Annals of Clinical Psychiatry, 20[4]:209–218, 2008

ISSN: 1040-1237 print / 1547-3325 online
DOI: 10.1080/10401230802437639

informa
healthcare

Factors Predicting Reduced Antidepressant Response: Experience with the SNRI Duloxetine in Patients with Major Depression

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Background: *To identify putative demographic and clinical variables that correlate with antidepressant response to the SNRI duloxetine in major depression.*
Methods: *The effect of 130 candidate treatment outcome predictors was examined on 3 dependent treatment outcome measures related to depression: 1) depression symptom outcome measured by HAMD-17 total and HAMD-17 percent change from baseline to endpoint, 2) remission (HAMD-17 ≤ 7 at endpoint) and response (≥ 50% reduction in HAMD-17 from baseline to endpoint) rates, and 3) time to response (days to ≥ 50% reduction in HAMD-17).*
Results: *Eleven variables had an overall predictive index of ≥ 20% and were associated with poorer treatment outcome: HAMD-17 total, duration of current MDD episode, leaden paralysis, fatigue, HAMA total, HAMA items 2 and 8, HAMD-17 anxiety/somatization subscale, anxiety-related comorbid conditions, and VAS overall pain and pain while awake.*
Conclusions: *Our results highlight the clinical relevance of more severe and/or persistent levels of depression, psychiatric and medical comorbidity, and symptoms characteristic of atypical depression (leaden paralysis and fatigue) and confirm findings from other studies that such patients may respond less well or take longer to respond to pharmacotherapy. Consistent with previous SNRI studies, we found no significant association between age, gender, and race/ethnicity and treatment outcome.*

Keywords Depression, Duloxetine, Predictors, Response, Clinical trial

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INTRODUCTION

Major depressive disorder (MDD) is a highly prevalent condition that is associated with significant levels of disability, morbidity, and mortality. Many different types of antidepressant drug therapies are available, but not all patients respond to treatment (1). Moreover, some patients may respond to some treatments but not others. From a clinical perspective, it would be ideal to be able to match an effective treatment to a particular patient without resorting to trial and error. Doing so would require an ability to predict treatment outcome based on knowledge about the treatment and/or the patient (2,3). From a scientific perspective, studies investigating predictors of antidepressant treatment outcome could be useful for identifying and characterizing the common or unique features of different antidepressant drugs that may be relevant to understanding their effectiveness, such as mechanism of action (4,5).

Historically, much of the clinical research on predictors has investigated the older generation tricyclic antidepressant (TCA) and monoamine oxidase inhibitor (MAOI) antidepressant drugs (6–8). Given their popularity and widespread use, however, most contemporary research has focused on the newer generation serotonin reuptake inhibitors (SRIs) (3,9–13). By contrast, other newer generation non-SRI antidepressant drugs have not been widely investigated in predictor studies (12,14,15).

Studies attempting to identify predictors of treatment outcome have investigated various demographic, social, psychological, biological, illness, and treatment factors, but they often have not yielded consistent findings. With respect to demographic characteristics (e.g., age, gender, and race/ethnicity), the most common finding from some studies has been gender differences (16). Studies of various social factors (e.g., marital, education, employment, and socioeconomic status) have generally shown that greater social support and socioeconomic status are associated with better treatment outcomes (9,13,15,17). Many aspects of psychological function (e.g., cognitive characteristics and personality traits, concomitant anxiety, temperaments, and disorders) have been investigated (18–21); higher levels of neuroticism have been most consistently associated with a poor treatment outcome (22). A large and diverse literature on biological factors exists (23–25). Classic studies of biological predictors have focused on neuroendocrine, biochemical, and sleep EEG investigations, without finding any consistent associations with treatment outcome. More recently, biological investigations using such contemporary technologies as pharmacogenetics (26,27), neuroimaging (28), and quantitative EEG (29) are exciting and promising approaches for studying predictors of treatment outcome. Different depressive illness features (e.g., severity, chronicity, recurrence, depressive subtype, and comorbidity) have also been investigated. The most consistent findings suggest that depressions characterized by more severe and chronic symptoms and higher degrees of psychiatric and medical comorbidity are less likely to respond well to treatment (13). Finally, treatment history (i.e., prior antidepressant non-response) has generally been shown to predict non-response to subsequent antidepressant treatment trials (1).

The lack of consistent findings across studies may be due to a variety of methodological issues, including differences in patient populations, sample sizes, drug treatment (type and dose), outcome measures, and length of follow-up. In the STAR*D study, a very large, diverse, and broadly representative group of depressed patients was systematically treated through a successive sequence of four treatment steps until they achieved a satisfactory treatment response (1). During the first level of STAR*D, all patients were treated with the SRI antidepressant citalopram. Patients who were Caucasian, female, employed, or had higher levels of education or income had higher remission rates, whereas patients with longer depressive episodes, more concurrent psychiatric disorders (especially anxiety disorders or substance use disorders), more general medical disorders, and lower baseline function and quality of life had lower remission rates (13).

