Impact of Pretreatment With Antidepressants on the Efficacy of Duloxetine in Terms of Mood Symptoms and Functioning: An Analysis of 15 Pooled Major Depressive Disorder Studies

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ABSTRACT

Objective: This post hoc analysis aimed to determine whether patients with major depressive disorder (MDD) in duloxetine trials who were antidepressant naive or who were previously exposed to antidepressants exhibited differences in efficacy and functioning.

Method: Data were pooled from 15 double-blind, placebo- and/or active-controlled duloxetine trials of adult patients with MDD conducted by Eli Lilly and Company. The individual studies took place between March 2000 and November 2009. Data were analyzed using 4 pretreatment subgroups: first-episode never treated, multiple-episode never treated, treated previously only with selective serotonin reuptake inhibitors (SSRIs), and previously treated with antidepressants other than just SSRIs. Measures included the 17-item Hamilton Depression Rating Scale (HDRS-17) total and somatic symptom subscale scores, Montgomery-Asberg Depression Rating Scale (MADRS) total score, and Sheehan Disability Scale total score. Response rates (50% and 30%) were based on the HDRS-17 total score and remission rates on either the HDRS-17 or MADRS total score.

Results: Response and remission rates were significantly greater ($P < .05$ in 11 of 12 comparisons) for duloxetine versus placebo in the 4 subgroups. A trend of greater response and remission occurred for first-episode versus multiple-episode patients; both groups were generally higher than the antidepressant-treated groups. Mean changes in efficacy measures were mostly significantly greater ($P < .05$ in 13 of 16 comparisons) for duloxetine versus placebo within each pretreatment subgroup, with some ($P < .05$ in 2 of 24 comparisons) significant interaction effects between subgroups on HDRS-17 total and somatic symptoms scores.

Conclusions: Duloxetine was generally superior to placebo on response and remission rates and in mean change on efficacy measures. Response and remission rates were numerically greater for first-episode versus multiple-episode and drug-treated patients. Mean change differences on efficacy measures among the 4 subgroups were inconsistent. Duloxetine showed a similar therapeutic effect independent of episode frequency and antidepressant pretreatment.

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Recent studies have found that first-episode, treatment-naive patients with major depressive disorder (MDD) may exhibit various biochemical and microstructural abnormalities in the brain.[1,2] Various other irregularities and deficits in multiple areas of gray and white matter of the brain have also been found in patients with MDD.[3–6] Importantly, several studies have shown that the more MDD episodes a patient experiences, the harder they become to treat, and the more likely these patients are to have a recurrence of MDD.[7–9] However, a recent analysis of 15 pooled clinical trials in MDD found that treatment response was not significantly influenced by the number of previous depressive episodes.[10]

Although studies have shown that approximately 40% of treated patients with MDD reach remitted status,[11,12] another 40% do not adequately respond to the first antidepressant with which they are treated.[4] Furthermore, results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study[13] found that an increasingly smaller percentage of patients respond or remit after trying a second or third drug after failing previous selective serotonin reuptake inhibitor (SSRI) treatment (level 1) and subsequent alternative antidepressant therapies. Hunter et al[14] conducted a study in patients with MDD comparing those who had never taken an antidepressant with those who had. After a 1-week placebo lead-in, patients were randomized to 8 weeks of double-blind treatment to either drug (fluoxetine or venlafaxine) or placebo. The mean improvement change in the 17-item Hamilton Depression Rating Scale (HDRS-17) total score was significantly greater in antidepressant-naive patients compared with patients who had previously received antidepressants.[14]

Duloxetine is a serotonin-norepinephrine reuptake inhibitor (SNRI) that has been approved for MDD treatment in Europe, the United States, and other regions. Lai and Hsu[15] studied duloxetine in first-episode, drug-naive patients who had both MDD and panic disorder. These patients had widespread gray matter deficits compared with healthy controls at baseline. After 6 weeks of duloxetine therapy, patients showed significant improvement in depressive and panic symptoms compared with baseline. Although remitted patients, or patients showing significant symptomatic improvement, had some increases in gray matter, it was not to the level of healthy controls. However, changes in gray matter volume were correlated with HDRS score improvement.[15]

