Research Article

ANXIETY DOES NOT PREDICT RESPONSE TO DULOXETINE IN MAJOR DEPRESSION: RESULTS OF A POOLED ANALYSIS OF INDIVIDUAL PATIENT DATA FROM 11 PLACEBO-CONTROLLED TRIALS

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Background: *Uncontrolled antidepressant trials suggest that anxious patients with major depressive disorder (MDD) are less responsive to antidepressant treatment than less anxious patients. The objective of this study is to determine whether specific antidepressant effects, estimated by drug-placebo differences, are reduced in anxious depression during treatment of MDD with duloxetine.* **Methods:** *This is a retrospective secondary pooled analysis of all placebo-controlled trials of duloxetine at therapeutic doses conducted by the sponsor in outpatients with nonpsychotic unipolar MDD, using the Hamilton Depression Rating Scale (HAMD). Anxious depression was defined by ≥ 7 on the anxiety/somatization factor of the HAMD. Response was defined as $\geq 50\%$ improvement from baseline to endpoint on the HAMD. Remission was defined as an endpoint HAMD ≤ 7. Analyses were performed in the intent-to-treat sample with at least one post-treatment rating.* **Results:** *Eleven trials included 2,841 patients of whom 1,326 were classified as anxious and 1,515 as nonanxious. Change on the HAMD was greater with duloxetine than placebo in both anxious (9.91 versus 7.55, $P<.001$) and nonanxious (6.65 versus 5.23, $P<.001$) patients. Level of anxiety had no effect on the drug–placebo differences. Response and remission rates were significantly greater in duloxetine than placebo-treated patients and drug–placebo differences were unaffected by anxious status. Use of HAMD items psychic and somatic anxiety to define anxious subgroups had similar outcomes.* **Conclusions:** *Duloxetine was more effective than placebo in achieving response and remission in both anxious and nonanxious patients. Anxious status did not affect the magnitude of the drug effect. Depression and Anxiety 27:12–18, 2010.*

INTRODUCTION

Major Depression is a common disorder affecting approximately 17% of the U.S. population.[1] While a number of antidepressants are available for the treatment of this disorder, a minority of patients achieve remission with initial treatment.[2] To improve treatment outcomes, investigators have searched for predictors or moderators of outcome that might guide treatment selection. Anxiety is one of the moderators identified.

During the tricyclic antidepressant era, some studies,[3–5] but not all,[6–8] found that depressed patients with high anxiety were less likely to respond to

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treatment or that they took more time to respond.[9] Anxiety has also been reported to decrease response to second-generation antidepressants. Fava et al.[10] reported that patients with MDD and co-morbid anxiety *disorders* responded less well to treatment with fluoxetine. Davidson et al.[11] found that remission rates were reduced in patients with high anxiety in a pooled analysis of five venlafaxine–fluoxetine comparison trials. In late-life depression, five studies found anxious symptoms were associated with less good outcome in older MDD patients,[12–16] although in two other trials of older patients, anxiety did not predict outcome.[17]

In the largest study[18] to examine the predictive value of anxious depression for outcome, STAR*D found that patients with higher scores on the anxiety/somatization factor (A/S factor)[19] of the Hamilton Depression Rating Scale (HAMD)[20] were less likely to respond or remit and were more intolerant of treatment. The finding was not simply the result of greater severity in the anxious group. In a separate report[21] they noted that anxious patients had other features that distinguished them from less anxious patients. Their findings as well as several of the findings reviewed above suggested that anxious depression might constitute a distinct subtype of MDD that was less responsive to treatment.

The studies that found patients with anxious depression less responsive were not placebo controlled. As a result it is not possible to determine whether the specific effect of antidepressants was reduced (estimated by the drug–placebo differences), or if overall response rates were lower because anxious patients were less responsive to the nonpharmacologic elements of treatment. The objective of this study is to examine placebo-controlled trials of duloxetine conducted in outpatients with MDD to determine whether patients with anxious depression are less responsive to the specific effects of drug treatment than less anxious patients. The anxiety/somatization factor of the HAMD was used to define anxious depression because this was the method employed in STAR*D and other recent studies.