Duloxetine is a serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SNRI) antidepressant that exhibits relatively comparable affinities for the 5-HT and NE transporters (30). The efficacy, tolerability, and safety of duloxetine, in doses ranging from 40 mg/day to 120 mg/day, in the treatment of MDD have been demonstrated in multiple double-blind, placebo-controlled clinical trials (31). Because of the relative paucity of predictor studies investigating non-SRI antidepressant drugs, the objective of this study was to identify putative demographic and clinical variables that may predict the antidepressant response to duloxetine in an independent and prospectively defined sample of patients with major depression, and to confirm and extend the findings from previous studies about predictors of antidepressant treatment response.

METHODS

This was a 12-week, open-label, multicenter trial involving 27 investigative sites. The study protocol was reviewed and approved by the institutional review board at each site, and all patients signed informed consent prior to participating in the study.

The study consisted of three 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). After screening, eligible patients were divided into two groups: a treatment-naïve group (patients who were not receiving antidepressant treatment at the time of study entry) and a treatment-switch group (patients who exhibited suboptimal response or poor tolerability to antidepressant treatment immediately prior to study entry).

Patients in the treatment-naïve group were randomized in a 1:1 ratio to receive duloxetine 30 mg/day or 60 mg/day for a 1-week initial treatment phase (Study Period II). Patients unable to tolerate duloxetine during this period were discontinued. At the end of Study Period II, patients receiving 30 mg/day were

required to increase their dose to 60 mg/day. During the remainder of the acute treatment phase (Study Period III), each patient's dose could be increased in 30 mg increments (based on response) from a minimum of 60 mg/day to a maximum of 120 mg/day. The dose could be increased (or decreased because of side effects) only at scheduled visits, and could be increased only if the 17-item Hamilton Rating Scale for Depression (HAMD-17) total score was >7 at the scheduled visit.

Patients in the treatment-switch group were receiving citalopram (≤ 40 mg/day), escitalopram (≤ 20 mg/day), fluvoxamine (≤ 150 mg/day), paroxetine (≤ 40 mg/day), sertraline (≤150 mg/day), or venlafaxine (≤150 mg/day) at study entry, which they continued during the screening period. Patients taking doses above these levels were excluded. Patients taking fluoxetine within the last 30 days were excluded (because of the long half-life of the drug and its active metabolites). Patients who had taken any of these antidepressants and had discontinued it within one month of the screening visit were required to wash out from that antidepressant for 21 days. They were then considered to be untreated and therefore eligible for the study as part of the treatment-naïve group. At the end of Study Period I, treatment-switch patients were immediately switched (without tapering or overlap) from their current medication to duloxetine 60 mg/day and they were required to remain on this dose for one week (Study Period II). Patients unable to tolerate duloxetine during Study Period II were discontinued. During Study Period III, the dose could be titrated in the same way described previously.

Male and female patients (18 years and older) meeting DSM-IV (32) criteria for MDD, who had a HAMD-17 total score ≥ 15 and a Clinical Global Impression-Severity of Illness (CGI-S) score ≥ 4, were eligible.

Exclusion criteria included bipolar disorder, schizophrenia, or other psychotic disorder; primary and current Axis II disorder; serious medical illness; clinically significant laboratory abnormality; serious suicide risk; treatment with a monoamine oxidase inhibitor within 14 days; lack of response during the current episode to two or more adequate antidepressant drugs (i.e., clinically appropriate dose for at least four weeks); any anxiety disorder as a primary diagnosis within six months; substance dependence within six months; or a positive urine drug screen.

Study assessments included the HAMD-17 (33), the Hamilton Rating Scale for Anxiety (HAMA) (34), the CGI-S scale (35), the Visual Analogue Scales (VAS), the Symptom Questionnaire Somatic Subscale (SQSS) (36), the Changes in Sexual Functioning Questionnaire (CSFQ) (37), and the HAMD-17 Anxiety/Somatization subscale (38). Prior antidepressant treatment was assessed with the Antidepressant Treatment Response Questionnaire (ATRQ) (39).

Statistical analyses for this study were conducted on data from all treatment-naïve and treatment-switch patients who had baseline measurements (from Study Period I) and at least one set of post-baseline measurements (from Study Period II or III).

The 130 candidate predictor variables (which may predict treatment outcome) that were examined are grouped into five broad categories: treatment group variables, demographic variables, depression-related variables, non-depression psychiatric variables, and non-psychiatric variables. These candidate predictor variables are described below. In each category, the values of the variables are those taken at baseline (from Study Period I).

