

# The short- and long-term effect of duloxetine on painful physical symptoms in patients with generalized anxiety disorder: Results from three clinical trials

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## Abstract

Generalized anxiety disorder (GAD) is associated with painful physical symptoms (PPS). These post hoc analyses of previous trial data assessed PPS and their response to duloxetine treatment in GAD patients. Studies 1 and 2 (n = 840) were 9- to 10-week efficacy trials; study 3 (n = 887) was a relapse prevention trial comprising a 26-week open-label treatment phase and a 26-week double-blind, placebo-controlled treatment continuation phase. Mean baseline visual analog scale scores (VAS, 0–100; n = 1727) ranged from 26 to 37 for overall pain, headache, back pain, shoulder pain, interference with daily activities, and time in pain while awake. In studies 1 and 2, improvement on all VAS scores was greater in duloxetin-treated than in placebo-treated patients ( $p \leq 0.01$ ). In study 3, pain symptoms worsened in responders switched to placebo compared with those maintained on duloxetine ( $p \leq 0.02$ ). In conclusion, duloxetine was efficacious in the short- and long-term treatment of PPS, which are common in GAD patients.

**Keywords:** Generalized anxiety disorder, Pain, Duloxetine, Relapse prevention, Serotonin and norepinephrine reuptake Inhibitor

## 1. Background

Generalized anxiety disorder (GAD) is a common condition in the general population (12-month prevalence, 2–3%; lifetime prevalence, 5–6%) (Beesdo, Pine, Lieb, & Wittchen, in press; Lieb, Becker, & Altamura, 2005; Ruscio et al., 2007; Wittchen, Zhao, Kessler, & Eaton, 1994) and ranks among the most frequently encountered mental disorders in primary care (Stein, 2003), with point prevalence rates of up to 14.8% (Ansseau et al., 2004; Olfson et al., 2000; Wittchen, Kessler et al., 2002). Primary care studies have also shown that GAD patients frequently remain undiagnosed or are misdiagnosed and poorly treated, which may be due to the fact that only 13% of GAD patients initially report anxiety symptoms as their reason for help seeking (Wittchen, Kessler et al., 2002). More often, they complain of a range of somatic problems, with pain being among the most frequent (35%) presenting symptoms. Because of the nature of GAD symptoms and its typically chronic course, GAD is associated with considerable burden in terms of impaired occupational, family, and social functioning, as well as high utilization of health care resources (Kessler, DuPont, Berglund, & Wittchen,

1999; Olfson & Gameroff, 2007; Wittchen, Beesdo, & Kessler, 2002; Wittchen, Carter, Pfister, Montgomery, & Kessler, 2000; Wittchen, Kessler et al., 2002).

Epidemiological data both from primary care (Means-Christensen, Roy-Byrne, Sherbourne, Craske, & Stein, 2008; Olfson & Gameroff, 2007) and from the general population (Beesdo, Jacobi et al., 2009; Demyttenaere et al., 2007; Fröhlich, Jacobi, & Wittchen, 2006; Gureje et al., 2008; McWilliams, Cox, & Enns, 2003; McWilliams, Goodwin, & Cox, 2004) confirm that painful physical symptoms are commonly associated with GAD. More recent evidence suggests that the association of pain and GAD is substantial, and that pain is a specific feature of GAD that is not seen at the same frequency or intensity in other anxiety disorders (Beesdo, Hoyer et al., 2009). Because of the high rates of comorbid GAD and pain and the demonstration that this pattern is associated with more adverse negative outcomes, such as higher disability, decreased quality of life, and increased service utilization, than either condition individually (Beesdo, Hoyer et al., 2009), there is need for optimized treatment strategies for patients suffering from GAD and pain.

Duloxetine is a selective dual reuptake inhibitor of serotonin and norepinephrine (Wong & Bymaster, 2002), which has been shown to be efficacious, safe, and well tolerated in the treatment of GAD (Davidson et al., 2008; Hartford et al., 2007; Koponen et al., 2007; Rynn et al., 2008). Clinical studies have also provided evidence for the efficacy of duloxetine for pain conditions. In the US, duloxetine is approved for the management of diabetic peripheral neuropathic pain (DPNP) (Goldstein, Lu, Detke, Lee, & Iyengar, 2005; Raskin et al., 2005) and reducing pain associated with fibromyalgia (Arnold et al., 2004, 2005; Russell, Mease et al., 2008). In addition, duloxetine has been shown to reduce painful physical symptoms associated with depression (Goldstein et al., 2004). In more recent clinical studies, duloxetine was also found to effectively reduce somatic symptoms and pain severity in patients with GAD (Hartford et al., 2008; Nicolini et al., 2008; Russell, Weisberg et al., 2008). Because previous analyses were based on the subgroup of patients who had clinically significant pain levels (visual analogue scale [VAS] scores  $\geq 30$  at baseline) (Hartford et al., 2008; Russell, Weisberg et al., 2008), additional investigation of the effect of duloxetine on painful physical symptoms in GAD patients from the overall clinical trial population would be informative to describe the presence and course of painful physical symptoms in patients with GAD.