MATERIALS AND METHODS

This is a retrospective analysis of data from double-blind, placebo-controlled, random assignment trials of duloxetine. All placebo-controlled trials, published and unpublished, in Major Depressive Disorder (MDD) conducted by the manufacturer were considered for inclusion. Characteristics of the studies are included in Table 1. All the trials were acute phase treatment studies that varied in length from 7 to 9 weeks. All the trials included men and women with MDD who were aged 18 years or older. All trials used the Mini International Neuropsychiatric Interview[22] to document the presence of DSM IV MDD and to exclude patients with a current or primary Axis I disorder other than MDD or an anxiety disorder as a primary diagnosis within one year of study entry. Patients with bipolar disorder or psychotic disorders also were excluded. Depression was rated using the 17-item Hamilton Rating Scale.[20] Anxious depression was defined as a score ≥ 7 on the anxiety/somatization factor of the HAMD.[19] As an alternative definition, scores greater than the median for the sum of HAMD items 10 and 11, psychic anxiety and somatic anxiety, were used to define an anxious depressed group.

Outcomes were examined using mean HAMD change, response rates, and remission rates. Response was defined as $\geq 50\%$ improvement on the HAMD scale. Remission was defined as an endpoint HAMD score of ≤ 7. In all cases, change, response, and remission were calculated using the last observation carried forward. Differences in response or remission rates between drug and placebo, stratified for anxious/nonanxious subgroups, and controlling for study were examined using Cochrane Mantel Haenszel tests.[23] Differences in response and remission between subgroups (anxious versus nonanxious) and the interaction between subgroup and treatment group were also examined. Differences in change in endpoint HAMD scores between treatment groups within anxious strata were assessed with ANCOVA entering study, baseline HAMD, anxious/nonanxious subgroup, and treatment group. Differences between anxious and nonanxious patients and the interaction between anxious subgroup and treatment groups were also assessed.

TABLE 1. Placebo-controlled trials of duloxetine in major depression

		Duloxetine					Placebo				
Study	Duration weeks	*N*	% female	Age mean±*SD*	Baseline HAMD mean±*SD*	% Anxious[a]	*N*	% female	Age mean±*SD*	Baseline HAMD mean±*SD*	% Anxious[a]
HMAQa[24]	8	70	62.9	42.3±10.8	18.4±4.0	27.9	70	68.6	41.3±13.2	19.2±5.0	40.9
HMAQb[25]	8	82	68.3	39.9±9.8	17.8±5.2	29.6	75	66.7	41.4±11.8	18.3±5.6	34.7
HMBHa[26]	9	123	65.0	42.4±13.7	21.4±4.1	48.8	122	68.0	42.3±12.6	21.1±3.7	51.3
HMBHb[27]	9	128	66.4	40.8±12.6	20.3±3.4	41.5	139	71.2	41.0±14.7	20.5±3.4	40.4
HMAYa[28]	8	188	74.5	43.9±10.9	20.0±3.5	60.8	93	74.2	43.7±12.2	19.9±3.6	55.9
HMAYb[29]	8	196	71.0	45.2±11.7	21.3±3.7	67.7	99	65.7	44.7±10.0	20.6±3.7	69.7
HMATa[30]	8	175	64.5	43.5±14.7	17.6±5.2	40.9	90	65.6	43.2±14.5	17.8±4.7	38.2
HMATb[31]	8	177	58.7	40.8±11.0	18.3±5.3	38.8	89	64.0	40.1±12.9	17.2±5.1	26.1
HMBV[32]	8	207	60.4	72.6±5.6	18.6±4.8	47.8	104	57.7	73.3±5.7	18.9±4.5	42.2
HMCB[33]	7	141	68.0	40.8±13.4	23.4±3.5	77.3	141	62.4	40.3±13.5	22.4±3.4	71.3
HMCR[34]	8	273	63.4	41.1±11.6	17.6±4.8	27.9	137	63.5	42.5±12.3	17.7±5.2	27.4

[a]Anxious depression defined as a score of ≥ 7 on the anxious/somatization factor of the HAMD.

RESULTS

Eleven placebo-controlled trials conducted by the sponsor were identified (Table 1).[24–34] Nine of these have been published.[24,26–29,31–34] Two trials (3327b and 4091a)[25,30] are presented in summary form at www.lillytrials.com. Four placebo-controlled trials of duloxetine in MDD were not included (three used doses below that recommended in depression, e.g. 20 or 30 mg/day [Lilly trial #1124, #1125, #1126] and one used a scale other than the HAMD, thus the A/S factor could not be derived [#8605]). The selected acute phase trials varied in length from 7 to 9 weeks. The trials included 2,841 randomized patients that had at least one post-treatment assessment. Of these, 1,710 received duloxetine and 1,131 placebo; 46.7% were classified as anxious using the A/S factor of the HAMD. Mean baseline HAMD scores in the anxious group were 22.3 versus 17.0 in the nonanxious patients. The percentage of females varied from 56 to 75%. In 10 trials, the mean age varied from 40 to 45 years. Mean age was 73 in the remaining trial. Further description of the patients is shown in Table 1.