Treatment Group Variables

Patients' treatment group status at the time of enrollment may complicate the analysis of predictors of treatment outcome. Treatment was classified as either treatment-naïve or treatment-switch. Treatment was also examined according to initial duloxetine dose (switch initial dose 60 mg; naive initial dose 30 mg; and naive initial dose 60 mg).

Demographic Variables

These include age, age category (less than 50 years old versus 50 years or greater), gender, and race/ethnicity.

Depression-Related Variables

These include DSM-IV major depression diagnosis (individual symptoms); MDD subtype (e.g., seasonal, anxious, melancholic, atypical); atypical depressive symptoms; melancholic depressive symptoms; depression history (e.g., patient's age at first MDD episode, length of the current MDD episode, number of previous episodes); HAMD-17 scale (total, subscales, and individual items); and antidepressant treatment history information (from the ATRQ).

Non-Depression Psychiatric Variables

These include the HAMA (total, subscales, and individual items); HAMD-17 Anxiety/Somatization subscale; anxiety-related psychiatric co-morbidity; and the number of axis I historical and secondary conditions (non-depression comorbidities) reported at baseline.

Non-Psychiatric Variables

These include body mass index (BMI); sustained hypertension at baseline; menopausal status based on age for females (premenopausal < 45 years old; perimenopausal 45–55 years old; postmenopausal > 55 years old); sexual functioning (CSFQ); physical pain (VAS); physical symptom burden (SQSS); and the number of axis III historical and secondary conditions reported at baseline.

The effect of candidate predictor variables was examined on outcomes related to depression that were continuous, categorical and time to event. The first type was continuous, for example, HAMD-17 total score and the HAMD-17 percent change from baseline to endpoint, and were analyzed using general linear models statistical procedures. The second type was categorical (binary), for example, remission (HAMD-17 = 7 at endpoint) and response (= 50% reduction in HAMD-17 from baseline to endpoint rates) and were analyzed using logistic regression procedures. The third type was time to response, which was defined as the number of days from initiation of duloxetine to the first date that the HAMD-17 total score was reduced to less than 50% and was analyzed using log-rank procedures.

The effects of candidate predictor variables on continuous, categorical and time to response treatment outcomes were assessed using one of seven statistical models. For the initial set of data analyses, the statistical models and procedures were applied to the entire group of patients. The first statistical analysis (Model I) examined the effect of candidate predictors for the entire patient population in the absence of therapy group (treatment-naïve or treatment-switch) and dose group (60 mg switch; 30 mg naïve; 60 mg naïve) terms. The second analysis (Model II) included a therapy term (naïve or switch) and a therapy-by-predictor covariate term. The third analysis (Model III) included a dose term (60 mg switch; 30 mg naïve; 60 mg naïve) and a dose-by-predictor covariate term.

For the next set of data analyses, the statistical models and procedures were applied to specific subgroups of patients. These statistical analyses examined the effect of candidate predictors for treatment-naïve patients (Model IV), treatment-switch patients (Model V), 30-mg treatment-naïve patients (Model VI), and 60-mg treatment-naïve patients (Model VII). The statistical analyses for the HAMD-17 percent change included only a term for percent change (without using the HAMD-17 baseline score as a covariate). The analyses for the raw HAMD-17 score at endpoint included a term for the raw score and the baseline HAMD-17 raw score value as a covariate.

The focus of these statistical analyses was to rank the strength in predicting outcome of several baseline variables for this SNRI study. A notable effect for any of the particular predictor and outcome combinations above was arbitrarily defined as an effect with a p-value of less than a cutoff of 0.05. The predictive index for a particular candidate predictor variable was defined as the percent of all analyses conducted that showed a notable main effect for the candidate predictor variable. A cutoff of 0.05 was used since it is familiar, but it is arbitrarily. Another cutoff level, for example a lower value to correct ostensibly for multiple testing, would admittedly have produced a different predictive index for the baseline variables. However, it would have nevertheless provided a similar ranking among the baseline variables in terms of their predictive strength for this study. Because the focus was only to rank variables among themselves, which is not susceptible to a type I error, and the focus was not to draw a confirmatory conclusion to a generalized population of depressed patients, which would be susceptible to a type I error, a correction to protect for multiple testing would not be valuable in this situation. Those baseline candidate predictive variables with at least a 20% predictive index were considered putative predictor variables.

RESULTS

There were 249 patients who entered the acute treatment phase (Study Period III) of the study. One hundred and seventy-seven patients completed Study Period III; 72 patients dropped out during this phase. There were 112 patients in the treatment-switch group; 29 patients (26%) dropped out during Study Period III (seven because of adverse events, 22 for lack of efficacy or other reasons). There were 67 patients in the treatment-naïve 30 mg group; 21 (31%) dropped out (9 for adverse events, 12 for lack of efficacy or other reasons). There were 70 patients in the treatment-naïve 60 mg group; 22 (31%) dropped out (13 for adverse events, 9 for lack of efficacy or other reasons). The relative proportion of patients dropping out because of adverse events was higher in both treatment-naïve groups compared to the treatment-switch group. The baseline clinical and demographic characteristics of these 2 groups of subjects and the main treatment outcome results from this study have been published (40).

