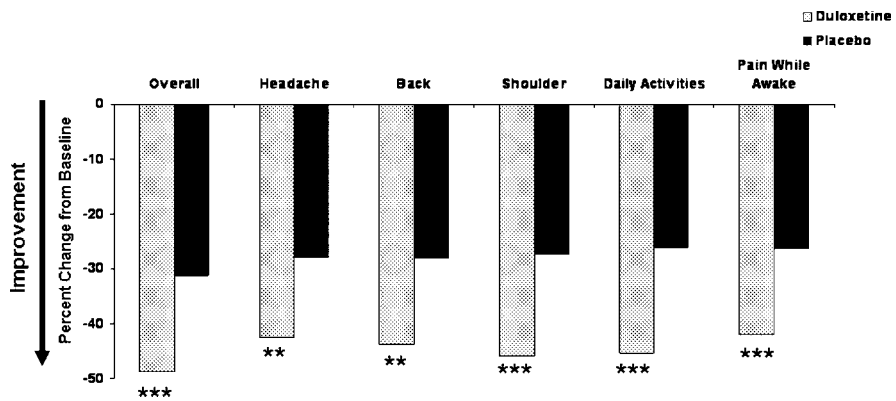

Figure 4. Percentage change from baseline to endpoint on the Visual Analog Scale (VAS) pain items (main effect of treatment) in patients with baseline VAS overall pain ≥30. **P<.01 duloxetine versus placebo, ***P<.001 duloxetine versus placebo.

In the path analysis, 71.7% of duloxetine's total effect on overall pain was independent of changes in anxiety symptoms, whereas 28.3% was an indirect effect based upon changes in anxiety symptoms (HAMA total score).

Patients achieving remission at endpoint had significantly greater improvement in mean VAS pain severity scores (all six pain items) compared with patients who failed to achieve remission (Fig. 5).

The relationship of percentage change in VAS pain severity scores at endpoint to final CGI-I scores showed that patients with lower CGI-I scores (indicating more improvement) had greater improvement in VAS pain severity scores (Table 3). For example, patients with a CGI-I endpoint score = 1 (very much improved) had a change of 77.4% on the VAS overall pain severity score compared with 15.4% for patients with CGI-I endpoint score = 4 (no change, $P<.001$) and 6.3% among patients with CGI-I endpoint score = 6 (very much worse, $P<.001$). Similar findings were also seen across the other five VAS pain items.

The relationship of percentage change in VAS pain severity scores at endpoint to final PGI-I scores showed that patients with lower PGI-I scores (indicating very much better) had greater improvement in VAS pain severity scores (Table 4). For example, patients with a PGI-I endpoint score = 1 (very much better) had a change of 76.4% on the VAS overall pain severity score compared with 17.1% for patients with PGI-I endpoint score = 4 (no change, $P<.001$) and −1.5% among patients with PGI-I endpoint score = 7 (very much worse, $P<.001$). Similar findings were also seen across the other five VAS pain items.

DISCUSSION

The results of this pooled analysis demonstrate that in GAD patients with clinically significant pain, duloxetine-treated patients had significantly greater improvement compared with placebo-treated patients on anxiety symptoms, patient functioning, and pain symptoms. GAD patients with VAS baseline score ≥30 had more anxiety symptoms and experienced greater impairments in baseline health status compared with patients with VAS scores <30. This was evidenced by consistently higher baseline HAMA total scores and SDS scores on global functional impairment and specific domains of work/school, social life, and family/home management. This is consistent with previous studies showing that patients with GAD reported greater impairment owing to somatic symptoms than other primary care patients, with a mean of 9.9 impairment/disability days in the past month compared with 1.4 for non-GAD/depression cases [Wittchen et al., 2002]. In a community survey of 4,181 participants, the prevalence of pain was significantly increased in patients with GAD, and GAD–pain comorbidity was associated with negative outcomes in terms of disability, QOL, and service utilization [Beesdo et al., 2005].