Using the A/S factor to define anxious depression, mean change on the HAMD was significantly greater during treatment with duloxetine than placebo respectively in both anxious (9.91 versus 7.55, $P<.001$) and nonanxious (6.65 versus 5.23, $P<.001$) patients. The treatment group by anxious subgroup interaction was not significant ($P=.166$), indicating that anxiety did not affect outcome in the two treatment groups and mean change with any treatment did not differ in the two subgroups, $P=.650$.

Response rates were significantly higher on duloxetine than placebo in both anxious and nonanxious patients (Fig. 1). In the anxious patients response rates were 51% (408/805) and 34% (176/521) on duloxetine and placebo respectively, $P=.001$. In nonanxious patients rates of response were 46% (412/905) and 35% (211/610) on duloxetine and placebo, $P<.001$. The interaction analysis indicated that anxiety did not affect drug–placebo differences ($P=.147$). The overall response rate in anxious patients, 44.0% (584/1,326), was slightly *higher* than in less anxious patients, 41.1% (623/1,515) ($P<.001$).

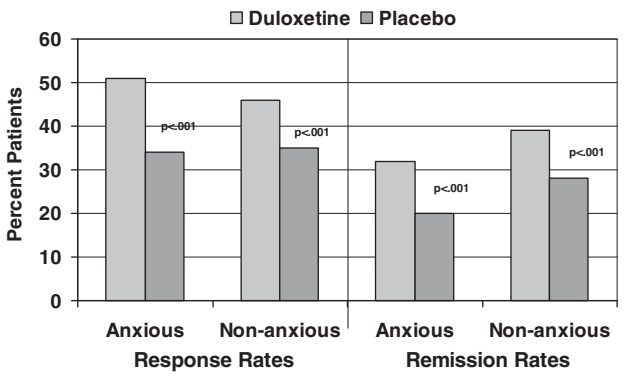

Figure 1. Response and remission rates in 1,326 anxious and 1,515 nonanxious depressed patients in 11 placebo-controlled trials of duloxetine.

Remission rates were also significantly greater in duloxetine-treated patients than placebo-treated patients in both the anxious and the nonanxious depressed patients. In the anxious patients, remission rates were 32% (259/805) on duloxetine and 20% (106/521) on placebo, $P<.001$. In the nonanxious patients, remission rates were 39% (353/905) on duloxetine and 28% (173/610) on placebo, $P<.001$. The interaction analysis indicated that anxiety did not affect drug–placebo differences ($P=.504$). Overall, however, the anxious patients were less likely to remit 27.5% (365/1,326) than less anxious patients, 34.7% (526/1,515), $P<.001$.

Outcome was also examined using the two HAMD anxiety items (psychic anxiety and somatic anxiety) to define anxious and less anxious patients (split at the median) (Tables 2 and 3). Use of this definition resulted in 1,519 anxious patients and 1,321 nonanxious patients. In the analyses of mean change, response, and remission, duloxetine was more effective than placebo in all comparisons. Comparison of overall remission rates indicated lower remission rates in the anxious patients 28.0% (426/1,519) than the less anxious patients, 35.2% (465/1,322) ($P<.001$), but no difference in overall change or response rates (42.3% versus 42.7%) in anxious and nonanxious patients. The interaction analysis of therapy and subgroup indicated no significant effect of anxiety on drug–placebo differences.

DISCUSSION

In these 11 trials of 2,841 depressed patients, those with anxious depression defined by the HAMD A/S factor or the items for psychic and somatic anxiety were no less responsive to the specific effects of duloxetine than were patients with less anxious depression. Duloxetine was significantly more effective than placebo in both anxious and less anxious patients using change scores, response rates, and remission rates. Overall, remission rates were lower in anxious patients using both definitions of anxious depression but drug–placebo differences were not affected.