Table 1 shows demographics and baseline clinical characteristics for both the treatment-naïve and treatment-switch groups. There was a significant difference in the percentage of

Table 1 Demographic and Baseline Characteristics

Demographic or Baseline Characteristic	Naïve Duloxetine 30 mgs (n = 67)	Naïve Duloxetine 60 mgs (n = 70)	Switch Duloxetine 60 mgs (n = 112)	p-Value
Age, y, mean (std)	42.3 (13.5)	42.0 (12.6)	44.5 (10.4)	.139
Height, cm, mean (std)	169.7 (10.4)[a]	170.1 (8.8)[b]	165.5 (11.4)[d]	.026
Weight, kg, mean (std)	79.5 (20.7)[a]	82.6 (21.1)	79.9 (19.3)	.679
CGI-S, mean (std)	2.4 (1.4)	2.3 (1.3)[c]	2.3 (1.3)[d]	.876
HAMA Total, mean (std)	8.3 (6.9)	8.3 (6.5)[c]	8.3 (6.4)[d]	.987
HAMD Total, mean (std)	8.7 (7.1)	9.2 (7.4)[c]	9.0 (7.5)[d]	.970
VAS Overall, mean (std)	17.6 (24.8)	17.2 (24.8)[c]	15.1 (21.3)[e]	.757
Gender				.008
Females, n (%)	38 (56.7)	44 (62.9)	87 (77.7)	
Ethnicity, n (%)				.523
African American	3 (4.5)	5 (7.1)	8 (7.1)	
Caucasian	59 (88.1)	59 (84.3)	95 (84.8)	
Hispanic	5 (7.5)	4 (5.7)	8 (7.1)	

[a]n = 66
[b]n = 69
[c]n = 65
[d]n = 110
[e]n = 109

Abbreviations: std = standard deviation; CGI-S = Clinical Global Impression-Severity of Illness; HAMA = Hamilton Rating Scale for Anxiety; HAMD = Hamilton Rating Scale for Depression; VAS = Visual Analogue Scales.

females among the treatment-switch, treatment-naïve 60 mg, and treatment-naïve 30 mg groups (87/112 [77.7%] vs. 44/70 [62.9%] vs. 38/67 [56.7%]; p = .008). Patients in the treatment-switch group reported significantly more pain (had higher scores) on the abdominal pain component of the VAS than did the patients in the treatment-naïve 30 mg group (16.8 ± 2.4 vs. 7.1 ± 1.5, respectively; p = .002). In addition, the treatment-switch patients reported significantly more pain on the VAS shoulder pain component compared to treatment-naïve 60 mg patients (20.2 ± 2.7 vs. 11.2 ± 2.5, respectively; p = .012). There was also a significant difference in height among the treatment-switch, treatment-naïve 60 mg, and treatment-naïve 30 mg groups. However, height might have little impact on response. There were no significant baseline differences in any other demographic or clinical variables at baseline.

As described in the Methods section, multiple assessments of predictive index were conducted on each of the candidate predictor variables. Table 2 lists candidate predictor variables with an overall predictive index of at least 10%. The table lists the overall predictive index of these candidate predictor variables in descending order (last 3 columns of the table), and the predictive indices of each variable for raw HAMD-17 total scores (first 3 columns of the table), percent HAMD-17 change from baseline to endpoint (second 3 columns of the table), response/remission (third 3 columns of the table), and time to response or remission (fourth 3 columns of the table). The number of days of treatment with duloxetine had the highest overall predictive index (64.3%), but would not be considered a valid candidate predictor variable because it is not a simple baseline variable and merely reflects the duration of treatment (a longer duration of treatment would be expected to be highly associated with a good treatment outcome).

As shown in Table 2, there are 11 baseline candidate predictive variables that meet the criteria for putative predictor variable status (i.e., they have at least an overall predictive index of 20% based on our analyses). These 11 candidate predictive variables have a putative predictive index and are associated with higher raw HAMD-17 scores at endpoint. Four are depression-related variables: the HAMD-17 total score, duration of the current MDD episode, leaden paralysis (an atypical depressive symptom), and fatigue (a DSM-IV depression criterion symptom). Five are non-depression psychiatric variables: the HAMA total score, HAMA item 2 (tension symptoms of anxiety), HAMA item 8 (somatic sensory symptoms of anxiety), the HAMD-17 Anxiety/Somatization subscale, and anxiety-related comorbid conditions. Two are non-psychiatric variables: overall pain and pain while awake from the VAS. Nine of these 11 candidate predictive variables have a putative predictive index and are associated with lower HAMD-17 percent changes from baseline to endpoint; the two that were not associated with this treatment outcome were the HAMD-17 total score and duration of current MDD episode.