This project explored whether patients with MDD in duloxetine trials who were antidepressant naive or who had previously been treated with antidepressants exhibited

Clinical Points

- Placebo response was greater in the previously nontreated, first-episode depression subgroup, so the bar is set higher for duloxetine in order to demonstrate efficacy.
- Duloxetine-treated patients in the multiple-episode and previously treated subgroups, when compared with matching placebo-treated patients, showed numerical, rather than statistical, differences in response and remission.
- Duloxetine showed a similar therapeutic effect and improvement in functionality independent of MDD episode frequency and antidepressant pretreatment status.

differences in efficacy and functioning measures. On the basis of the studies presented above, one would expect less clinical improvement in those patients previously treated with antidepressants who did not show adequate symptomatic improvement. Moreover, the treatment-naive patients were further assessed by comparing those patients having their first major depressive episode with those who have experienced more than 1 episode. As noted in the literature, patients experiencing multiple MDD episodes are generally more difficult to treat and are more likely to relapse.[7,16,17]

METHOD

Study Design

Data were pooled from 15 randomized, double-blind, placebo- and/or active-controlled trials of duloxetine[18–31] for MDD treatment conducted by Eli Lilly and Company (Table 1). The individual studies took place between March 2000 and November 2009. Data were taken from the acute treatment phase of those studies that had extensions. Studies with a relapse prevention design were not included in the analysis set. Only studies with a randomized dose of duloxetine 60 mg/d or higher were included. These 15 studies comprised the full set of available studies at the time this work was initiated.

All study protocols were developed in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. Before studies began, all patients provided written informed consent, and each clinical study site's institutional review board approved the protocol.

Patient Population

Male or female inpatients or outpatients with MDD, as defined by criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) or Fourth Edition, Text Revision (*DSM-IV-TR*), who were 18 years and older were included. Patients were excluded from each study if they had any current primary psychiatric diagnosis other than MDD (mild dementia was allowed in 1 study), had a serious medical illness, had a history of substance abuse or dependence within 1 year of study entry, or had a positive urine drug screen. Details for each study can be found in the primary publication (Table 1). Patient data were analyzed based on 4 pretreatment subgroups as follows: (1) patients naive to antidepressant treatment and experiencing their first episode of depression (hereafter called "first episode"), (2) patients naive to antidepressant treatment and having experienced >1 major depressive episode (hereafter called "multiple episode"), (3) patients who were previously treated with SSRIs only (hereafter called "SSRI"), and (4) patients who were treated with other antidepressants in addition to or instead of SSRIs (hereafter called "non-SSRI"). For studies including dose arms < 60 mg/d, only patients randomized to a dose arm ≥ 60 mg/d are included.

Outcome Measures

The primary analysis measure was the HDRS-17.[32] The Montgomery-Asberg Depression Rating Scale (MADRS)[33] was used for those studies that did not include the HDRS-17. Response rates (≥ 50% improvement baseline to endpoint) were based only on the HDRS-17 total score. Remission rates were taken from the HDRS-17 (total score ≤ 7 at endpoint) or the MADRS (total score ≤ 10 at endpoint). The Sheehan Disability Scale (SDS)[34] assessed functional impairment. Baseline measures for pain and functioning were assessed using the Brief Pain Inventory (BPI),[35] and overall improvement was evaluated via the Clinical Global

Table 1. Summary of the 15 Randomized, Double-Blind, Placebo- or Active-Controlled Studies of Major Depressive Disorder in Adults Used in the Analyses

Study Identifier	Study Phase	Placebo, n	Duloxetine, n (dosage, mg/d)	Treatment Duration, wk	Primary Publication
HMATa	III	90	84 (80)	8	Nemeroff et al[18]
HMATb	III	89	91 (80)	8	Goldstein et al[19]
HMAYa	III	93	188 (80, 120)	8	Detke et al[20]
HMAYb	III	99	196 (80, 120)	8	Perahia et al[21]
HMBHa	III	122	123 (60)	9	Detke et al[22]
HMBHb	III	139	128 (60)	9	Detke et al[23]
HMBU	IV	…	166 (60)	12	Perahia et al[24]
HMBV	IV	104	207 (60)	8	Raskin et al[25]
HMCB	IIIb	141	141 (60)	7	Brannan et al[26]
HMCQ	IV	…	164 (60)	12	Perahia et al[24]
HMCR	IIIb	137	273 (60)	8	Nierenberg et al[27]
HMCV	III	…	238 (60)	9	Lee et al[28]
HMFA	IV	121	249 (60)	12	Robinson et al[29]
HMFS	IV	258	518 (60–120)[a]	36	Oakes et al[30]
HMFT	IV	…	372 (60–120)	12	Martinez et al[31]

[a]HMFS: 60 mg for 12 wk, then could be titrated to 120 mg.