The present study further investigates previous findings through a post hoc analysis of data from three independent clinical studies from the duloxetine clinical trial program. The objective of these analyses was to provide a more detailed and sufficiently powered examination of the frequency, clinical presentation, and course of painful physical symptoms in GAD patients. The analyses also aimed to provide data on the response of painful physical symptoms to short- and long-term treatment with duloxetine in patients with GAD.

## **2. Methods**

### *2.1. Overview*

Data were included in the analyses from two short-term, multicenter, randomized, double-blind, placebo-controlled, phase 3 trials and one long-term, multicenter, randomized, double-blind, placebo-controlled, phase 3 relapse prevention trial of the efficacy and safety of duloxetine in patients with a principal diagnosis of GAD. In all three studies, ethical review boards provided approval of the study protocols in accordance with the principles of the Declaration of Helsinki, and all patients provided written informed consent.

Studies 1 and 2 each consisted of a 1-week, single-blind, placebo lead-in phase; a 9-week fixed-dose (study 1) or 10-week flexible-dose (study 2) double-blind treatment phase; and a 2-week discontinuation phase. Patients in study 1 received duloxetine 60 mg once daily, duloxetine 120 mg once daily, or placebo. Patients in study 2 received duloxetine 60–120 mg once daily, according to the investigator's judgment and patient tolerance, or placebo. A total of 840 patients were randomly assigned to treatment in these two studies; of these, 780 had postbaseline VAS measures for pain variables. These studies are described in detail in previous publications (Koponen et al., 2007; Rynn et al., 2008).

Study 3 was a long-term relapse prevention study comprised of a 26-week open-label, flexible-dose treatment phase during which all patients received duloxetine; a 26-week double-blind, placebo-controlled treatment continuation phase; and a 3-week taper/ follow-up therapy phase. In the open-label phase, patients received 60–120 mg once daily according to the physician's judgment and patient tolerance. At the end of the open-label phase, patients who met the response criteria (responders) were randomized to receive either duloxetine (maintained at the same dose as received during the open-label phase), or placebo for 26 weeks. Response was defined as a decrease from the baseline Hamilton Anxiety Rating Scale (HAMA) total score of at least 50% to a score no higher than 11 and a Clinical Global Impressions of Improvement (CGI-Improvement) score of 1 or 2 for the last two consecutive visits prior to randomization. A total of 887 patients were randomly assigned to treatment in study 3. Of these, 739 had post-baseline VAS pain measures during the open-label phase, and 392 responded to treatment in the open-label phase and had post-baseline VAS measurements during the placebo-controlled treatment continuation phase. This study is described in detail in a previous publication (Davidson et al., 2008).

## 2.2. Patients

In all three studies, eligible patients were at least 18 years old and met the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), criteria for GAD. Diagnosis was determined on the basis of the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) and was confirmed by a psychiatrist. GAD had to be at least moderately severe as indicated by a rating of  $\geq 4$  (moderate) on the Clinical Global Impressions of Severity (CGIS) Scale (Guy, 1976), a Hospital Anxiety and Depression Scale (HADS) anxiety subscale score of  $\geq 10$  (Zigmond & Snaith, 1983), and a Covi Anxiety Scale (CAS) score of  $\geq 9$  (Lipman & Covi, 1976). To ensure predominance of anxiety symptoms, none of the five items on the Raskin Depression Rating (RDR) scale (Raskin et al., 1969) could be scored  $>3$  and the CAS score had to be greater than the RDR total.

Patients were excluded if they had a recent (past 6 months) diagnosis of major depressive disorder or substance abuse or dependence; a history in the past year 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 not to take excluded medications within predefined periods before the start of the placebo lead-in phase (studies 1 and 2) or the open-label phase (study 3) of the studies. Patients were also excluded if they had any medical condition that would contraindicate the use of duloxetine and if their GAD had not responded to two or more adequate trials of pharmacological treatment. Detailed descriptions of the inclusion and exclusion criteria applied in these studies have been published previously (Davidson et al., 2008; Koponen et al., 2007; Rynn et al., 2008).

### 2.3. Pain measures—visual analogue scale (VAS)

In all three studies, patients rated their pain using six visual analog scales (DeLoach et al., 1998). Each scale consisted of a 100- mm line anchored on the ends by 0 or 100. Patients used separate scales to rate overall pain, shoulder pain, back pain, and headache from 0 (none) to 100 (as severe as I can imagine); time during the day in pain from 0 (none of the time) to 100 (all of the time); and interference with activities due to pain from 0 (not at all) to 100 (complete disability).

