Early Symptom Change Prediction of Remission in Depression Treatment

By Martin M. Katz, Adam L. Meyers, Apurva Prakash, Paula J. Gaynor, John P. Houston

ABSTRACT - Objectives: This study investigated hypothesized early symptom changes as differential predictors of long-term remission for duloxetine and escitalopram.

Experimental Design: This was a post-hoc analysis from a placebo-controlled, randomized, double-blind study of patients with major depressive disorder treated for 8 weeks with duloxetine 60 mg/day (N = 273) or escitalopram 10 mg/day (N = 274), and for another 6 months with duloxetine up to 120 mg/day or escitalopram up to 20 mg/day. Odds ratios (ORs) for successful treatment (sustained remission), defined as a 17-item Hamilton Depression Rating Scale (HAMD-17) score $\leq 7$ over 8 months, were determined for improvement in HAMD-17 depressed mood, retardation, and anxiety symptom factor subscales (20% decrease), along with associated positive predictive values (PPVs) and negative predictive values (NPVs).

Principal Observations: For both drugs, 2-week HAMD-17 improvement on all symptom subscales (except sleep for duloxetine) significantly predicted remission with ORs $> 2.0$. In a follow-up analysis, specific subscale items for psychological anxiety, motor retardation, and suicidality significantly predicted remission for duloxetine, and psychological and somatic anxiety for escitalopram. Notably, high NPVs on the Maier subscale indicated that a lack of 20% improvement on the “core” depression factor by Week 2 was highly predictive of unsuccessful treatment outcome over 8 months.

Conclusions: In accord with hypotheses, early symptom changes were specific to treatment, with early response in the core depression factor (Maier subscale), anxiety, and motor activity for duloxetine, and core factor and anxiety for escitalopram. Lack of early response in depression symptom subscales was highly predictive of lack of sustained remission. Psychopharmacology Bulletin. 2009;42(1):94–107.

INTRODUCTION

Recently published meta-analyses$^{1,2}$ and comparative treatment studies$^{3,4}$ have shown that the onset of therapeutic actions for antidepressants can occur, in treatment-responsive patients, within the first 2 weeks of treatment. In the treatment of depression, early symptom improvement may be a clinically useful indicator for
Successful treatment outcome or treatment failure. In addition, published analyses have suggested that early, drug-specific symptom improvement is predictive of greater overall response and symptom resolution at endpoint. Previous work by Katz and colleagues found that antidepressant drugs with pharmacologically different mechanisms of action produced different early therapeutic effects. In that study, moderately to severely depressed patients treated with the selective norepinephrine reuptake inhibitor (NRI) desipramine showed early improvement in psychomotor retardation and depressed mood, whereas the selective serotonin reuptake inhibitor (SSRI) paroxetine produced early improvement in anxiety and depressed mood. Duloxetine, a dual serotonin and norepinephrine reuptake inhibitor (SNRI), has shown early separation from placebo (within the first 2 weeks of treatment) on core depressive symptoms, including depressed mood, guilt, suicidal ideation, psychomotor retardation, and psychic anxiety.

A recently completed placebo-controlled study, designed specifically to compare the speed of onset of antidepressant efficacy for duloxetine, an SNRI, with escitalopram, an SSRI, reported that both duloxetine and escitalopram showed significantly greater improvement on the primary efficacy measure (17-item Hamilton Depression Rating Scale [HAMD-17] Maier subscale) compared with placebo over the 8-week, acute-treatment period. Further, both drugs showed significant separation from placebo by the 1-week assessment time point. The study had the additional strength of including a 6-month, extension-treatment period, allowing for assessment of depressive symptom improvement and remission over the 8-month course of the study. Rates of sustained remission were similar for duloxetine (36% [98/273]) and escitalopram (36% [98/274]).

The purpose of the current analysis was to investigate early symptom improvement as a predictor of successful treatment outcome (sustained remission) for duloxetine and escitalopram. This is one of the first assessments testing early symptom changes as predictors of outcome in a long-term treatment study. Basic research shows the patterns of behavioral associations of the central neurotransmitter systems to differ, with the noradrenergic system primarily associated with arousal and activity, and the serotonergic with anxiety. We hypothesized that based on the different pharmacological mechanisms of action of the 2 drugs investigated, different drug-specific early symptom improvement (depressed mood, psychic anxiety, and psychomotor retardation for duloxetine; and depressed mood and psychic anxiety for escitalopram) would occur and that these changes would be predictive of successful treatment outcome for each of the 2 drugs.
MATERIALS AND METHODS

Study Design

This was a randomized, double-blind, placebo- and active comparator-controlled study (Lilly protocol F1J-US-HMCR)\textsuperscript{13,14} conducted at 36 sites (psychiatric clinical settings) in the United States. In accordance with the principles of the Declaration of Helsinki, all patients provided written informed consent prior to administration of any study drug or study procedures. Patients were enrolled in the study from December 2003 to September 2004.

