The Efficacy and Tolerability of Duloxetine in the Treatment of Anxious Versus Non-Anxious Depression: A Post-Hoc Analysis of an Open-Label Outpatient Study

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Background. *This study compares the efficacy and tolerability of 12 weeks of open-label duloxetine in adult outpatients with anxious versus non-anxious depression.*

Methods. *Participants in a major depressive episode (N = 249) began duloxetine treatment at 30 or 60 mg daily for the first week, followed by up to 11 weeks of flexibly dosed duloxetine (60, 90, or 120 mg daily). Efficacy measures included HAMD$_{17}$, HAMA, and CGI-S. Safety and tolerability were assessed by early discontinuation and adverse event rates. Anxious depression was defined by a HAMD$_{17}$ Anxiety/Somatization Factor score ≥ 7.*

Results. *Duloxetine treatment was associated with a significantly greater reduction in total HAMD$_{17}$ scores and HAMD$_{17}$ Anxiety/Somatization Factor scores among patients with anxious depression compared to non-anxious depression. Differences in CGI-S and HAMA scores at the end of the trial between groups were not statistically significant. Remission and response rates at endpoint were similar between groups, but anxious depressives had a significantly shorter median time to response. Discontinuation rates due to any reason, discontinuation due to adverse events, and treatment-emergent adverse events were similar between groups, except for the significantly greater occurrence of influenza in anxious depressives.*

Conclusions. *Duloxetine's efficacy in anxious depression was somewhat superior to non-anxious depression; tolerability was comparable between groups.*

Keywords   Duloxetine, Depression, Anxiety, Serotonin uptake inhibitors

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INTRODUCTION

Anxiety, nervousness, and their somatic correlates are common symptoms among patients who suffer from major depressive disorder (MDD). For example, a study by Fawcett and Kravitz (1) showed that patients with MDD reported high rates of excessive worrying (72%), psychic anxiety (62%), and somatic anxiety (42%). Anxious depression has often been defined in the literature as MDD with high levels of anxiety symptoms and has been found to be associated with greater severity of illness as well as with greater functional impairment (2), chronicity (3), delayed response to treatment (4), and an increased risk of suicidality (5). A recent report based on the large STAR*D population has shown a 46% prevalence of anxious depression among 1450 MDD outpatients (6). In the same study, patients with anxious MDD were significantly more likely, before and after adjustment for severity of depression, to be older, unemployed, less educated, more severely depressed, and to have suicidal ideation (6). They were also significantly more likely, before and after adjustment for severity of depression, to endorse symptoms related to generalized anxiety, obsessive compulsion, panic, post-traumatic stress, agoraphobia, hypochondriasis, and somatoform disorders (6).

The presence of anxious depression has typically been associated with poorer treatment outcome compared to non-anxious depression. In fact, in most (7–9) but not all studies (5,10), individuals with anxious depression were also found to be less likely to respond to antidepressant treatment than those without anxious depression, regardless of the type of antidepressant used. In addition, no significant differences in efficacy have typically been shown among antidepressants of the same (11) or different class (5), with the exception of a pooled analysis showing significantly higher rates of remission with the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine compared to the selective serotonin reuptake inhibitor (SSRI) fluoxetine (8). The association between anxious depression and poorer response to antidepressant treatment may account for the results of a recent study showing that the concomitant use of anxiolytics/hypnotics was a significant predictor of treatment resistance in older adults with depression (12). Finally, residual symptoms of anxiety have been reported to be associated with greater risk of relapse in patients with MDD (7,13).

Duloxetine is a dual reuptake inhibitor of serotonin (5-HT) and norepinephrine (NE) that exhibits relatively comparable affinities for both 5-HT and NE transporters (14). The efficacy and safety of the SNRI duloxetine, in doses ranging from 40 to 120 mg/day, in the treatment of MDD have been demonstrated in double-blind, placebo-controlled clinical trials of up to 9 weeks' duration (15–19). Given duloxetine's dual action on NE and 5-HT and the previous observation of a greater efficacy of the SNRI venlafaxine compared to the SSRI fluoxetine (8) in anxious depression, we hypothesized that duloxetine would be more efficacious in anxious depression compared to non-anxious depression. Therefore, the aims of our study were as follows: 1) to compare the efficacy, in terms of degree of improvement in depressive symptoms and rates of response and remission, of open-label treatment with duloxetine among outpatients with anxious versus non-anxious depression, and 2) to compare the tolerability of duloxetine among these 2 groups.