In these post hoc analyses, duloxetine-treated patients experienced significant improvement in HAMA total score and all domains of the SDS, compared with placebo-treated patients. Duloxetine-treated patients

TABLE 3. Relationship of percentage change in VAS pain severity scores at endpoint to final CGI-I scores

VAS Pain Item	Final CGI-I Score					
	1	2	3	4	5	6
		P value*	*P* value*	*P* value*	*P* value*	*P* value*
Overall pain	−77.4	−55.7	−40.5	−15.4	−9.3	−6.3
		.002	<.001	<.001	<.001	<.001
Headache	−82.2	−52.8	−30.2	−4.3	14.9	−13.1
		.005	<.001	<.001	<.001	.023
Back pain	−78.9	−52	−33.5	−6.2	−7.5	−23.7
		.002	<.001	<.001	<.001	.012
Shoulder pain	−81.7	−56.7	−34.2	−10.3	−7.2	19.5
		.005	<.001	<.001	<.001	<.001
Daily activities	−77.9	−62.8	−37.2	3.5	1.1	12.5
		.081	<.001	<.001	<.001	<.001
Pain while awake	−72.7	−52.1	−30.3	−6.4	5.9	−1.6
		.009	<.001	<.001	<.001	<.001

CGI-I, Clinical Global Impression of Improvement, VAS, Visual Analog Scales.
CGI-I scale range: 1 = "very much improved", 4 = "no change", 6 = "much worse."
*P value compared with patients with a final CGI-I score = 1.

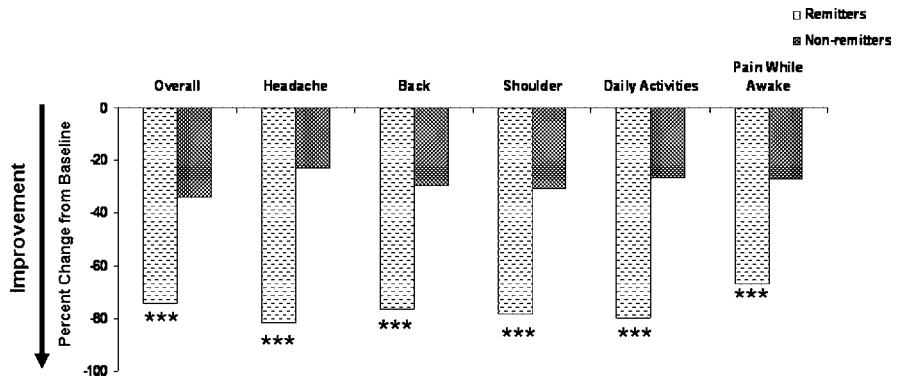

Figure 5. Percentage change in Visual Analog Scale (VAS) pain severity scores at endpoint in patients achieving remission versus those not achieving remission at endpoint (Remission is defined as a Hamilton Anxiety Scale total score ≤7 at endpoint), in patients with baseline VAS overall pain ≥30. ***P<.001 duloxetine versus placebo.

TABLE 4. Relationship of percent change in VAS pain severity scores at endpoint to final PGI-I scores

	Final PGI-I Score						
VAS Pain Item	1	2 *P* value*	3 *P* value*	4 *P* value*	5 *P* value*	6 *P* value*	7 *P* value*
Overall pain	−76.4	−58.1	−40.9	−17.1	9.2	−7.7	1.5
		.010	<.001	<.001	<.001	<.001	<.001
Headache	−82.9	−59.2	−28.3	9.5	25.7	24.1	−17.7
		.016	<.001	<.001	<.001	<.001	<.001
Back pain	−70.8	−56.9	−37.3	−3.7	10.2	29.5	−39.6
		.151	<.001	<.001	<.001	<.001	.093
Shoulder pain	−86.6	−58.6	−34.2	−15.3	15.5	15.1	6.7
		.012	<.001	<.001	<.001	<.001	<.001
Daily activities	−79.2	−62.0	−34.8	−7.3	25.8	18.1	31.0
		.047	<.001	<.001	<.001	<.001	<.001
Pain while awake	−73.6	−52.5	−30.1	−12.9	5.9	16.3	24.8
		.009	<.001	<.001	<.001	<.001	<.001