Table 2. Baseline Patient Characteristics of Treatment Subgroups

Characteristic	First Episode (no previous episode) (n = 876)	Multiple Episode (> 1 episode) (n = 1,210)	SSRI (previously treated with SSRI only) (n = 1,621)	Non-SSRI (previously treated with other antidepressants) (n = 789)
Age, mean (SD)	42.2 (15.4)	47.4 (16.8)	48.6 (16.0)	49.8 (14.9)
Range, y	18–87	19–90	18–90	19–88
Gender, n (%)				
Female	509 (58.1)	771 (63.7)	1,098 (67.7)	556 (70.5)
Male	367 (41.9)	439 (36.3)	523 (32.3)	233 (29.5)
Race, n (%)				
White	604 (68.9)	865 (71.5)	1,266 (78.1)	635 (80.5)
Black/African American	76 (8.7)	154 (12.7)	129 (8.0)	45 (5.7)
Asian	126 (14.4)	51 (4.2)	45 (2.8)	33 (4.2)
Native American	1 (0.1)	2 (0.2)	2 (0.1)	0
Hispanic	64 (7.3)	132 (10.9)	169 (10.4)	71 (9.0)
Other/missing	5 (0.6)	6 (0.5)	10 (0.6)	5 (0.6)
Geography, n (%)				
United States	522 (59.6)	976 (80.7)	1,287 (79.4)	530 (67.2)
Europe	187 (21.3)	133 (11.0)	202 (12.5)	150 (19.0)
Other	167 (19.1)	101 (8.3)	132 (8.1)	109 (13.8)
Prior treatment for MDD, n (%)				
Any	0	0	1,621 (100)	789 (100)
SSRI	0	0	1,621 (100)	470 (59.6)
SNRI	0	0	0	480 (60.8)
Duration of current MDD episode, mean (SD), mo	16.3 (37.7)	9.7 (16.9)	12.8 (27.3)	10.1 (32.4)
No. of previous episodes of MDD, mean (SD)	0	5.8 (18.7)	5.4 (20.1)	6.6 (27.9)
BPI average pain score, mean (SD)	3.7 (2.4)	3.8 (2.5)	4.0 (2.6)	3.9 (2.6)
BPI interference summary score, mean (SD)	2.7 (3.3)	3.3 (2.9)	3.5 (2.9)	3.5 (3.0)
CGI-S score, mean (SD)	4.3 (0.6)	4.2 (0.7)	4.4 (0.7)	4.4 (0.7)
SDS total score, mean (SD)	19.0 (6.3)	18.9 (6.6)	19.7 (6.3)	20.1 (6.3)
MADRS total score, mean (SD)	26.2 (6.7)	26.9 (7.0)	28.7 (6.5)	27.9 (6.5)
HDRS-17, mean (SD)				
Total score	21.0 (4.0)	20.5 (5.1)	21.2 (5.2)	21.0 (5.1)
Maier	10.5 (2.3)	10.4 (2.7)	10.8 (2.7)	10.7 (2.8)
Retardation	7.4 (1.8)	7.2 (2.0)	7.4 (1.9)	7.4 (2.0)
Sleep	3.5 (1.7)	3.6 (1.7)	3.6 (1.8)	3.5 (1.8)
Bech	11.1 (2.4)	11.0 (2.7)	11.4 (2.7)	11.2 (2.7)
Mood	8.3 (2.2)	8.2 (2.4)	8.5 (2.4)	8.4 (2.4)
Anxiety/somatization	6.8 (1.9)	6.5 (2.2)	6.8 (2.2)	6.7 (2.3)
HARS total score, mean (SD)	17.1 (5.2)	16.4 (6.5)	16.4 (5.6)	17.5 (5.9)

Abbreviations: BPI = Brief Pain Inventory, CGI-S = Clinical Global Impressions–Severity of Illness scale, HARS = Hamilton Anxiety Rating Scale, HDRS-17 = 17-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, SDS = Sheehan Disability Scale, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

Impressions–Severity of Illness scale (CGI-S).[36] The BPI and CGI-S were only measured at baseline to determine whether any differences occurred among the subgroups that may have influenced study outcomes.