METHODS

Study Design

This was a 12-week, open-label, multicenter trial involving 21 investigative sites. The study protocol was reviewed and approved by the ethical review board at each site, in accordance with the principles of the Declaration of Helsinki, and all patients signed informed consent documents prior to the administration of any study procedures or study drug. Data were collected from November 2002 through October 2004.

The study consisted of 3 phases: Study Period I (1-week screening period); Study Period II (1-week duloxetine fixed-dose treatment period); Study Period III (11-week open-label, flexible-dose period). All study participants entered the 1-week screening period. Eligible participants were then divided into 2 groups: 1) participants who were not receiving antidepressant treatment at the time of study entry ("treatment-naïve" group), and 2) participants who exhibited suboptimal response or poor tolerability to treatment with venlafaxine or a selective serotonin reuptake inhibitor (SSRI), except fluoxetine, immediately prior to study entry ("treatment-switch" group).

(a) Participants initiating duloxetine therapy ("treatment-naïve" group)—Participants untreated at the time of study entry were randomized in a 1:1 ratio to receive duloxetine 30 mg QD (once-daily) or 60 mg QD for a 1-week initial treatment phase (Study Period II). Participants unable to tolerate duloxetine treatment during this period were discontinued. At the end of the 1-week initial treatment phase, participants receiving 30 mg QD were required to have their dose increased to 60 mg QD. During the remainder of the acute therapy phase (Study Period III), each participant's duloxetine dose could be titrated on the basis of degree of response within a range from 60 mg QD (minimum) to 120 mg QD (maximum), with 90 mg QD as an intermediate dose. The duloxetine dose could be increased or decreased in 30-mg increments only at scheduled visits, and could be increased only if the patient's 17-item Hamilton Rating Scale for Depression ($HAMD_{17}$) total score was >7 at the scheduled visit.

(b) Participants switching to duloxetine therapy ("treatment-switch" group)—Participants receiving citalopram (≤ 40 mg/d), escitalopram (≤ 20 mg/d), fluvoxamine (≤ 150 mg/d), paroxetine (≤ 40 mg/d), sertraline (≤ 150 mg/d), or venlafaxine (≤ 150 mg/d) at study entry were allowed to continue their current antidepressant medication during the screening period. Participants receiving doses above these levels were excluded. Participants who had received fluoxetine therapy within the last 30 days were also excluded (due to the long half-life of its

active metabolites). Participants who had received SSRI treatment (other than fluoxetine) and discontinued the SSRI within 1 month of the screening visit were required to wash out from the SSRI treatment for a period of 21 days, and were then considered to be untreated ("treatment-naïve" group). At the conclusion of the screening period (Study Period I), eligible participants were immediately switched from their current medication to duloxetine 60 mg QD. No intermediate tapering or titration was employed, and no combination or augmentation therapy was permitted. All participants were required to remain on duloxetine 60 mg QD for 1 week (Study Period II). Participants unable to tolerate duloxetine treatment during this period were discontinued. During Study Period III, each participant's duloxetine dose could be titrated to efficacy as previously described.

Study Participants

Study participants were adult males and females (≥ 18 years of age) meeting *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) criteria for MDD, based on the Mini International Neuropsychiatric Interview (MINI). Participants were required to have a 17-item Hamilton Rating Scale for Depression ($HAMD_{17}$) (20) total score ≥15, and a Clinical Global Impression-Severity of Illness (CGI-S) (21) score ≥4 at two consecutive screening visits.

Exclusion criteria included a diagnosis of bipolar disorder, schizophrenia, or other psychotic disorder; the presence of a primary and current Axis II disorder; a serious medical illness (any cardiovascular, hepatic, respiratory, hematologic, endocrinologic, or neurologic disease, or clinically significant laboratory abnormality); participants judged to be at serious suicidal risk; treatment with fluoxetine within 30 days prior to Visit 1; treatment with a monoamine oxidase inhibitor within 14 days prior to Visit 1; lack of response of the current episode to 2 or more adequate courses of antidepressant therapy at a clinically appropriate dose for a minimum of 4 weeks, or meeting criteria for treatment-resistant depression; any anxiety disorder as a primary diagnosis within the past 6 months; a history of substance dependence within the past 6 months; or a positive urine drug screen. Prior exposure to antidepressant treatment was assessed with the self-rated Massachusetts General Hospital (MGH) Antidepressant Treatment Response Questionnaire (ATRQ) (22) administered by automated Interactive Voice Response (IVR) via a touch tone telephone.