The finding that anxiety does not reduce the efficacy of duloxetine is similar to three other placebo-controlled trials of antidepressants. Tollefson et al.[7] reviewed 19 double blind, randomized, comparison, or placebo-controlled trials of fluoxetine that included 3,183 patients with MDD. Fluoxetine was superior to placebo in both anxious and nonanxious groups and response rates did not differ significantly in the two groups (55.7% versus 60.7%). Remission rates were significantly *higher* in anxious patients than in nonanxious patients, 38.3% versus 29.5%. Davidson et al.[11] found that remission rates were reduced in patients with high anxiety in a pooled analysis of five

TABLE 2. Differences in response and remission rates with duloxetine and placebo in anxious and nonanxious patients using psychic and somatic anxiety items (9 and 10) to define anxious depression[a,b]

	Anxious subgroup	Treatment group	Response *N* (%)	Within subgroup, duloxetine versus placebo	Between anxious subgroups	Treatment group by anxious subgroup interaction
Response	Anxious	Duloxetine *N* = 914	449 (49%)	*P* <.001	*P* = .36	*P* = .21
		Placebo *N* = 605	199 (33%)			
	Nonanxious	Duloxetine *N* = 796	371 (47%)	*P* <.001		
		Placebo *N* = 525	188 (36%)			
Remission	Anxious	Duloxetine *N* = 914	301 (33%)	*P* <.001	*P* <.001	*P* = .33
		Placebo *N* = 605	125 (21%)			
	Nonanxious	Duloxetine *N* = 796	311 (39%)	*P* = .001		
		Placebo *N* = 525	154 (29%)			

[a]Anxious and nonanxious subgroups defined using a median split of the total score on HAMD items 9 and 10 for psychic and somatic anxiety.
[b]Differences in response or remission rates between drug and placebo treatment groups, stratified for anxious/nonanxious subgroups, and controlling for study were examined using Cochrane Mantel Haenszel tests. Differences in response and remission between subgroups (anxious versus nonanxious) and the interaction between subgroup and treatment group also were examined.

TABLE 3. Differences in mean change on the HAMD with duloxetine and placebo in anxious and nonanxious patients using psychic and somatic anxiety items (9 and 10) to define anxious depression

Anxious subgroup[a]	Treatment group	Baseline HAMD mean ± *SD*	Change HAMD LSMean	Within subgroup, duloxetine versus placebo[b]	Between anxious subgroups[c]	Treatment group by anxious subgroup interaction[c]
Anxious	Duloxetine *N* = 914	21.1 ± 4.2	−9.0	*P* <.001	*P* = .41	*P* = .39
	Placebo *N* = 606	21.2 ± 4.1	−6.8			
Nonanxious	Duloxetine *N* = 796	17.5 ± 4.6	−7.2	*P* <.001		
	Placebo *N* = 525	17.7 ± 4.4	−5.7			

[a]Anxious and nonanxious subgroups defined using a median split of the total score on HAMD items 9 and 10 for psychic and somatic anxiety.
[b]Within subgroup analysis by ANCOVA entering baseline HAMD, LOCF HAMD by treatment group, controlling for study.
[c]Between subgroup and subgroup by treatment group interaction analysis by ANCOVA entering baseline HAMD and LOCF HAMD for subgroup, treatment group, controlling for study.

placebo-controlled venlafaxine–fluoxetine comparison trials in 1,454 patients; however, level of anxiety did not appear to affect drug-placebo differences for either drug. My colleagues and I performed a meta-analysis of placebo-controlled late life depression studies.[35] Eight of these trials used the HAMD from which the A/S factor scores could be determined. In these 8 trials with 10 contrasts and 3,709 patients, level of anxiety did not significantly affect drug–placebo differences in response rates. In patients receiving drug treatment, pooled response rates were 49 and 44% in the anxious and less-anxious subgroups.

Other meta-analyses of antidepressant studies appear to be consistent. Papakostas et al.[36] performed a meta-analysis of 10 double-blind, randomized trials with 2,122 patients comparing bupropion with various SSRIs. The intent of the meta-analysis was to compare the efficacy of SSRIs and bupropion in anxious depression defined with the A/S factor of the HAM-D. While the SSRIs were slightly *more* effective than bupropion in anxious patients, these data indicated very similar response rates in high anxious patients and less anxious patients, 62.3 and 63.3%, respectively. Fawcett et al. reported a meta-analysis of eight controlled trials of mirtazapine that found mirtazapine more effective than placebo for reducing anxiety symptoms in MDD patients with high levels of anxiety.[37] Taken together, the data from these reports argue strongly that anxiety does not diminish the specific effects of antidepressant treatment in MDD. To this author's knowledge, there are no placebo-controlled trials suggesting otherwise.

The current findings and those of the systematic reviews or meta-analyses cited above[7,11,35–37] are also noteworthy because each of these reports included all the trials within a particular domain, e.g. all the controlled trials of mirtazapine in MDD or all the placebo-controlled trials in late life MDD. As a consequence they appear to be less vulnerable to publication bias. This is particularly important because to date, all the examinations of the effect of anxiety on response in MDD have been retrospective secondary analyses. Positive findings are much more likely to be considered worthy of reporting. Negative findings for

specific variables may not be reported and even if they are reported, are more difficult to retrieve in a literature search.