### 2.4. Statistical methods

Baseline data from studies 1, 2, and 3 were pooled and descriptive statistics, including mean, median, standard deviation, and 25th and 75th percentiles, were calculated to provide a profile of the presentation of painful physical symptoms at baseline.

The short-term response to treatment was assessed on the basis of pooled data from the duloxetine and placebo arms of studies 1 and 2. Differences in VAS scores between the treatment arms in the changes from baseline to endpoint were examined with an analysis of covariance (ANCOVA) model that included treatment and study as main effects and baseline VAS score as the covariate. Changes from baseline in pain scores by treatment group and remission (HAMA total score  $\leq 7$  at endpoint) and response ( $\geq 50\%$  reduction from baseline in HAMA total score) status were examined using ANCOVA.

The long-term response to treatment was assessed on the basis of data from the placebo-controlled treatment continuation phase of study 3. Changes from baseline to endpoint in VAS scores during the 26-week open-label treatment phase were compared with zero to determine if within-treatment change was significant. Differences between the treatment groups in the changes in VAS scores from the baseline of the 26-week placebo-controlled treatment continuation phase to the study endpoint were examined with an ANCOVA model that included treatment and investigator as main effects and baseline VAS score at randomization as a covariate. In analyses similar to those performed for studies 1 and 2, changes from baseline in pain scores by treatment group and remission and response status were examined in the open-label acute therapy phase using ANCOVA.

Differences between the treatment groups in the changes in VAS scores from baseline were also examined by relapse status in the placebo-controlled treatment continuation phase with an ANCOVA model that included treatment as a main effect and baseline VAS score at randomization as a covariate. Relapse was defined as an increase from randomization in CGI-S score of at least 2 points to a score greater than or equal to 4, a MINI diagnosis of GAD (excluding the requirement for duration of  $\geq 6$  months), or discontinuation due to lack of efficacy. The changes in VAS scores from baseline to endpoint in the open-label treatment phase were examined by relapse status in the placebo-controlled treatment continuation phase with the same ANCOVA model.

Effect sizes were calculated for changes from baseline in mean VAS pain scores in combined data from studies 1 and 2, and in the placebo-controlled continuation phase of study 3 according to the methods described by Hedges and Olkin (1985).

All analyses used last observation carried forward (LOCF) to handle missing data or drop outs and the intent to treat sample (ITT), which is defined as patients who were randomly assigned to a treatment, even if they deviated from the protocol or course of treatment.

### 3. Results

#### 3.1. Baseline patient demographics and presentation of painful physical symptoms

Within studies 1 and 2, the treatment groups were similar with respect to baseline demographic characteristics ( $p \geq 0.239$ ; Table 1). In the sample of pooled data from studies 1, 2, and 3 ( $n = 1727$ ), the mean (standard deviation) baseline VAS scores were 32.9 (25.5) for overall pain, 26.7 (27.0) for headache, 28.5 (27.9) for back pain, 26.6 (28.6) for shoulder pain, 27.5 (26.9) for interference with daily activities, and 37.1 (30.5) for time in pain while awake. Given the large standard deviations, baseline median values for VAS scores were also examined. At least 50% of the patients had scores  $\geq 28$  for overall pain,  $\geq 19$  for headache,  $\geq 20$  for back pain,  $\geq 15$  for shoulder pain,  $\geq 18$  for pain interference with daily activities, and  $\geq 31$  for pain while awake.

#### 3.2. Short-term response to treatment

##### 3.2.1. Overall

In studies 1 and 2, the placebo and duloxetine groups were similar at baseline with respect to all six VAS pain scores ( $p \geq 0.088$ ). In these studies, improvement from baseline on all VAS pain scores was significantly greater in duloxetine-treated patients than in placebo-treated patients ( $p \leq 0.01$  to  $\leq 0.001$ ; Fig. 1). On average, duloxetine-treated patients experienced significant reductions from baseline of at least 30% in each of the pain scales assessed ( $p \leq 0.001$ ). The effect sizes for duloxetine for the changes from baseline in the six VAS pain measures ranged from 0.15 to 0.21.

The findings during the 26-week, open-label treatment phase of study 3 were consistent with and supported those in studies 1 and 2. The mean VAS scores at endpoint were significantly lower than those at baseline for all six pain scales, reflecting improvement in pain symptoms during open-label duloxetine treatment (each  $p \leq 0.001$ ). On average, these patients experienced reductions in baseline pain scale scores of at least 34% on each pain scale.