Statistical Analysis

The baseline variables were analyzed by the 4 pretreatment subgroups using descriptive statistics. The continuous endpoints were analyzed by analysis of covariance (ANCOVA) as follows: 1 ANCOVA model was calculated for each study, with the fixed effects including treatment, pretreatment groups, treatment by pretreatment variable interaction, and baseline score of the endpoint evaluated as covariates. Effect sizes in each model were calculated for least-squares mean differences, divided by the standard deviation (SD) of the residuals provided by the model of this study. Overall least-squares mean estimates and effect sizes were calculated as a weighted mean of the corresponding estimates in all studies, with weights based on within-study variance, assuming a fixed study effect. The binary outcomes were analyzed using a logistic regression model adjusting for study and using the same factors and covariate as the ANCOVA model. For all endpoints, missing values were calculated using last observation carried forward. All confidence intervals (CIs) presented are 95% CIs, and statistical significance is defined as $P < .05$. As this was a post hoc analysis, no adjustment for multiplicity was made, and the results should be interpreted as being exploratory in nature. All analyses were performed using SAS version 9.2 software (SAS Institute, Cary, North Carolina).

RESULTS

A total of 4,496 of 4,531 patients had taken at least 1 dose of study drug and therefore were included in this post hoc analysis. The majority of patients were white (75%) and women (65%), with a mean age of 47.3 years (SD = 16.1 years). Baseline patient characteristics are shown by pretreatment subgroup in Table 2. The patients were moderately ill, with a mean CGI-S score of 4.3 (SD = 0.7) and a mean HDRS-17 score of 20.9 (SD = 5.0). The number of patients completing the study in which they were enrolled ranged from 72% to 73% for each of the pretreatment subgroups (Table 3). Individual reasons for discontinuing a study early were broadly similar among the 4 subgroups.

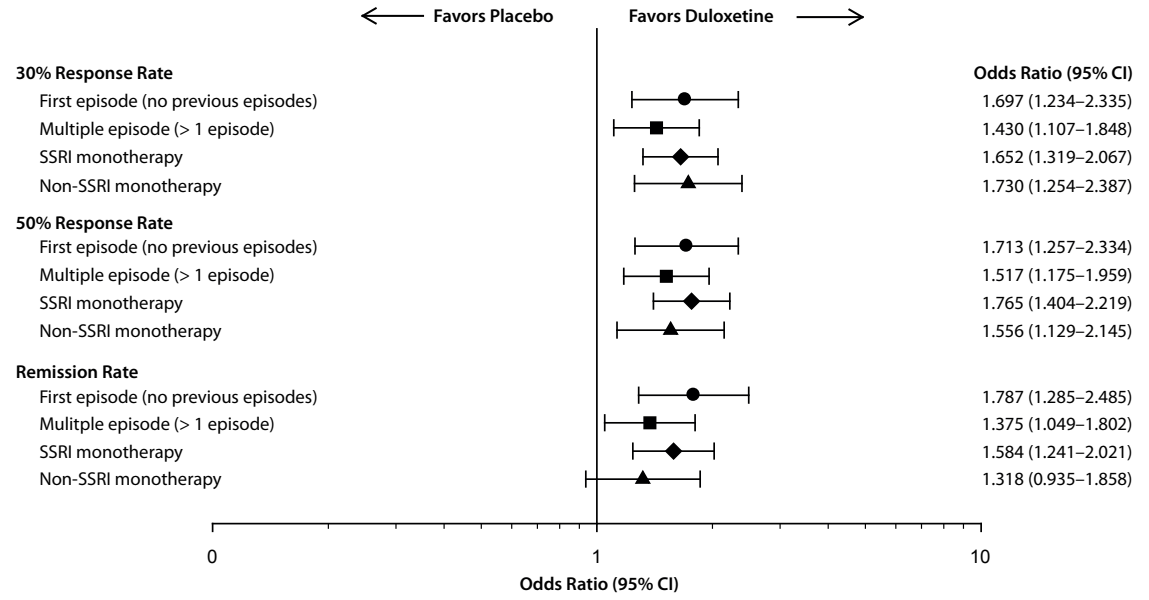
Table 3. Patient Disposition of Treatment Subgroups[a]