Among these 11 candidate predictive variables, 9 have a putative predictive index (at least 20%) and are associated with lower rates of response/remission. Three are depression-related variables: the HAMD-17 total score, duration of the current MDD episode, and leaden paralysis. Four are non-depression psychiatric variables: the HAMA total score, HAMA item 2, HAMA item 8, and the HAMD-17 Anxiety/Somatization subscale. Two are non-psychiatric variables: overall pain and pain while awake from the VAS. The two candidate predictor variables that were not associated with lower rates of response/remission were fatigue and anxiety-related comorbid conditions.

Among these 11 candidate predictive variables, 5 have a putative predictive index (at least 20%) and are associated with longer times to response/remission. Three are depression-related variables: the HAMD-17 total score, duration of the current MDD episode, and fatigue. Two are non-depression psychiatric variables: the HAMA total score and HAMA Question #8 (somatic sensory symptoms of anxiety).

DISCUSSION

The results from our study demonstrate that 11 candidate predictive variables had significant predictive indices and were associated with a relatively poorer treatment outcome with duloxetine among patients with major depression. Four of the variables were related to more severe depression: the HAMD-17 total score, the duration of the current MDD episode, the atypical depressive symptom of leaden paralysis, and the DSM-IV depression symptom of fatigue. Five variables were related to higher anxiety: the HAMA total score, the tension and somatic sensory anxiety items from the HAMA, the Anxiety/Somatization subscale items from the HAMD-17, and the presence of anxiety-related comorbid conditions. The two final variables were greater overall pain and pain while awake as measured on the VAS.

Our results highlight the clinical relevance of more severe and/or persistent levels of depression (41), and they confirm the findings from other studies that such patients may respond less well or take longer to respond to pharmacotherapy (42,43). Psychiatric comorbidity (e.g., anxiety and substance use disorders) and medical comorbidity influence the severity and morbidity of major depression (44–46). Our results (that high levels of anxiety symptoms, concurrent anxiety disorders, and physical pain were associated with a reduced response to duloxetine) are consistent with other studies demonstrating that patients with concurrent anxiety disorders, medical comorbidity, and high levels of somatic symptoms respond less well to treatment (13,47,48). However, they are not consistent with the findings of a separate analysis in this database which had shown that remission and response rates at endpoint were similar between anxious and non-anxious depressive groups, and that anxious depressives had a significantly shorter median time to response (49).

There are two analytical reasons that explain this difference. Firstly, in the study by Fava and colleagues (49), the logistic regression used included patient type (Naïve or Switch) and a covariate term for the anxious/non-anxious group. This grouping