##### 3.2.2. Comparison of pain outcomes by treatment group and remission and response status

Changes from baseline in pain scores were assessed in patients in the two treatment groups in studies 1 and 2 on the basis of GAD remission status (remitters and nonremitters) and on the basis of response status (responders and nonresponders) (Table 2). In both treatment groups, the changes from baseline in all pain measures were numerically greater in remitters and responders than in nonremitters and nonresponders. Among remitters and responders, the changes from baseline in pain scores did not differ significantly between the placebo and duloxetine groups. In contrast, among nonremitters and nonresponders, the improvement from baseline in overall pain was significantly greater in the duloxetine group than in the placebo group. This pattern was noted for all pain variables except for headache among nonremitters and nonresponders and interference with daily activities and pain while awake among nonresponders.

Changes from baseline in pain scores were also assessed in patients in study 3 who did and did not achieve remission and those who did and did not achieve response during open-label treatment with duloxetine. As in studies 1 and 2, changes from baseline in all pain measures were numerically greater in remitters and responders than in nonremitters and nonresponders (Table 3). Both remitters and nonremitters as well as responders had significant changes from baseline in all pain measures whereas nonresponders did not.

### 3.3. Long-term response to treatment

#### 3.3.1. Overall

In study 3, the placebo and duloxetine groups were similar with respect to all six VAS pain scores at the baseline of the 26-week placebo-controlled treatment continuation phase ( $p \geq 0.181$ ). The study design allows comparison of the specific long-term effects between responders who either continued duloxetine treatment or were randomized to placebo. During this phase, responders randomized to placebo experienced least-squares mean increases in pain scale scores ranging from 5.2 to 8.7, whereas those who continued duloxetine treatment experienced only slight fluctuations in their pain scores, ranging from -1.6 to 0.6 (Fig. 2). The differences in the least-squares mean changes in VAS pain scores between the duloxetine- and placebo-treated patients during this phase were significant for each of the six pain scales ( $p \leq 0.02$  to  $p \leq 0.001$ ; Fig. 2). On average, patients in the placebo group had increases from the baseline of the placebo-controlled phase in pain scale scores of 32–62%. In contrast, mean changes from baseline in the pain scores for patients in the duloxetine group ranged between -6% and 7% of baseline scores. Effect sizes for duloxetine for the changes in the six VAS pain measures after long-term treatment ranged from 0.17 to 0.38.

#### 3.3.2. Comparison of pain outcomes in patients who relapsed and those who did not

The changes in pain scores during the placebo-controlled treatment continuation phase of study 3 were compared between responders who relapsed during this phase (relapsers) and those who did not (nonrelapsers). Overall, patients who relapsed showed greater worsening in pain symptoms than nonrelapsers (Fig. 3). In nonrelapsers, pain scores continued to decrease among duloxetine-treated patients and to increase among placebo-treated patients. Differences in these changes between the placebo and duloxetine groups were significant for overall pain ( $p = 0.002$ ) and shoulder pain ( $p = 0.009$ ). In relapsers, pain scores increased in both treatment groups, and the increases were numerically greater in the placebo group than in the duloxetine group for four of the six measures, although the differences were not significant (Fig. 3). In both treatment groups, there was a trend for pain scores at the baseline of the placebo-controlled treatment continuation phase to be higher in relapsers (range, 13.5–23.2 in the placebo group; 19.6–28.4 in the duloxetine group) than in nonrelapsers (9.4–14.8 in the placebo group; 9.8–14.2 in the duloxetine group). Examination of changes from baseline in pain scores during the open-label treatment phase of the study showed that responders who did not relapse during the continuation phase had experienced a significantly greater reduction in pain during the open-label therapy phase than relapsers (Table 4).

## 4. Discussion

The results of these post hoc analyses from three duloxetine trials yielded three principal findings. First, painful physical symptoms in these patients were part of the clinical presentation of GAD and varied widely in severity. Second, duloxetine was significantly more effective than placebo in reducing painful physical symptoms of GAD after short-term treatment. And third, patients who discontinued duloxetine treatment experienced a worsening of their painful physical symptoms, whereas patients who continued duloxetine treatment did not. Worsening of painful physical symptoms tended to be greater in patients who had relapse of their GAD symptoms. Similarly, improvement in painful physical symptoms tended to be less among patients who did not achieve remission or a response in their GAD symptoms than in those who did.

The patients entered in these trials had a principal diagnosis of DSM-IV GAD of at least moderate severity, but were not required to meet a minimum threshold for pain. Nevertheless, at study entry, the mean VAS scores for overall pain and time in pain exceeded 30 and were therefore indicative of clinically significant pain (Collins, Moore, McQuay, 1997). This study differs from previous analyses in that patients were not selected on the basis of pain at baseline (Hartford et al., 2008; Russell, Weisberg et al., 2008); the findings in this large general clinical population of patients with GAD suggest that painful physical symptoms are common in GAD and are relevant as a part of this disease state.