Reason	First Episode (no previous episodes) (n = 876)	Multiple Episode (> 1 episode) (n = 1,210)	SSRI (previously treated with SSRI only) (n = 1,621)	Non-SSRI (previously treated with other antidepressants) (n = 789)
Completed	634 (72.4)	883 (73.0)	1,168 (72.1)	573 (72.6)
Discontinued	242 (27.6)	327 (27.0)	453 (27.9)	216 (27.4)
Reason for discontinuation				
Adverse event	63 (7.2)	109 (9.0)	110 (6.8)	61 (7.7)
Subject decision	70 (8.0)	81 (6.7)	105 (6.5)	46 (5.8)
Lost to follow-up	54 (6.2)	68 (5.6)	96 (5.9)	32 (4.1)
Lack of efficacy	23 (2.6)	30 (2.5)	86 (5.3)	59 (7.5)
Protocol violation	24 (2.7)	26 (2.1)	38 (2.3)	12 (1.5)
Physician decision	2 (0.2)	7 (0.6)	11 (0.7)	3 (0.4)
Sponsor decision	3 (0.3)	3 (0.2)	5 (0.3)	2 (0.3)
Entry criteria exclusion	1 (0.1)	0	1 (0.1)	0
Other	2 (0.2)	1 (0.1)	0	0
Death	0	1 (0.1)	1 (0.1)	0
Satisfactory response	0	1 (0.1)	0	1 (0.1)

[a]All data are presented as n (%).
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Table 4. Response and Remission Rates of Treatment Subgroups[a]

Measure	First Episode (no previous episodes)		Multiple Episode (> 1 episode)		SSRI (previously treated with SSRI only)		Non-SSRI (previously treated with other antidepressants)	
	Placebo (n = 261)	Duloxetine (n = 615)	Placebo (n = 392)	Duloxetine (n = 818)	Placebo (n = 487)	Duloxetine (n = 1,134)	Placebo (n = 243)	Duloxetine (n = 546)
30% Response rate, %	55.6	72.4	53.8	67.0	50.5	65.5	51.0	67.9
50% Response rate, %	39.8	58.9	38.3	53.2	34.5	50.8	36.2	50.9
Remission rate, %	36.8	51.7	34.4	44.1	30.0	40.1	34.2	41.4