Concomitant medications with primarily central nervous system activity were not allowed. Participants were required to immediately discontinue prescribed SSRI therapy when duloxetine treatment was initiated. The use of beta-blockers, diuretics, ACE inhibitors, antiarrhythmics, anticoagulants, and calcium channel blockers was permitted, provided the participant had been on a stable dose for a minimum of 3 months prior to study enrollment.

Efficacy Measures

Efficacy measures included the $HAMD_{17}$ total score, the Hamilton Rating Scale for Anxiety (HAMA) (23) total score, the CGI-S scale, and the $HAMD_{17}$ Anxiety/Somatization subscale (6,24). Response was defined as a ≥ 50% reduction in $HAMD_{17}$ total score from baseline, whereas remission was defined as a $HAMD_{17}$ total score ≤ 7 (25).

Safety and Tolerability Assessments

Assessment of the safety and tolerability of duloxetine was based on information about reasons for discontinuation and adverse events. An adverse event was defined as any untoward medical occurrence in a patient administered study medication, without regard to the possibility of a causal relationship. All unsolicited reports of adverse events were reported on clinical (case) report forms. Additionally, if clinically significant abnormal electrocardiograms or laboratory values led to, or were associated with, clinical symptoms, the diagnosis was reported as an adverse event. Treatment-emergent adverse events were defined as adverse events that newly occurred or worsened after baseline. Serious adverse events included medical occurrences that resulted in one of the following outcomes: (a) death; (b) initial or prolonged hospitalization; (c) persistent or significant disability/incapacity; (d) congenital anomaly (in the offspring of a study participant).

Statistical Methods

Efficacy Outcomes

As with previous studies (6), anxious depression was defined as MDD with high levels of anxiety symptoms ($HAMD_{17}$ Anxiety/Somatization Factor score ≥ 7). The Anxiety/Somatization factor, derived from a factor analysis of the $HAMD_{17}$ scale conducted by Cleary and Guy (24), includes 6 items from the original 17-item version: item 10—Anxiety (psychic); item 11—Anxiety (somatic); item 12—Somatic Symptoms (Gastrointestinal); item 13—Somatic Symptoms (General); item 15—Hypochondriasis; item 17—Insight. The range of possible scores for the $HAMD_{17}$ Anxiety/Somatization Factor score is 0 to 18. Significance was set at $p ≤ .05$, except for interactions, where significance was set at $p ≤ .10$.

Baseline scores for $HAMD_{17}$, HAMA, and CGI-S, and continuous sociodemographic measures were compared for anxious versus non-anxious patients using analysis of variance (ANOVA), with investigator and naïve/switch in the model as covariates; categorical variables were compared with the Fisher's exact test.

A likelihood-based, mixed-effects model repeated measures analysis (MMRM) was used to analyze change from baseline to subsequent visits in CGI-S score, HAMA total score,

$HAMD_{17}$ Anxiety/Somatization Factor score, and $HAMD_{17}$ total score. The model included the fixed categorical effects of group (anxious/non-anxious), investigator, and whether the patient was treatment-naïve or switched from previous treatment. Time of assessment was modeled as a continuous effect by including linear and quadratic terms for days on therapy, as well as the interaction of the linear term with group. Time was included as a continuous effect because the visit intervals had more flexibility than often seen in acute phase trials; modeling time as continuous accounted for the unequal visit timing. Baseline $HAMD_{17}$ total score was included in all analyses as a covariate, along with baseline value of the outcome measure being analyzed; for example, for analysis of HAMA total score, both the baseline value of $HAMD_{17}$ score and the baseline value of HAMA score were included in the model. Within-patient error terms were modeled using an unstructured covariance matrix. The Kenward-Roger method was used to estimate denominator degrees of freedom.

Response and remission rates were compared using Fisher's exact test, using an intent-to-treat (ITT) approach, with the last-observation-carried-forward (LOCF). Rates were also modeled using a logistic regression model with baseline $HAMD_{17}$ total score and naïve/switch in the model as covariates. Time to response/remission was compared between anxious/non-anxious patients using Kaplan-Meier survival curves and the log-rank test to compare curves. In addition, a Cox proportional hazard regression model was used with baseline $HAMD_{17}$ total score and switch/naïve in the model as covariates.