Our findings that painful physical symptoms are commonly associated with GAD are consistent with data from epidemiological studies (Beesdo, Hoyer et al., 2009; Demyttenaere et al., 2007; Gureje et al., 2008; McWilliams et al., 2003; McWilliams et al., 2004; Von Korff et al., 2005). These studies provide evidence that, among the anxiety disorders, GAD appears to be particularly strongly related to pain (Beesdo, Hoyer et al., 2009; Demyttenaere et al., 2007; Von Korff et al., 2005) and that the presence of GAD is generally associated with pain symptoms in multiple body sites (Gureje et al., 2008; McWilliams et al., 2004). There are also indications that GAD-pain link persists even when adjustments are made for the presence of factors that may contribute to this association, such as demographics and comorbidities (Beesdo, Hoyer et al., 2009; McWilliams et al., 2004; Means-Christensen et al., 2008). In both the pooled analyses of data from studies 1 and 2 and analysis of data from the open-label phase of study 3, duloxetine treatment was associated with clinically significant reductions in pain (Farrar et al., 2001). Effect sizes ranged from 0.15 to 0.21 after short-term treatment (studies 1 and 2) and from 0.17 to 0.38 after long-term treatment (study 3). Turner, Matthews, Linardatos, Tell, and Rosenthal (2008) showed that for positive neuroscience studies which contribute to successful regulatory submissions across 74 Food and Drug Administration (FDA)-registered studies, the average effect size was 0.33; across 12 approved antidepressant agents, the average effect size was 0.31 (Turner et al., 2008). Given that the patients included in our analyses were not selected for the presence or severity of pain symptoms, the effect sizes observed are considerable, particularly those for long-term treatment.

In study 3, as reported previously, patients who responded to duloxetine treatment and were subsequently switched to placebo treatment were significantly more likely to experience relapse of anxiety symptoms of GAD than patients who continued duloxetine treatment (41.8% vs. 13.7%;  $p \leq 0.001$ ) (Davidson et al., 2008). The current analyses revealed that patients who discontinued duloxetine treatment also experienced a worsening of their painful physical symptoms, whereas patients who continued duloxetine treatment maintained their improvements. These findings suggest that painful physical symptoms may reoccur with relapse of GAD and that continuation of duloxetine treatment after abatement of symptoms continues to protect patients from relapse of painful physical symptoms.

Indeed, our comparison of patients who had GAD relapse with those who did not revealed that painful physical symptoms worsened to a greater extent in GAD relapsers than in nonrelapsers. These analyses also showed that among both relapsers and nonrelapsers, duloxetine-treated patients tended to have lower pain severity than placebo-treated patients, particularly among nonrelapsers. Our finding that relapsers tended to have a better response to duloxetine than to placebo on most pain scales supports a previous finding that suggested that duloxetine's effect on pain is at least in part independent of changes in anxiety symptoms (Russell, Weisberg et al., 2008). These findings, combined with our observation that some GAD nonrelapsers experienced worsening of their pain symptoms, especially when switched to placebo, suggest that painful physical symptoms may be somewhat independent of other core anxiety symptoms in GAD. Nevertheless, co-occurring painful physical symptoms

should be carefully considered in the management of GAD patients. Comparison of the pain response to duloxetine during open-label treatment between GAD relapsers and nonrelapsers showed that nonrelapsers had a significantly greater reduction in their pain symptoms during open-label treatment than relapsers. These findings suggest that better pain management may be associated with sustained GAD treatment response.

The results of comparisons of pain outcomes in remitters and nonremitters and responders and nonresponders showed that patients who achieved remission or response in their GAD symptoms tended to have greater improvement in pain measures than those who did not. These analyses also showed that among nonremitters and nonresponders in studies 1 and 2, improvement in pain symptoms were significantly greater in duloxetine- than placebo-treated patients, suggesting that duloxetine treatment is associated with improvement in pain symptoms even in patients whose GAD symptoms have not responded. This finding supports our earlier observation that duloxetine's effect on pain may be to some degree independent of changes in anxiety symptoms.

During the open-label phase of study 3, pain symptoms were significantly improved among nonremitters but not among nonresponders. Such discrepancy can be understood when the criteria for response and remission are considered. Patients who satisfied response criteria may not have satisfied remission criteria; therefore, the group of nonremitters may have included some responders who experienced improvement in VAS pain scores. The pain scores for these responders would have led to increased values for the change from baseline in pain scores for the group of nonremitters. Thus, in study 3, unlike in studies 1 and 2, patients whose GAD symptoms did not respond to treatment did not experience a significant improvement in their pain symptoms. The difference in the outcomes of these analyses between studies 1 and 2 and study 3 may be related to the differences in blinding and duration of treatment in these studies. If response in GAD does not occur despite treatment over a longer period of time (26 weeks vs. 9/10 weeks), it is also likely that pain symptoms remain present over the long run. This patient group may require particular medical attention.