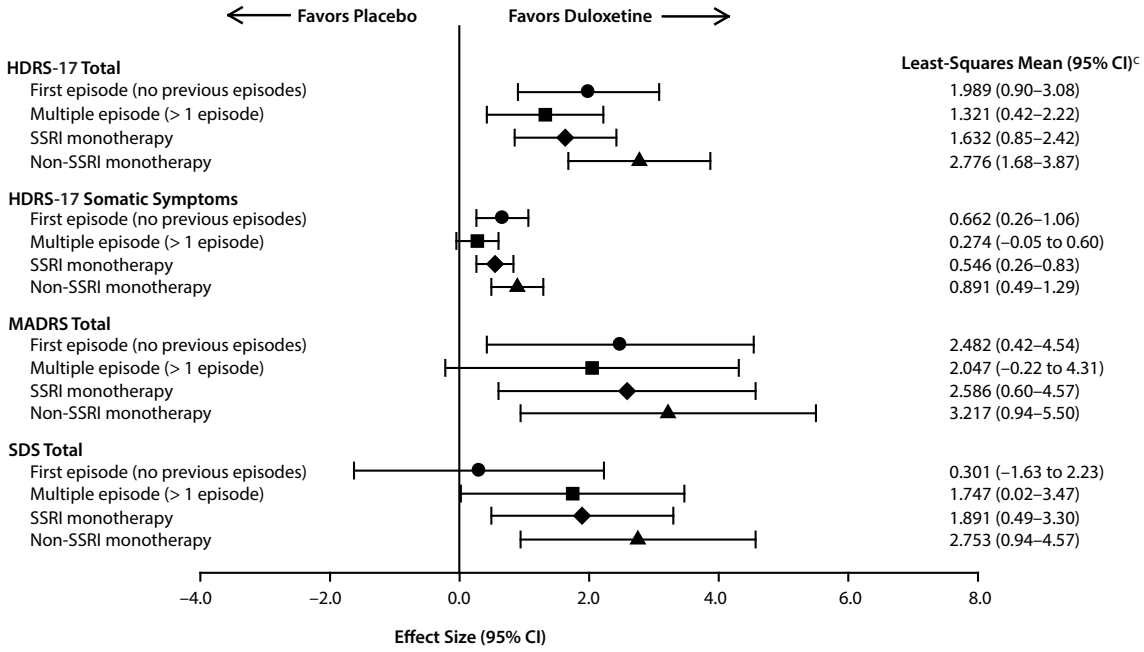


[a]The response rates are the percent baseline to endpoint improvement on the HDRS-17 total score (≥ 30% and ≥ 50%). Remission is defined as a score ≤ 7 on the HDRS-17 total score or a score ≤ 10 on the Montgomery-Asberg Depression Rating Scale total score at endpoint.
Abbreviations: HDRS-17 = 17-item Hamilton Depression Rating Scale, SSRI = selective serotonin reuptake inhibitor.

Although the number of patients responding to duloxetine at the 30% and 50% levels (percent improvement on HDRS-17 total score from baseline to endpoint) was numerically greater in the treatment-naive subgroups than in the drug-therapy subgroups, the difference in response rate from placebo in each subgroup was generally similar (Table 4). The odds ratios (ORs) were all in favor of duloxetine versus placebo in all response rate comparisons. The OR for obtaining a 30% response rate was not significantly different between any comparisons of the 4 subgroups (OR range, 1.010–1.182). However, for the 50% response rates, the ORs (95% CIs) were significantly in favor of the following: first episode versus SSRI (OR = 1.226; 95% CI, 1.055–1.424), first episode versus non-SSRI (OR = 1.316; 95% CI, 1.108–1.563),

Table 5. Efficacy Measures for Treatment Subgroups[a]

Measure[b]	First Episode (no previous episodes)	Multiple Episode (> 1 episode)	SSRI (previously treated with SSRI only)	Non-SSRI (previously treated with other antidepressants)
HDRS-17 total score	−1.989***	−1.321**	−1.632***	−2.776***
HDRS-17 somatic symptoms score	−0.662**	−0.274	−0.546***	−0.891***
MADRS total score	−2.482*	−2.047	−2.586*	−3.217**
SDS total score	−0.301	−1.747*	−1.891**	−2.753**



[a]The Ns vary across measures, with the highest N for the HDRS-17 measures and the smallest N for the MADRS measures as follows: treatment naive no previous episodes, duloxetine: 148–615, placebo: 90–261; treatment naive > 1 episode, duloxetine: 120–818, placebo: 96–392; SSRI, duloxetine: 165–1134, placebo: 108–487; non-SSRI, duloxetine: 124–546, placebo: 68–243.
[b]Duloxetine minus placebo at endpoint.
[c]Least-squares mean estimates were used for the comparison.
*$P < .05$ versus placebo.
**$P < .01$ versus placebo.
***$P < .001$ versus placebo.
Abbreviations: HDRS-17 = 17-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, SDS = Sheehan Disability Scale, SSRI = selective serotonin reuptake inhibitor.

multiple episode versus SSRI (OR = 1.143; 95% CI, 1.001–1.305), and multiple episode versus non-SSRI (OR = 1.227; 95% CI, 1.045–1.441).

For both duloxetine- and placebo-treated patients, remission rates were numerically lower in the multiple-episode subgroup than in the first-episode subgroup, and the rates were even lower in the SSRI and non-SSRI subgroups. In addition, the difference between duloxetine and placebo was 5 to 8 percentage points smaller in the multiple-episode, SRRI, and non-SSRI subgroups compared with the first-episode subgroup. However, the ORs were in favor of duloxetine compared with placebo in all but the non-SSRI subgroup. Between subgroups, ORs (95% CIs) were significantly in favor of the same subgroup comparisons as the 50% response rates: first episode versus SSRI (OR = 1.230; 95% CI, 1.053–1.437), first episode versus non-SSRI (OR = 1.364; 95% CI, 1.141–1.632), multiple episode versus SSRI (OR = 1.160; 95% CI, 1.011–1.330), and multiple episode versus non-SSRI (OR = 1.286; 95% CI, 1.087–1.522).