Safety and Tolerability Outcomes

The Cochran-Mantel-Haenszel (CMH) test was used to compare discontinuation rates between anxious and non-anxious patients while controlling for treatment status at study entry ("treatment-switch" vs. "treatment-naïve"), using an ITT approach. The Breslow-Day test was used to look for an interaction between anxiety and "treatment-switch"/"treatment-naïve" status (e.g., to examine whether the difference in rates of discontinuation between anxious and non-anxious patients depended on whether patients were switched from an SSRI or venlafaxine, or were treatment-naïve before starting duloxetine). An interaction test of $p < .10$ was considered significant.

Kaplan-Meier survival analyses were implemented on time to discontinuation for any reason and time to discontinuation due to adverse events, and differences were compared between anxious and non-anxious patients with a log-rank test.

The rates of treatment-emergent adverse events were noted, and comparisons were made between anxious and non-anxious patient subgroups using the CMH test, adjusted by "treatment-naïve" and "treatment-switch" status as well as Fisher's exact test. Treatment-emergent adverse events were also grouped into event categories, including central nervous system (CNS), gastrointestinal, neuromuscular and skeletal, and CNS anxiety; and Kaplan-Meier survival analyses were performed on time to occurrence of treatment-emergent adverse event groupings in anxious and non-anxious patient groups.

RESULTS

Study Participants

A total of 249 patients were included in this analysis, of whom 112 were switched directly from SSRI or venlafaxine therapy and 137 were untreated at the time of study entry. The most frequently used concomitant medications were ibuprofen, acetaminophen, multivitamins, aspirin, zolpidem, and naproxen sodium. A summary of stabilized duloxetine doses at the end of the 12-week acute therapy phase is provided in Table 1. There were no significant differences in the proportion of switched or initiating patients who received 60 mg QD, 90 mg QD, or 120 mg QD as the final stabilized duloxetine dose.

Of the 249 patients who received duloxetine in the study, a total of 109 (44%) had anxious depression, as defined by $HAMD_{17}$ Anxiety/Somatization Factor scores ≥ 7, and 140 (56%) had non-anxious depression. There were no significant differences between anxious and non-anxious depression groups in terms of demographic characteristics (age, gender, and ethnicity) and of percentage of patients who were treatment-naïve. However, patients with anxious depression were significantly more ill (on the CGI-S), depressed ($HAMD_{17}$), and anxious (HAMA) than patients with non-anxious depression.

Table 1   Stabilized Duloxetine Dose in "Treatment-Naïve" and "Treatment-Switch" Participant Groups

	Participant Group		
	Switching to Duloxetine (n = 83)	Initiating Duloxetine (n = 94)	P
Duloxetine 60 mg QD, N (%)	29 (34.9%)	24 (25.5%)	.191
Duloxetine 90 mg QD, N (%)	20 (24.1%)	32 (34.0%)	.186
Duloxetine 120 mg QD, N (%)	34 (41.0%)	36 (38.3%)	.759
Other,[a] N (%)	0 (0.0)	2 (2.1%)	.499

[a]Received 30 mg QD due to down titration and discontinuation.
Abbreviations: QD = once daily.

Efficacy

HAMD$_{17}$ Total Score

The MMRM for HAMD$_{17}$ total score detected significant interaction ($p = .092$) between non-anxious/anxious and days in treatment, indicating that the difference between treatment groups was dependent upon time in treatment. As can be seen in Table 2 and Figure 1, there was no significant difference between anxious patients and non-anxious patients early in the treatment; however, anxious patients had a significantly larger improvement later in the course of treatment (Week 12, $p < .05$).

HAMD$_{17}$ Anxiety/Somatization Factor Score

Similar results were seen for HAMD$_{17}$ Anxiety/Somatization Factor score as were seen for the HAMD$_{17}$ total score (see Table 2 and Figure 2). Although the interaction effect between non-anxious/anxious and days in treatment was not quite significant ($p = .101$), anxious patients had a statistically significantly greater change on HAMD$_{17}$ Anxiety/Somatization Factor score from Day 42 onward ($p < .05$), but not at the earlier time points.