Because of the evidence of increased disability, poorer quality of life, and higher health service use in patients with co-occurring GAD and painful physical symptoms compared with patients with either condition alone (Beesdo, Hoyer et al., 2009), therapies that effectively treat both GAD and pain would be advantageous. The efficacy of duloxetine for the treatment of GAD has been demonstrated in five large, double-blind, randomized trials (Davidson et al., 2008; Hartford et al., 2007; Koponen et al., 2007; Nicolini et al., 2008; Rynn et al., 2008). Further, this agent has demonstrated efficacy in animal models of persistent pain (Iyengar et al., 2004) and in clinical studies of pain associated with diabetic neuropathy (Goldstein et al., 2005; Raskin et al., 2005; Wernicke et al., 2006), fibromyalgia (Arnold et al., 2004, 2005; Russell, Mease et al., 2008), and depression (Goldstein et al., 2004). The analyses reported here demonstrated that patients with GAD who were treated with duloxetine for 9–26 weeks experienced on average significant reductions in each of the aspects of painful physical symptoms assessed, and patients treated for up to 52 weeks continued to report reduced painful physical symptoms throughout the treatment period. Patients who discontinued duloxetine treatment, however, experienced a worsening of these symptoms.

The large size of the study population is a strength of these analyses. Nevertheless, several limitations may restrict the generalizability of the results. Our findings are based on a post hoc analysis of pooled data from three separate clinical trials and cannot be interpreted with the same degree of confidence as a prospectively designed study in a randomly selected clinical population. Also, all three studies were characterized by a lack of ethnic diversity and

excluded patients with primary Axis I disorders other than GAD, significant depressive symptoms, any lifetime history of psychotic disorder, or serious or unstable medical comorbidity. This may limit the ability to generalize these findings to a typical clinical population.

In conclusion, results of these analyses indicate that painful physical symptoms are associated with the clinical presentation of GAD and vary widely in severity. Both short- and long-term duloxetine treatments were associated with improvement in painful physical symptoms in GAD. Patients who responded to duloxetine treatment and subsequently discontinued treatment experienced a worsening of painful symptoms. These findings suggest that painful physical symptoms reoccur with relapsing GAD and indicate a need for ongoing treatment in patients with GAD and concurrent painful physical symptoms.

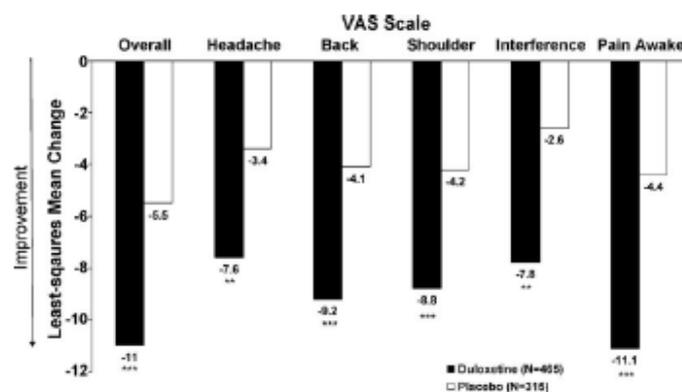


Fig. 1. Response of painful physical symptoms to short-term therapy by treatment group in studies 1 and 2. Note that statistical significance of each item varied within the individual studies. \*  $p \leq 0.05$ , \*\*  $p \leq 0.01$ , \*\*\*  $p \leq 0.001$  (Placebo,  $n = 315$ ; duloxetine,  $n = 465$ ;  $n =$  number of patients with post-baseline measurements).

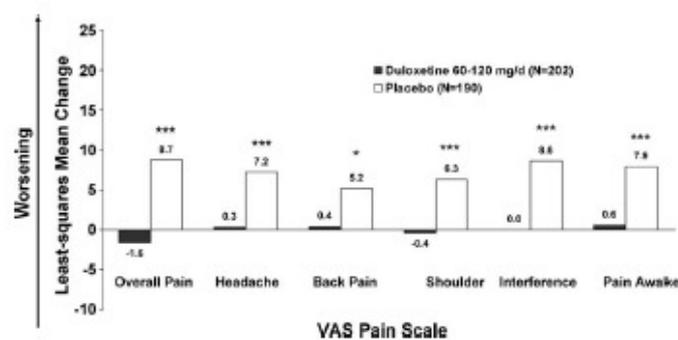


Fig. 2. Least-squares mean change from the baseline to the endpoint of the 26-week placebo-controlled treatment continuation phase in study 3 by treatment group. \*  $p \leq 0.05$ , \*\*  $p \leq 0.01$ , \*\*\*  $p \leq 0.001$ , placebo vs. duloxetine ( $n = 392$ ;  $n =$  number of patients who responded to treatment during the open-label phase and had post-baseline measurements in the placebo-controlled treatment continuation phase).