Table 2 Candidate Predictors with Overall Predictive Index of at least 10%

	Outcome			Percent Change			Response/Remission			Time to Response or Remission			Overall		
Candidate Predictor	Notable[a]	Total[a]	Percent	Notable[a]	Total[a]	Percent	Notable[a]	Total[a]	Percent	Notable[a]	Total[a]	Percent	Notable[a]	Total[a]	Percent
HAMA item 8	17	35	(48.6)	15	35	(42.9)	8	14	(57.1)	3	14	(21.4)	43	98	(43.9)
HAMA Total	20	35	(57.1)	9	35	(25.7)	11	14	(78.6)	3	14	(21.4)	43	98	(43.9)
Visual Analogue Scale - Overall	17	35	(48.6)	14	35	(40.0)	6	14	(42.9)	1	14	(7.1)	38	98	(38.8)
MIMI - Leaden Paralysis	14	35	(40.0)	11	35	(31.4)	6	14	(42.9)	0	14	(0.0)	31	98	(31.6)
HAMA item 2	10	35	(28.6)	13	35	(37.1)	5	14	(35.7)	1	14	(7.1)	29	98	(29.6)
Anxiety Related Co-morbidity	15	35	(42.9)	13	35	(37.1)	0	14	(0.0)	0	14	(0.0)	28	98	(28.6)
HAMD Anxiety Somatization Total	15	35	(42.9)	9	35	(25.7)	4	14	(28.6)	0	14	(0.0)	28	98	(28.6)
HAMD Total Score (items 1–17)	17	35	(48.6)	2	35	(5.7)	6	14	(42.9)	3	14	(21.4)	28	98	(28.6)
Visual Analogue Scale –Pain while Awake	9	35	(25.7)	8	35	(22.9)	11	14	(78.6)	0	14	(0.0)	28	98	(28.6)
Fatigue DSM-IV Question A6	9	35	(25.7)	11	35	(31.4)	0	14	(0.0)	5	14	(35.7)	25	98	(25.5)
Duration of Current MDD Episode	8	35	(22.9)	4	35	(11.4)	9	14	(64.3)	3	14	(21.4)	24	98	(24.5)
Visual Analogue Scale –Stomach ache	7	35	(20.0)	7	35	(20.0)	0	14	(0.0)	5	14	(35.7)	19	98	(19.4)
HAMA item 7	2	35	(5.7)	3	35	(8.6)	10	14	(71.4)	3	14	(21.4)	18	98	(18.4)
HAMD10:Anxiety/ Psychic	11	35	(31.4)	5	35	(14.3)	0	14	(0.0)	0	14	(0.0)	16	98	(16.3)
HAMD Retardation Total	4	35	(11.4)	4	35	(11.4)	5	14	(35.7)	3	14	(21.4)	16	98	(16.3)
HAMD12:Somatic Symptoms/Gastro	5	35	(14.3)	0	35	(0.0)	0	14	(0.0)	10	14	(71.4)	15	98	(15.3)
Visual Analogue Scale – Daily	3	35	(8.6)	4	35	(11.4)	3	14	(21.4)	4	14	(28.6)	14	98	(14.3)
Visual Analogue Scale –Shoulder pain	5	35	(14.3)	5	35	(14.3)	4	14	(28.6)	0	14	(0.0)	14	98	(14.3)
Depressed Mood DSM-IV Question A1	4	34	(11.8)	8	34	(23.5)	0	14	(0.0)	1	13	(7.7)	13	95	(13.7)
Insomnia DSM-IV Question A4	5	35	(14.3)	7	35	(20.0)	1	14	(7.1)	0	14	(0.0)	13	98	(13.3)
Patient Age At First MDD Episode	4	35	(11.4)	3	35	(8.6)	5	14	(35.7)	0	14	(0.0)	12	98	(12.2)
Duration of Last MDD Episode (Weeks)	5	35	(14.3)	0	35	(0.0)	6	14	(42.9)	1	14	(7.1)	12	98	(12.2)
MINI - Psychomotor Retardation	0	35	(0.0)	6	35	(17.1)	6	14	(42.9)	0	14	(0.0)	12	98	(12.2)
HAMD05:Insomia Middle	5	35	(14.3)	3	35	(8.6)	3	14	(21.4)	0	14	(0.0)	11	98	(11.2)
HAMDSS5T: Subscale 5 Total	2	35	(5.7)	0	35	(0.0)	5	14	(35.7)	4	14	(28.6)	11	98	(11.2)
SQSS - Total	4	35	(11.4)	7	35	(20.0)	0	14	(0.0)	0	14	(0.0)	11	98	(11.2)
Loss of Pleasure DSM-IV Question A2	2	20	(10.0)	4	20	(20.0)	0	8	(0.0)	0	8	(0.0)	6	56	(10.7)
HAMA item 11	2	35	(5.7)	3	35	(8.6)	0	14	(0.0)	5	14	(35.7)	10	98	(10.2)

[a]total = total number of analyses conducted.

[b]notable = number of analyses for which $p < .05$.

Abbreviations: HAMA = Hamilton Rating Scale for Anxiety; MINI = Mini International Psychiatric Interview; HAMD = Hamilton Rating Scale for Depression; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; MDD = major depressive disorder; SQSS = Symptom Questionnaire Somatic Subscale.

is derived from the dichotomization of the HDRS sub-factor for Anxiety and Somatization in those analyses of remission and response rates at endpoint ($p = .458$ and $p = .413$, respectively). In the current manuscript, to improve statistical power, the HDRS Anxiety and Somatization sub-factor was not dichotomized and we used response and remission at any time, which increased rates by about 10% compared to those at endpoint. In addition, the continuous covariate of HAMA total in these data outperformed the continuous covariate HDRS subfactor for Anxiety and Somatization for its ability to explain improvement in depressive symptoms at any time. Importantly, it is not exceptional to find conflicting conclusions within the same database about the predictive index of anxiety based on different psychiatric instruments. In STAR*D, depressive anxiety is a significant predictor for QIDS but not for HRDS (49). Our findings therefore support the notion that more severe, chronic, and complicated depressions have a less robust response to treatment.

That leaden paralysis and fatigue may be associated with a poorer treatment outcome is not easy to explain and may represent a spurious finding. One of the more consistent findings in the literature, however, is that atypical depression (characterized in part by leaden paralysis and fatigue) is relatively less responsive to TCAs than to MAOIs (50). In consideration of the putative similarities and differences in the pharmacology and mechanism of action of the SNRI duloxetine compared to TCA and MAOI drugs, it would be of interest to investigate the relative effectiveness of these different antidepressant drugs in a larger study of patients diagnosed with atypical depression (51).