Table 5 presents the least-squares mean estimate (95% CI) for each of the treatment subgroups for the HDRS-17 total and somatic symptoms subscale scores, MADRS total score, and SDS total score. All measures were significantly in favor of duloxetine compared with placebo, except in the multiple-episode subgroup for the HDRS-17 somatic symptoms subscale and MADRS total and the first-episode subgroup for the SDS total score. There was a significant interaction in the HDRS-17 total score between the multiple-episode and non-SSRI subgroups ($P = .045$) and a significant interaction in the HDRS-17 somatic symptoms score between the multiple-episode and non-SSRI subgroups ($P = .020$).

DISCUSSION

The results of these analyses demonstrate that response and remission rates for both duloxetine- and placebo-treated patients were numerically greater for the first-episode versus multiple-episode and drug-treated patients. The difference in rates between duloxetine and placebo also decreased in the same manner for the 50% response and remission rates but

not for the 30% response rate. These trends were generally small, for example, decreases of 2%–8% in response and remission rates for the duloxetine and placebo groups in the multiple-episode patients compared with first-episode patients. Although the response and remission rates were lower in previously treated patients and in multiple-episode patients experiencing > 1 MDD episode, duloxetine was an effective treatment in these patients. Moreover, duloxetine was found to be significantly better than placebo for both the response and remission rates in all 4 subgroups, except for the remission rate in the non-SSRI group, in which the confidence interval just included 1.0. The similarity of the confidence intervals across the subgroups for these measures demonstrates the consistent effect of duloxetine in treating patients with MDD.

Although, in general, there was a decrease in response and remission rates for patients who had experienced previous MDD episodes (treated and nontreated), this was not demonstrated when assessing differences between duloxetine and placebo at endpoint for depressive and functional outcomes. This finding was most conspicuous for the SDS total score. The endpoint score on the SDS total was approximately 11 to 12 for duloxetine in each of the subgroups. However, the endpoint score for placebo was approximately 11 in the first-episode subgroup and approximately 13, 14, and 14.6 in the multiple-episode, SSRI, and non-SSRI subgroups, respectively. Thus, the difference between duloxetine and placebo was greater in the multiple-episode and the 2 treatment subgroups. It has been shown that functional impairment increases with increasing MDD episodes.[37] It is difficult to know why patients taking placebo responded better on the SDS total score in the first-episode group, although it is known that first-episode patients are less likely to have an MDD recurrence and are easier to treat than patients previously taking antidepressants.[7,8] In addition, the average duration of the current MDD episode was 4 to 6 months longer in the first-episode subgroup than in the other 3 subgroups. Perhaps this variation in episode duration contributed to the smaller difference between duloxetine and placebo (ie, less improvement anticipated for duloxetine- versus placebo-treated patients).

A previous pooled analysis of duloxetine studies found similar results when comparing patients experiencing 3 or fewer MDD episodes with patients experiencing more than 3 MDD episodes, as well as patients with no previous MDD episode and at least 1 previous MDD episode.[10] The differences were approximately 3%–5% for the HDRS-17 50% response and remission rates. Although having more MDD episodes is a prognostic factor for generally lower response and remission rates, these differences were not statistically significant, and the authors' conclusion was that the number of prior MDD episodes may not be a predictor of treatment response.[10] Beevers et al[38] found that patients with a greater number of MDD episodes were less likely to improve during treatment. They also found that patients with more MDD episodes had worsened cognition, which contributed significantly to the lower response to treatment.[38] Although we did not study these phenomena in our trials, an increased number of MDD episodes has been shown to correlate with a reduced hippocampal volume and autoimmune activity against serotonin, an increase in inflammatory markers, and an imbalance of neurotrophins.[37] All of these factors may lead to susceptibility to further MDD episodes, which could result in patients being more difficult to treat regardless of therapy type. Interestingly, some studies have shown that treatment to remission may normalize these changes, such as increases in hippocampal volume.[39–41] Beyond the possibility of less improvement with increased MDD episodes, several studies have found that the number of previous MDD episodes is a significant predictor of relapse or recurrence of depression,[7,8,16,17,42,43] although some studies have not found this relationship.[44–46]