Table 2 Change from Baseline in Efficacy Outcome Measures in Anxious versus Non-Anxious Depressed Participant Groups

| | Change From Baseline Least-Squares Mean (SE) From MMRM Model | | |
	Days From Randomization	Non-Anxious Group	Anxious Group	P
HAMD$_{17}$ total	7	−4.76 (0.43)	−5.22 (0.49)	.499
	14	−6.12 (0.40)	−6.72 (0.46)	.366
	28	−8.46 (0.40)	−9.33 (0.46)	.178
	42	−10.28 (0.43)	−11.40 (0.49)	.087
	56	−11.56 (0.46)	−12.95 (0.54)	.051
	84	−12.54 (0.55)	−14.47 (0.67)	.032
HAMD$_{17}$ Anxiety subtotal	7	−1.23 (0.19)	−1.73 (0.24)	.158
	14	−1.62 (0.18)	−2.17 (0.23)	.112
	28	−2.30 (0.17)	−2.95 (0.22)	.055
	42	−2.82 (0.18)	−3.57 (0.23)	.028
	56	−3.19 (0.19)	−4.04 (0.24)	.016
	84	−3.46 (0.22)	−4.50 (0.28)	.009
CGI-S	7	−0.46 (0.07)	−0.49 (0.08)	.800
	14	−0.75 (0.07)	−0.80 (0.08)	.635
	28	−1.24 (0.07)	−1.34 (0.08)	.361
	42	−1.63 (0.08)	−1.77 (0.09)	.210
	56	−1.92 (0.09)	−2.11 (0.10)	.143
	84	−2.20 (0.11)	−2.48 (0.13)	.105
HAMA total	7	−4.46 (0.43)	−3.47 (0.49)	.146
	14	−5.41 (0.39)	−4.64 (0.46)	.235
	28	−7.04 (0.38)	−6.69 (0.44)	.581
	42	−8.30 (0.40)	−8.38 (0.46)	.892
	56	−9.19 (0.42)	−9.71 (0.50)	.450
	84	−9.89 (0.53)	−11.26 (0.64)	.112

Abbreviations: MMRM = mixed-effects model repeated measures analysis; HAMD$_{17}$ = 17-item Hamilton Rating Scale for Depression; CGI-S = Clinical Global Impression-Severity of Illness; HAMA = Hamilton Rating Scale for Anxiety.
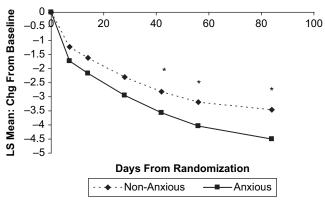
Change From Baseline: HAMD$_{17}$ Total Score

Figure 1 Change from Baseline for HAMD$_{17}$ Total Score; Least-Square Means from MMRM Model. Abbreviations: MMRM = mixed-effects model repeated measures analysis; HAMD$_{17}$ = 17-item Hamilton Rating Scale for Depression.

*p Value < .05.

Change From Baseline: HAMD$_{17}$ Anxiety Subtotal

*p Value < .05.

Figure 2 Change from Baseline for HAMD$_{17}$ Anxiety Subtotal; Least-Square Means from MMRM Model. Abbreviations: MMRM = Mixed-effects model repeated measures analysis; HAMD$_{17}$ = 17-item Hamilton Rating Scale for Depression.

CGI-S

The interaction between non-anxious/anxious and days in treatment was not significant ($p = .147$), nor were there any significant differences between groups at any of the time points, although anxious patients tended to have greater change on CGI-S scores later in the treatment (see Table 2).
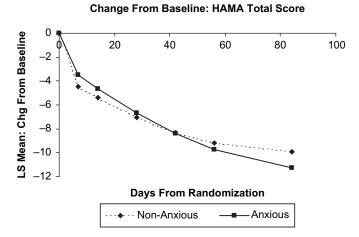
HAMA Total Score

For HAMA total score, the interaction effect of non-anxious/anxious and days in treatment was statistically significant ($p = .007$); however, there was not a significant difference between groups at any specific point during therapy. The

interaction was driven by the criss-cross nature of the patterns over time (see Figure 3).