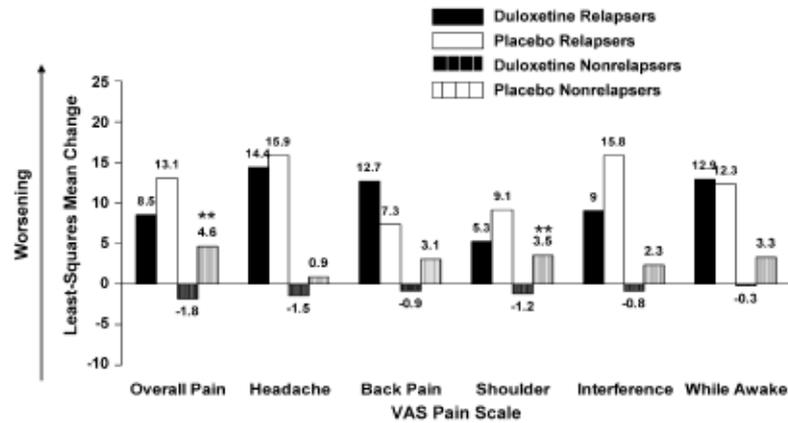


Fig. 3. Comparison of least-squares mean changes in VAS pain scores during the double-blind continuation therapy phase of study 3 between patients who relapsed during this phase and those who did not. <sup>a</sup> $p \leq 0.05$ , placebo vs. duloxetine ( $n = 387$ ;  $n =$  number of patients with relapse data).

**Table 1**  
Baseline demographic characteristics of patients.

Characteristic	Study 1, Treatment phase <sup>a</sup>			Study 2, Treatment phase <sup>a</sup>		Study 3, Open-label treatment phase	All patients ( $n = 1727$ )
	Placebo ( $n = 175$ )	Duloxetine 60 mg OD ( $n = 168$ )	Duloxetine 120 mg OD ( $n = 170$ )	Placebo ( $n = 159$ )	Duloxetine 60–120 mg OD ( $n = 168$ )	Duloxetine 60–120 mg OD ( $n = 887$ )	
Sex, n (%)							
Female	117 (66.9)	108 (64.3)	123 (72.4)	99 (62.3)	103 (61.3)	541 (61.0)	1091 (63.2)
Age, years							
Mean $\pm$ SD	44.1 (13.4)	43.1 (12.9)	44.1 (12.6)	41.0 (14.2)	42.2 (13.9)	43.3 (13.4)	43.1 (13.4)
Racial origin, n (%)							
Caucasian	173 (98.9)	163 (97.0)	169 (99.4)	124 (78.0)	134 (79.8)	754 (85.0)	1517 (87.8)
African	1 (0.6)	1 (0.6)	1 (0.6)	21 (13.2)	20 (11.9)	17 (1.9)	61 (3.5)
Hispanic	1 (0.6)	0	0	12 (7.6)	7 (4.2)	98 (11.1)	118 (6.8)
East Asian	0	2 (1.2)	0	0	3 (1.8)	11 (1.2)	16 (0.9)
West Asian	0	2 (1.2)	0	2 (1.3)	4 (2.4)	7 (0.8)	15 (0.9)

OD: once daily; SD: standard deviation.

<sup>a</sup> The placebo and duloxetine groups did not differ significantly with respect to baseline demographic characteristics.

**Table 2**  
Least squares mean change (standard error) from baseline in pain scores during treatment with placebo or duloxetine during studies 1 and 2 in patients who had remission (remitters),<sup>a</sup> patients who did not have remission (nonremitters), patients who had a response<sup>b</sup> (responders), and patients who did not (nonresponders).