PGI-I, Patients Global Impression of Improvement; VAS, Visual Analog Scales.
PGI- I scale range: 1 = "very much better", 4 = "no change", 7 = "very much worse".
**P* value compared with patients with a final PGI-I score = 1.

also demonstrated significantly greater improvement compared with placebo-treated patients in painful physical symptoms. When treatment effects were pooled over all visits, duloxetine-treated patients demonstrated significantly greater reduction in mean VAS pain scores compared with placebo-treated patients on all six assessed measures (overall, headache, back pain, shoulder pain, daily interference due to pain, proportion of day while awake with pain).

The path analysis demonstrated that a majority of duloxetine's total effect on pain was a direct effect versus the percentage arising from indirect effects that occurred secondarily as a result of improvement in anxiety symptoms. This is consistent with previous studies of duloxetine in the treatment of diabetic peripheral neuropathic pain and fibromyalgia which have also demonstrated that the treatment effect of duloxetine on pain reduction was independent of the effect on mood [Arnold et al., 2004, 2005; Goldstein et al., 2005].

There was a strong association between improvements in pain outcomes and improvements in clinician- and patient-rated global outcomes, thus demonstrating the importance of treating painful physical symptoms in GAD. Patients whose anxiety symptoms had remitted had greater improvement in pain scores, as demonstrated by significant differences in mean VAS pain severity scores between patients achieving remission at endpoint compared with patients who failed to achieve remission. This is consistent with an earlier study examining treatments received by primary care patients with comorbid generalized anxiety and back pain [Maki et al., 2005], which revealed that patients treated for their pain had a greater chance of remission of GAD. This again demonstrates the importance of recognizing and treating painful physical symptoms in patients with GAD.

Serotonin-NE reuptake inhibitors are shown to be effective in the treatment of GAD [Kelsey, 2000]. Duloxetine is effective in treating pain in animal models [Iyengar et al., 2001, 2004] and is also effective in the management of diabetic peripheral neuropathic pain [Raskin et al., 2005; Wernicke et al., 2006], and in reducing the severity of painful physical symptoms associated with depression in patients with MDD [Goldstein et al., 2004b]. Noradrenergic and serotonergic neurons may modulate endogenous pain inhibitory pathways [Basbaum and Fields, 1984, Clark and Proudfit, 1993]. Although the link between GAD and pain is poorly understood, duloxetine, a potent selective 5-HT and NE reuptake inhibitor, may correct a dysregulation of 5-HT and NE neurotransmission.

LIMITATIONS

Generalizability of these results is limited by the fact that patients in these studies were carefully selected to exclude psychiatric and medical co-morbidities, and could be less severely ill than GAD patients in the general population. In addition, this was a post hoc analysis and patients were not screened specifically for pain symptoms. A vast majority of the patients were Caucasian and hence there was a lack of racial/ethnic diversity in this group of patients. Although the SDS, PGI-I, and VAS measures used in the study are validated instruments, these measures are self-reported. The results are based on treatment duration of 9–10 weeks and may not generalize to longer periods of treatment. Additional studies are needed to demonstrate a maintenance of effect in functional improvements associated with long-term treatment with duloxetine.

CONCLUSION

The present analysis of pooled results from two placebo-controlled studies demonstrate that duloxetine is an effective treatment in reducing anxiety symptoms, pain severity, and in improving functioning in patients with GAD who present with clinically significant pain symptoms. There is a high prevalence of pain symptoms in GAD patients, and it is important to recognize and treat pain in patients with GAD. Further prospective randomized studies in patients with clinically significant pain symptoms and anxiety disorders are warranted.

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