Response and Remission Rates

The remission rates at endpoint for anxious patients and non-anxious patients were 50.9% and 54.4%, respectively (Fisher's exact test; $p = .61$). After adjusting for baseline $HAMD_{17}$ total score and naïve/switch in a logistic regression model, the effect for anxious/non-anxious remained non-significant (odds ratio of anxious vs. non-anxious is 1.25; $p = .458$). The response rate at endpoint for anxious patients

Figure 3 Change from Baseline for HAMA Total Score; Least-Square Means from MMRM Model.

and non-anxious patients was 67.9% and 65.4%, respectively ($p = .78$). In the logistic regression model, the effect of anxious/non-anxious remained non-significant (odds ratio of anxious vs. non-anxious is 1.30; $p = .413$).

Time to Remission

The median time to remission for anxious and non-anxious patients was 57 days and 68 days, respectively ($p = .65$). Time to remission was also analyzed using a Cox regression model adjusting the effect of anxious/non-anxious by baseline $HAMD_{17}$ total score and naïve/switch. The adjusted remission hazard ratio for anxious versus non-anxious was not significant (hazard ratio = 1.39 with 95% CI 0.94-2.06 $p = .095$).

Time to Response

In a survival analysis for time to response (see Figure 4), the medians of time to response for anxious and non-anxious patients were 28 days and 46 days, respectively ($p = .031$). The hazard ratio from the Cox regression model was 1.61 with 95% CI 1.13-2.28 ($p = .008$).

Safety and Tolerability

Early Discontinuation Rates

A total of 34% of anxious patients and 25% of non-anxious patients discontinued early from the study ($p = .11$). Analysis using the CMH test to evaluate reasons for early

Figure 4 Kaplan-Meier Estimates of Time to Response.

discontinuation comparing anxious and non-anxious patients (while controlling for "treatment-switch" vs. "treatment-naïve" status at study entry) revealed that anxious patients had a higher rate of being lost to follow-up than non-anxious patients (7% vs. 2%, respectively; CMH test $p = .033$, not corrected for multiple comparisons). The Breslow-Day test, used to look for an interaction between anxiety and treatment-switch/treatment-naïve status (e.g., to examine whether the difference in rates of discontinuation between anxious and non-anxious patients depended on whether patients were switched from an antidepressant to duloxetine or were treatment-naïve before starting duloxetine), was not significant. Discontinuation rates due to any reason or due to adverse events did not differ significantly between anxious and non-anxious depressives. Additionally, Kaplan-Meier survival analyses did not show significant differences between anxious and non-anxious depressed patients in median time to discontinuation due to any reason (103 days vs. 108 days, respectively; $p = .09$) or due to adverse events.

Treatment-Emergent Adverse Events

The most common adverse events (AEs), reported by at least 15% of the patients, were nausea (28%), headache (24%), dry mouth (23%), insomnia (18%), and diarrhea (15%). A total of 87% of anxious patients and 90% of non-anxious patients reported at least 1 treatment-emergent adverse event ($p = .55$). No significant differences in the rates of specific treatment-emergent adverse events were noted between anxious and non-anxious groups with the exception of influenza (5% vs. 1%; CMH $p = .045$). The Breslow-Day test was significant ($p < .10$) for decreased libido (9% in anxious and 6% in non-anxious depression), abdominal upper pain (6% in anxious and 7% in non-anxious depression), stomach discomfort (7% in anxious and 6% in non-anxious depression), abdominal pain (7% in anxious and 4% in non-anxious depression), sedation (3% in anxious and 6% in non-anxious depression), and initial insomnia (2% in anxious and 6% in non-anxious depression), indicating that the differences between anxious and non-anxious patients may depend on whether the patient was treatment-naïve or not. For the treatment-naïve patients, there was no significant difference in any of these events; however, for the switch patients, the anxious patients had a significantly higher rate of decreased libido than the non-anxious patients (11.5% vs. 1.7%, $p = .048$). No significant differences were noted between anxious and non-anxious patients in time to the occurrence of treatment-emergent adverse events grouped according to central nervous system (CNS), gastrointestinal system, neuromuscular and skeletal system, and CNS anxiety symptoms. Additionally, within the anxious depressed patient cohort, no significant differences in the rates of specific treatment-emergent adverse events were noted between treatment-naïve and treatment-switch patients.