Pain measure	Remitters			Nonremitters			Responders			Nonresponders		
	Placebo ( $n = 64$ )	Duloxetine ( $n = 149$ )	p-Value	Placebo ( $n = 250$ )	Duloxetine ( $n = 315$ ) <sup>c</sup>	p-Value	Placebo ( $n = 93$ )	Duloxetine ( $n = 240$ ) <sup>d</sup>	p-Value	Placebo ( $n = 221$ )	Duloxetine ( $n = 224$ )	p-Value
Overall pain	-17.0 (1.86)	-15.7 (1.29)	0.529	-3.3 (1.58)	-8.5 (1.40)	0.009	-17.9 (1.96)	-15.9 (1.30)	0.363	0.1 (1.73)	-4.8 (1.67)	0.031
Headache	-16.4 (1.48)	-15.9 (1.03)	0.754	-0.7 (1.67)	-4.3 (1.48)	0.090	-13.7 (1.80)	-14.1 (1.19)	0.812	0.8 (1.86)	-1.5 (1.79)	0.342
Back pain	-14.5 (1.96)	-13.1 (1.36)	0.519	-2.9 (1.47)	-8.1 (1.30)	0.005	-16.0 (1.89)	-13.7 (1.25)	0.270	0.2 (1.62)	-5.7 (1.56)	0.006
Shoulder pain	-11.9 (1.51)	-10.7 (1.04)	0.466	-2.2 (1.40)	-7.1 (1.25)	0.004	-12.3 (1.62)	-12.0 (1.08)	0.891	0.6 (1.43)	-4.1 (1.38)	0.011
Interference with activities	-15.7 (1.92)	-13.7 (1.33)	0.336	-0.5 (1.68)	-5.4 (1.50)	0.019	-13.7 (1.90)	-14.0 (1.27)	0.888	1.4 (1.81)	-1.0 (1.74)	0.306
Pain while awake	-19.2 (2.48)	-16.5 (1.72)	0.338	-2.1 (1.87)	-8.7 (1.66)	0.004	-16.0 (2.47)	-17.4 (1.64)	0.618	0.3 (1.99)	-3.6 (1.92)	0.206

<sup>a</sup> Remission was defined as a Hamilton Anxiety Rating Scale (HAMA) total score (Hamilton, 1959) less than or equal to 7 at endpoint (with last observation carried forward).

<sup>b</sup> Response was defined as 50% reduction in the HAMA total score (Hamilton, 1959) from baseline to endpoint (with last observation carried forward).

<sup>c</sup> For shoulder pain, interferences with activities, and pain while awake,  $n = 314$ .

<sup>d</sup> For shoulder pain, interference with activities, and pain while awake,  $n = 239$ .

**Table 3**

Change (standard deviation) from baseline in pain scores during the open-label treatment phase in study 3 in patients who had remission (remitters),<sup>a</sup> patients who did not have remission (nonremitters), patients who responded (responders),<sup>b</sup> and patients who did not respond (nonresponders).

Pain measure	Remitters (n = 350)		Nonremitters (n = 387) <sup>c</sup>		Responders (n = 514)		Nonresponders (n = 223) <sup>d</sup>	
	Change	p-Value	Change	p-Value	Change	p-Value	Change	p-Value
Overall pain	-18.2 (26.4)	<0.001	-7.0 (28.8)	<0.001	-17.6 (27.1)	<0.001	-0.2 (27.2)	0.896
Headache	-16.5 (28.2)	<0.001	-3.9 (30.4)	0.012	-14.4 (29.4)	<0.001	0.5 (28.9)	0.788
Back pain	-16.8 (27.6)	<0.001	-8.3 (27.1)	<0.001	-16.7 (27.2)	<0.001	-2.0 (25.8)	0.243
Shoulder pain	-19.3 (28.4)	<0.001	-7.5 (33.0)	<0.001	-18.8 (29.7)	<0.001	-0.1 (31.7)	0.973
Interference with activities	-17.1 (28.1)	<0.001	-6.1 (32.7)	<0.001	-17.0 (28.9)	<0.001	1.8 (32.0)	0.407
Pain while awake	-21.3 (31.9)	<0.001	-7.8 (33.3)	<0.001	-20.4 (31.7)	<0.001	-0.1 (32.7)	0.982

<sup>a</sup> Remission was defined as a Hamilton Anxiety Rating Scale (HAMA) total score (Hamilton, 1959) less than or equal to 7 at endpoint (with last observation carried forward).

<sup>b</sup> Response was defined as 50% reduction in the HAMA total score (Hamilton, 1959) from baseline to endpoint (with last observation carried forward).

<sup>c</sup> For shoulder pain, interference with activities, and pain while awake, n = 386.

<sup>d</sup> For shoulder pain, interference with activities, and pain while awake, n = 222.

**Table 4**

Least squares mean change from baseline in pain scores during the open-label treatment phase of study 3 in patients who did not relapse (nonrelapsers) and patients who did relapse (relapsers) during the placebo-controlled treatment continuation phase of the study.

Pain measure	Relapsers (n = 112)			Nonrelapsers (n = 294)		
	Baseline	Endpoint	Change	Baseline	Endpoint	Change
Overall pain	35.8	21.8	-12.1**	34.5	13.7	-19.7
Headache	25.7	15.9	-9.5*	26.7	10.7	-15.6
Back pain	32.9	18.8	-12.2**	31.5	11.4	-19.1
Shoulder pain	32.4	15.1	-16.0*	30.4	10.0	-19.9
Interference with activities	31.8	17.7	-12.5*	29.0	10.1	-18.6
Pain while awake	38.5	24.7	-13.4**	38.9	14.4	-23.0

\* Significantly different from nonrelapsers;  $p \leq 0.05$ .

\*\* Significantly different from nonrelapsers;  $p \leq 0.001$ .

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