Some studies have suggested that age, gender, and race/ethnicity may be important moderator factors (52,53) that influence treatment outcome (13,54). Our study did not find any significant association between these variables and treatment outcome. In our sample, we examined age both as a continuous variable as well as a categorical variable (comparing those younger than 50 years with those older than 50 years). Menopausal status may also be associated with treatment outcome (55). We examined the potential effect of menopausal status in women indirectly by using age as a proxy (premenopausal < 45 years; postmenopausal > 55 years), but found no significant association. These results confirm the findings from previous studies on age and gender with duloxetine (16,56,57). These results are also similar to the findings from studies on age, gender, and menopause with the SNRI venlafaxine (58). Unfortunately, our study did not collect data to know the actual menopausal status of our patients.

Our study had several strengths. The sample size was larger than many previously published studies of antidepressant predictors. Multiple clinical variables in several different domains were assessed prospectively and were collected using standard measures. Several different dependent treatment outcome variables were investigated. Different statistical models were applied to the data set, depending on the treatment outcome variables, candidate predictor variables, and subgroups of the patient sample. Duloxetine treatment during the acute phase was vigorous (using doses ranging from 60 mg/day to 120 mg/day and optimized according to regular periodic HAMD-17 assessments), lessening the chance that patients would be less responsive because of under-treatment. Also, patients initially intolerant to duloxetine (during Study Period II) were excluded, decreasing the likelihood that patients later would be under-treated because of medication intolerance. Hence, the reduced treatment response in our patients cannot be clearly attributed to under-treatment with duloxetine. This enhances the validity of our findings that our predictor variables were moderating the reduced response to duloxetine.

This study is unique in investigating a novel SNRI antidepressant. Most previous studies of predictors have investigated other antidepressant drug classes (i.e., TCAs, MAOIs, and SRIs). Our findings therefore fill an important "niche" in the literature on predictors of treatment outcome, and they will complement the findings from other studies investigating different antidepressant drugs. In STAR*D, for example, patients having an unsatisfactory response to citalopram at the end of level 1 could move to level 2 treatment, which involved either switching medications (to bupropion, sertraline, or venlafaxine) or augmenting with a second medication (by adding bupropion or buspirone to citalopram). Because our study included a subgroup of patients with an unsatisfactory response to an SRI, it will be of particular interest to compare and contrast our results with the predictors of outcome at level 2 when this type of data analysis are reported from STAR*D (43,59).

One limitation of our study was the lack of a placebo control, which would have been useful for a comparison of treatment outcomes and comparing predictors of treatment outcome (2,60). Another limitation is that more specific and comprehensive psychosocial functioning and quality of life data were not collected. These factors have been found to influence treatment outcome (9,13,15). In addition, this study had 27 sites and our analysis did not adjust for variability among the sites in assessments. Also, similar to most clinical trials, some of the inclusion and exclusion criteria of the study may have biased the sample and limited the generalizability of our findings.

Future studies investigating predictors of treatment outcome are necessary and warranted (2,4,61). Such studies should be broadly inclusive of all types of patients with depression to make the findings meaningful and generalizable (13). They should include assessments of multiple domains (demographic, psychosocial, clinical, and biological) with a large enough sample size to identify relevant and significant predictors. Of particular interest would be studies directly comparing antidepressant drugs with different mechanisms of action, to better identify and characterize predictors of treatment response that would be clinically useful for practitioners.

ACKNOWLEDGMENTS

This study was funded by Eli Lilly and Company, Indianapolis, IN, USA. Robert Howland received research support from Aspect