DISCUSSION

Given duloxetine's dual action on NE and 5-HT and the previous observation of a greater efficacy of the SNRI venlafaxine compared to the SSRI fluoxetine (8) in anxious depression, we had hypothesized that duloxetine would be more efficacious in anxious depression compared to non-anxious depression. Our results only partially support our hypothesis. At the end of this 12-week, open-label study of duloxetine, patients with anxious depression had a significantly greater reduction than non-anxious depressives in depression and anxiety/somatization, as evidenced by the $HAMD_{17}$ and the $HAMD_{17}$ Anxiety/Somatization Factor scores, but the differences in CGI-S and HAMA scores at the end of the trial between these 2 groups were not statistically significant, and the remission and response rates were rather similar at endpoint. The partial, superior efficacy of duloxetine in anxious depression is in sharp contrast with the effects of the relatively noradrenergic tricyclic antidepressant nortriptyline (7) or the SSRI fluoxetine (8,9), as both these agents were significantly less efficacious in individuals with anxious depression compared to those with non-anxious depression (7–9). The rapid efficacy of the SNRI duloxetine in anxious depression, as suggested by the shorter time to response and remission compared to non-anxious depression, is indeed consistent with the results of a pooled analysis showing significantly higher rates of remission with the SNRI venlafaxine compared to the SSRI fluoxetine (8).

One possible explanation for the observed differences in our study is that patients with greater severity of symptoms at baseline (such as those with anxious depression) may have experienced a relatively greater reduction in symptoms due to a regression-toward-the-mean phenomenon. This explanation, however, does not take into account the fact that patients with anxious depression in other studies actually had significantly lesser improvement than patients without anxious depression (7–9).

In general, the safety and tolerability of duloxetine therapy was similar between anxious and non-anxious depressed patients. Both anxious and non-anxious patients experienced similar rates of early discontinuation due to any reason or due to adverse events, median times to early discontinuation due to any reason or due to adverse events, and percentage of patients reporting at least 1 adverse event. Additionally, discontinuation rates due to adverse events were low in both groups (16% and 9%, respectively), and no single treatment-emergent adverse event occurred to a significantly greater degree in anxious versus non-anxious patients except influenza; however, differences were not corrected for multiple comparisons. Additionally, within the anxious cohort of patients, no significant differences were noted in the overall occurrence of adverse events or in rates of specific adverse events between treatment-naïve patients and treatment-switch patients.

A number of limitations of the current study should be noted. Firstly, this was an open-label study. In the absence of a

placebo group, interpretation of efficacy results should be approached with a degree of caution. For this reason, the discussion of efficacy has been limited to a comparison of overall magnitude of improvement between anxious and non-anxious depressives. Secondly, this clinical trial had specific inclusion and exclusion criteria that may have biased the sample and limited the generalizability of the findings. An additional limitation of the study is related to the fact that those who administered the efficacy measures were not blind to the status of the patients (anxious vs. non-anxious depression).

In summary, at the end of this 12-week trial, open treatment with duloxetine was accompanied by a significantly greater reduction in total $HAMD_{17}$ and $HAMD_{17}$ Anxiety/Somatization Factor scores among patients with anxious depression compared to non-anxious depressed patients. Although remission and response rates were similar at endpoint between anxious and non-anxious depressives, patients with anxious depression had a more rapid improvement, displaying a significantly shorter median time to response than non-anxious depressives. Additionally, safety and tolerability of duloxetine treatment was comparable in anxious and non-anxious depressed participants. These findings suggest that the presence of anxious depression is associated with improved outcome among patients treated with the SNRI duloxetine, while poorer outcome is typically reported among patients treated with SSRIs.

ACKNOWLEDGMENTS

REFERENCES

1. Fawcett J, Kravitz HM: Anxiety syndromes and their relationship to depressive illness. *J Clin Psychiatry* 1983; 44(8 Pt 2):8–11

2. Joffe RT, Bagby RM, Levitt A: Anxious and nonanxious depression. *Am J Psychiatry* 1993; 150(8):1257–1258

3. Vanvalkenburg C, Akiskal HS, Puzantian V, Rosenthal T: Anxious depressions. Clinical, family history, and naturalistic outcome—comparisons with panic and major depressive disorders. *J Affect Disord* 1984; 6(1):67–82

4. Clayton PJ, Grove WM, Coryell W, Keller M, Hirschfeld R, Fawcett J: Follow-up and family study of anxious depression. *Am J Psychiatry* 1991; 148(11):1512–1517