The efficacy of duloxetine for the treatment of anxious depression is consistent with the findings of a study of patterns of symptom response in MDD during duloxetine treatment. Shelton and colleagues found psychic anxiety was one of three HAMD symptoms (with depressed mood and decreased interest) showing the greatest change during duloxetine treatment.[38] Responsiveness of psychic anxiety during antidepressant treatment has also been reported for sertraline, fluoxetine, and reboxetine.[39,40] In addition, four scales[41–44] designed to assess *core symptoms* of depression all include psychic anxiety as one of the core symptoms. Finally, the effectiveness of duloxetine for treating anxious symptoms would appear to be consistent with its effectiveness in generalized anxiety disorder (GAD).[45,46]

The findings with respect to remission in anxious and nonanxious patients, independent of the type of treatment, are mixed. In the duloxetine trials reviewed here, in STAR*D,[18] and in the analysis of venlafaxine and fluoxetine trials performed by Davidson et al.[11] overall remission rates were lower in anxious than in nonanxious patients. In the current sample it appears that the lower remission rate in anxious patients may be the product of higher initial HAMD scores. In this pooled sample, the mean baseline HAMD in the anxious patients was 22.3 versus 17.0 in the nonanxious group defined by the A/S factor. Although mean change in the anxious patients in the duloxetine group was −9.9 versus −6.6 in the nonanxious patients, the anxious patients were still less likely to achieve an absolute score ≤ 7 on the HAMD in a 7 to 9 week period. This interpretation is consistent with the findings of this study and several other reviews[7,11,35,36] that *response rates* did not differ or were higher in anxious than in nonanxious patients. This study does not address the question of whether anxious depressed patients might achieve remission rates similar to nonanxious patients with longer treatment.

The clinical trials of duloxetine reviewed here differed from some prior individual trials, including STAR*D, in that patients with co-morbid *anxiety disorders* were excluded. STAR*D included patients with co-morbid anxiety disorders. In fact, only 35% of the STAR*D sample did not have a co-morbid psychiatric disorder. Several of the anxiety disorders—OCD, panic, PTSD, and somatization disorder—were more predictive of poor outcome than were anxious symptoms (odds ratios ranging from .40 to .67 for these anxiety disorders versus an odds ratio of .77 for anxious symptoms).[47] It is possible that anxiety disorders do predict less good outcome while anxious symptoms, in the absence of these disorders, do not. It is noted that the STAR*D data do not address the question of whether co-morbid anxiety disorders reduce the specific effects of drug treatment in depression. A 12-week study of venlafaxine in MDD found that co-morbid GAD did not reduce the magnitude of the drug–placebo difference, but there was a suggestion that remission rates in the placebo group were lower if co-morbid GAD was present than if it was not.[48]

Throughout the study we refer to anxious and nonanxious depression using the HAMD anxiety/somatization factor to define subgroups as STAR*D[18] and recent studies have done.[35,36] A dichotomous definition of anxious depression was employed because anxious depression has been proposed as a subtype of major depression. It is noted that this is an arbitrary distinction. STAR*D found that anxiety scores on the A/S factor were normally distributed[18] and patients in the "nonanxious" group often report anxious symptoms albeit less severe symptoms.

The study has several limitations. This is a retrospective analysis of the data. However, examinations of the effects of anxiety on response usually have been retrospective and this limitation is to some extent offset by our ability to combine data from several previous trials. Another limitation is that drug treatment was limited to one antidepressant—duloxetine. It is possible that other antidepressants might perform differently. Other alternative methods to define anxious depression might produce different results; however, the HAMD A/S factor was used in STAR*D and other recent studies. In addition, an alternative definition of anxious depression using two HAMD symptoms for psychic and somatic anxiety produced results similar to those using the A/S factor. In these studies patients with a primary anxiety disorder were excluded. A recent report of the STAR*D study found that only 22% of that sample would meet criteria for inclusion in a typical clinical trial.[49] While this may limit the generalizability of the current findings, it does allow for assessment of anxious symptoms without the confounding effects of co-morbid anxiety disorders.

CONCLUSION

In this pooled data set from 11 controlled trials, anxiety symptoms did not reduce the efficacy of duloxetine in major depression. The findings are similar to other placebo-controlled antidepressant trials. Anxious depression may have other distinctive attributes, but these data contradict the notion that anxious depression is less responsive to antidepressant treatment.

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