Although antidepressant treatment may lead to normalization of brain structures and levels of various molecules such as cytokines, this usually occurs if the patient remits on his or her antidepressant.[39,41] For those patients previously treated with SSRIs or other antidepressants, it would be expected for them to have changes in brain structure and connectivity compared with healthy controls or remitted patients. The response and remission results would support this hypothesis to some extent, but mean changes in the efficacy and functioning measures do not. However, research has also shown changes in brain structure and worsened treatability in patients with multiple MDD episodes.[5,7–9] Moreover, a longer duration of a current MDD episode can also lead to patients being harder to treat. As pretreatment and the number of previous MDD episodes play a role in the placebo response, indirect comparisons using placebo response as a common reference should take this variable into account. Furthermore, when comparing treatment groups, adjusting for these factors may help improve the precision of the analysis. Finally, studies focusing on such subgroups may need fewer patients, although they would also be harder to recruit.

One limitation of this study is that analyses were done post hoc. It would have been informative if magnetic resonance imaging and measurements of various brain dysfunction markers had been done at the beginning and conclusion of the duloxetine studies to determine how brain volume varied in patients with first and multiple MDD episodes and in patients who remitted. Another limitation is that the clinical trials had several exclusions, such as comorbid psychiatric disorders and various other medical illnesses. Indeed, an analysis of the STAR*D data suggests that phase III trials do not recruit a representative sample of depressed patients.[47] Thus, one should be cautious in extrapolating these results to the general population of patients with MDD. Moreover, these analyses should not be used to compare the efficacy of duloxetine with other antidepressants.

There are several strengths of these analyses. One is that the pooled data all came from randomized, double-blind, placebo- and/or active comparator-controlled trials. The analyses contained a large number of patients, including more than 3,100 and 1,350 patients taking duloxetine and

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placebo, respectively. Importantly, another strength is that the study designs of the 15 clinical trials used in these pooled analyses were similar, including most of the inclusion and exclusion criteria. Finally, patient-level analyses were used rather than meta-regression, which not only reduces the potential for aggregation bias, as is commonly seen when using group-level analyses, but also are generally required to determine whether patient characteristics are related to treatment.

In this pooled analysis of duloxetine studies in MDD, there was a numerical decrease in improvement in response and remission rates with increased MDD episodes and previous treatment with antidepressants, which is a correspondent finding of the demonstrated kindling pathophysiology of MDD. Regardless of whether depressed patients presented with their first MDD episode or a recurrent MDD episode or had been treated previously with SSRIs or other antidepressants, duloxetine was significantly more efficacious than placebo in nearly all measures for the 4 subgroups. This numerical decrease did not occur for mean changes in the efficacy measures and was actually reversed in the SDS total score. In this regard, it has been shown that results may differ depending on the outcome measures used, as well as how the outcome is defined (eg, level of response rates).[48]

This post hoc analysis shows how splitting patients into subgroups based on previous frequency of depressive episodes and antidepressant pretreatment has an impact on the interpretation of results of the experimental antidepressant versus placebo. It is interesting to see the placebo response is greater in the first-episode group, thus making it more difficult for discriminating with scales the larger therapeutic effect intuitively expected in that group. Although intuitively multiple-episode patients and patients previously treated with antidepressants would be more difficult groups to respond and remit, the data show that the differences in those patients when compared with those treated with placebo tend to be numerical rather than statistically significant. Thus, it is worth highlighting the homogenization in outcomes that duloxetine achieved in this differentiated depressed patient population; for example, duloxetine showed a similar therapeutic effect independent of MDD episode frequency and antidepressant pretreatment. Further highlighting this homogenization in the results between subgroups is the functioning outcomes measured with the SDS; independent of the subgroup, results were similar versus placebo, showing how the therapeutic effect on functionality is also independent of the patient MDD episode frequency and antidepressant pretreatment status.

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

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