5. Tollefson GD, Holman SL, Sayler ME, Potvin JH: Fluoxetine, placebo, and tricyclic antidepressants in major depression with and without anxious features. *J Clin Psychiatry* 1994; 55(2):50–59

6. Fava M, Alpert JE, Carmin CN, Wisniewski SR, Trivedi MH, Biggs MM, Shores-Wilson K, Morgan D, Schwartz T, Balasubramani GK, Rush AJ: Clinical correlates and symptom patterns of anxious depression among patients with major depressive disorder in STAR*D. *Psychol Med* 2004; 34(7):1299–1308

7. Flint AJ, Rifat SL: Anxious depression in elderly patients. Response to antidepressant treatment. *Am J Geriatr Psychiatry* 1997; 5(2):107–115

8. Davidson JR, Meoni P, Haudiquet V, Cantillon M, Hackett D: Achieving remission with venlafaxine and fluoxetine in major depression: Its relationship to anxiety symptoms. *Depress Anxiety* 2002; 16(1):4–13

9. Fava M, Uebelacker LA, Alpert JE, Nierenberg AA, Pava J, Rosenbaum JF: Major depressive subtypes and treatment response. *Biol Psychiatry* 1997; 42:568–576

10. Russell JM, Koran LM, Rush J, Hirschfeld RM, Harrison W, Friedman ES, Davis S, Keller M: Effect of concurrent anxiety on response to sertraline and imipramine in patients with chronic depression. *Depress Anxiety* 2001; 13(1):18–27

11. Fava M, Rosenbaum JF, Hoog SL, Tepner RG, Kopp JB, Nilsson ME: Fluoxetine versus sertraline and paroxetine in major depression: Tolerability and efficacy in anxious depression. *J Affect Disord* 2000; 59(2):119–126

12. Bosworth HB, Hays JC, George LK, Steffens DC: Psychosocial and clinical predictors of unipolar depression outcome in older adults. *Int J Geriatr Psychiatry* 2002; 17(3):238–246

13. Ramana R, Paykel ES, Cooper Z, Hayhurst H, Saxty M, Surtees PG: Remission and relapse in major depression: A two-year prospective follow-up study. *Psychol Med* 1995; 25(6):1161–1170

14. Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, Shaw JL, Thompson L, Nelson DL, Hemrick-Luecke SK, Wong DT: Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. *Neuropsychopharmacology* 2001; 25(6):871–880

15. Detke MJ, Lu Y, Goldstein DJ, Mcnamara RK, Demitrack MA: Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression. *J Psychiatr Res* 2002; 36(6): 383–390

16. Detke MJ, Lu Y, Goldstein DJ, Hayes JR, Demitrack MA: Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. *J Clin Psychiatry* 2002; 63(4):308–315

17. Goldstein DJ, Mallinckrodt C, Lu Y, Demitrack MA: Duloxetine in the treatment of major depressive disorder: A double-blind clinical trial. *J Clin Psychiatry* 2002; 63:225–231

18. Goldstein DJ, Lu Y, Detke MJ, Wiltse C, Mallinckrodt C, Demitrack MA: Duloxetine in the treatment of depression: A double-blind placebo-controlled comparison with paroxetine. *J Clin Psychopharmacol* 2004; 24(4):389–399

19. Nemeroff CB, Schatzberg AF, Goldstein DJ, Detke MJ, Mallinckrodt C, Lu Y, Tran PV: Duloxetine for the treatment of major depressive disorder. *Psychopharmacol Bull* 2002; 36(4):106–132

20. Hamilton M: A rating scale for depression. *J Neurol, Neurosurg, and Psychiatry* 1960; 23:56–62

21. Guy W (Ed): *ECDEU Assessment Manual for Psychopharmacology*. Rev Ed DHEW Pub. No. (ADM) 7–338. Rockville, Maryland: National Institute of Mental Health; 1976

22. Fava M: Diagnosis and definition of treatment-resistant depression. *Biol Psychiatry* 2003; 53(8):649–659

23. Hamilton M: The assessment of anxiety states by rating. *Br J Med Psychol* 1959; 32(1):50–55

24. Cleary P, Guy W: Factor analysis of the Hamilton Depression Scale. *Drugs Exp Clin Res* 1977; 1:115–120

25. Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weissman MM: Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. *Arch Gen Psychiatry* 1991; 48(9):851–855