Medical Systems, Bristol-Myers Squibb, Cederroth, Cyberonics, Forest, Lilly, Northstar Neuroscience, National Institutes of Mental Health, and the National Center for Complementary and Alternative Medicine and is a member of the speaker board for AstraZeneca. Michael Wilson has provided consultation to, received honoraria from, or holds retirement investments with Abbott Laboratories, Alcon, Astra-Zeneca, Biogen, Biomet, Bristol-Myers Squibb, Elan, Eli Lilly and Company, Forest Laboratories, Genentech, GlaxoSmithKline, Guidant Corporation, Johnson & Johnson, King, Merck & Co Inc, Pfizer, Sanofi-Aventis, Schering-Plough Corp, Teva, and Wyeth-Ayerst. Susan Kornstein has received grant/research support from the Department of Health and Human Services, the National Institute of Mental Health, Pfizer, BristolMyersSquibb, Eli Lilly, Forest, GlaxoSmithKline, Mitsubishi-Tokyo, Merck, Biovail Laboratories, Wyeth, Berlex Laboratories, Novartis Pharmaceuticals, Sepracor, Boehringer-Ingelheim, Sanofi-Synthelabo, and Astra-Zeneca; has received honoraria from and/or served on advisory boards for Pfizer, Wyeth, Eli Lilly, BristolMyersSquibb, Warner-Chilcott, Biovail Laboratories, Berlex Laboratories, Forest, Sepracor, and Neurocrine; and has received book royalties from Guilford Press. Anita Clayton is a consultant for Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly and Company, Fabre-Kramer Pharmaceuticals, GlaxoSmithKline, Novartis, Pfizer Inc.,Vela, and Wyeth; has received grant/research support from Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly and Company, Forest Pharmaceuticals, GlaxoSmithKline, Neurontics, Pfizer Inc., Sanofi-Aventis, and Wyeth; has received honoraria from Eli Lilly and Company, GlaxoSmithKline, Pfizer Inc., and Wyeth; and is a member of the speakers/advisory boards for Boehringer Ingelheim, GlaxoSmithKline, Eli Lilly and Company, Pfizer Inc., and Wyeth. Madhukar Trivedi has received research support from Bristol-Myers Squibb, Cephalon Inc, Corcept Therapeutics Inc, Cyberonics Inc, Eli Lilly and Company, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica, Merck, National Institute of Mental Health, National Alliance for Research in Schizophrenia and Depression, Novartis, Pfizer Inc, Pharmacia & Upjohn, Predix Pharmaceuticals, Solvay Pharmaceuticals Inc, and Wyeth-Ayerst Laboratories; has received consulting fees from Abbott Laboratories Inc, Akzo (Organon Pharmaceuticals Inc), AstraZeneca, Bayer, Bristol-Myers Squibb, Cephalon Inc, Cyberonics Inc, Eli Lilly and Company, Fabre-Kramer Pharmaceuticals Inc, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica Products LP, Johnson & Johnson PRD, Meade Johnson, Neuronetics, Parke-Davis Pharmaceuticals Inc, Pfizer Inc, Pharmacia & Upjohn, Sepracor, Solvay Pharmaceuticals Inc, VantagePoint, and Wyeth-Ayerst Laboratories; and is on the Speakers Bureau for Abdi Brahim, Akzo (Organon Pharmaceuticals Inc), Bristol-Myers Squibb, Cephalon Inc, Cyberonics Inc, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica Products LP, Eli Lilly and Company, Pharmacia & Upjohn, Solvay Pharmaceuticals Inc, and Wyeth-Ayerst Laboratories. Madelaine Wohlreich is a stock shareholder and full-time employee of Eli Lilly and Company. Dr. Fava has received research support from Abbott Laboratories, Lichtwer Pharma GmbH, Lorex Pharmaceuticals; as well as honoraria from Bayer AG, Compellis, Janssen Pharmaceutica, Knoll Pharmaceutical Company, Lundbeck, Dov Pharmaceuticals, Biovail Pharmaceuticals, Inc., BrainCells, Inc., Cypress Pharmaceuticals, Fabre-Kramer Pharmaceuticals, Inc., Grunenthal GmBH, MedAvante, Inc., Sepracor, and Somerset Pharmaceuticals. In addition, Dr. Fava has received both research support and honoraria from Aspect Medical Systems, Astra-Zeneca, Bristol-Myers Squibb Company, Cephalon, Eli Lilly & Company, Forest Pharmaceuticals Inc., GlaxoSmithkline, J & J Pharmaceuticals, Novartis, Organon Inc., Pharmavite, Pfizer Inc, Roche, Sanofi/Synthelabo, Solvay Pharmaceuticals, Inc., and Wyeth-Ayerst Laboratories.

The authors thank the principal investigators and their clinical staff: Lesley Arnold, MD (Cincinnati, OH); Linda Austin, MD (Bangor, ME); Tom Barringer, MD (Charlotte, NC); Kathleen Brady, MD (Charleston, SC); Anita Clayton, MD (Charlottesville, VA); Beatriz Currier, MD (Miami, FL); Pedro Delgado, MD (Cleveland, OH); David Dunner, MD (Seattle, WA); Maurizio Fava, MD (Boston, MA); John Greist, MD (West Allis, WI); Robert Howland, MD (Pittsburgh, PA); Ethan Kass, MD (Coral Springs, FL); Susan Kornstein, MD (Richmond, VA); Andrew Leuchter, MD (Los Angeles, CA); James Lohr, MD (San Diego, CA); James Martinez, MD (Houston, TX); Brendan Montano, MD (Cromwell, CT); Rodrigo Munoz, MD (San Diego, CA); Philip Ninan, MD (Atlanta, GA); John O'Reardon, MD (Philadelphia, PA); Steven Roose, MD (New York, NY); Stephen Stahl, MD (Carlsbad, CA); Christopher Ticknor, MD (San Antonio, TX); Madhukar Trivedi, MD (Dallas, TX); Herbert Ward, MD (Gainesville, FL); Thomas Wise, MD (Falls Church, VA).

We also thank the many patients who generously agreed to participate in this clinical trial, and the Clinical Operations staff and statistical analysts of the Duloxetine Antidepressant Team for their excellent implementation of the trial.

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