Patients meeting entry criteria were randomly assigned (2:2:1 ratio) to duloxetine 60 mg once daily (QD), escitalopram 10 mg QD, or placebo for the 8-week, acute-treatment phase of the study. During this initial phase, study drug doses were fixed, and dose adjustments (either increases or decreases) were not allowed. Both drugs were administered at the lowest dose that had demonstrated replicated statistical significance versus placebo on the primary efficacy analysis in published clinical trials (escitalopram 10 mg/day, duloxetine 60 mg/day).\textsuperscript{16-20}

Because longer-term treatment outcomes are of great concern, and because the American Psychiatric Association Practice Guidelines have recommended continuation of antidepressant medication for a minimum of 16 to 20 weeks following symptom remission,\textsuperscript{21} this study included a 24-week extension phase. Patients completing the 8-week, acute-treatment phase continued into the 24-week, double-blind extension phase. During the extension phase, changes in study medication dose were permitted in order to optimize treatment response, and patients in the placebo group who failed to meet the pre-defined response criteria were “rescued” to active treatment. The flexible dosing used in the extension phase was based on the full range of doses as specified in the escitalopram Package Insert (10 to 20 mg/day) or as reported to be efficacious and well tolerated in previous duloxetine clinical trials conducted in depressed patients (60 to 120 mg/day).

Concomitant medications with primarily central nervous system activity were not allowed. Chronic use of cough and cold medications containing pseudoephedrine or the sedating antihistamine diphenhydramine was not allowed. Patients were allowed episodic use of benzodiazepines and certain hypnotics or sedatives, provided that use (intermittent or consecutive) occurred on no more than 50% of the total days between visits. Use of non-narcotic prescription and over-the-counter pain medications was allowed. Episodic use of narcotic analgesics was allowed only upon approval of the Lilly physician or designee. Chronic use of certain prescription medications, such as
angiotensin-converting enzyme (ACE) inhibitors, alpha- and beta-blockers, antiarrhythmics, and calcium channel blockers, was permitted, provided the patient had been on a stable dose for a minimum of 3 months prior to study enrollment.

Selection of Patients

Study participants were adult outpatients at least 18 years of age. All patients met diagnostic criteria for major depressive disorder (MDD) as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). The diagnosis of MDD was confirmed by the Mini-International Neuropsychiatric Interview (MINI). Patients were required to have a Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥22 and a Clinical Global Impressions of Severity (CGI-S) score ≥4 at the screening and baseline study visits.

Patients were excluded for the following reasons: any current primary Axis I disorder other than MDD; any previous diagnosis of bipolar disorder, schizophrenia, or other psychotic disorder; any anxiety disorder as a primary diagnosis within the past 6 months (including panic disorder, agoraphobia, obsessive-compulsive disorder, posttraumatic stress disorder, generalized anxiety disorder, and social phobia); serious suicidal risk; serious medical illness or clinically significant laboratory abnormalities that, in the judgment of the investigator, would be likely to require intervention, hospitalization, or an excluded medication during the course of the study; lack of response of the current depressive episode to 2 or more adequate courses of antidepressant therapy at a clinically appropriate dose for a minimum of 4 weeks, or treatment-resistant depression; a history of a lack of response, at any time, to an adequate trial of duloxetine (≥60 mg/day for ≥4 weeks), escitalopram (≥10 mg/day for ≥4 weeks), or citalopram (≥20 mg/day for ≥4 weeks); a current and primary Axis II disorder that could interfere with compliance with the study protocol; DSM-IV-defined history of substance dependence within the past 6 months, excluding nicotine and caffeine; a positive urine drug screen for any substances of abuse; electroconvulsive therapy or transcranial magnetic stimulation within the past year; initiating, stopping, or changing psychotherapy during the study; treatment with a monoamine oxidase inhibitor (MAOI) within 14 days prior to Visit 2; treatment with fluoxetine within 30 days prior to Visit 2.

Statistical Methods

This was a post-hoc analysis. All analyses were conducted on an intent-to-treat basis, unless otherwise stated. All patients initially randomly assigned to active drug (duloxetine or escitalopram) who had at
least 1 post-baseline assessment were included in the efficacy analyses. For total scores calculated from individual items, the total score was considered to be missing if any of the individual items were missing.

Analyses comparing active drugs to placebo were not completed due to the placebo-rescue strategy employed after the acute-treatment period (first 8 weeks) of the study. For ethical reasons, patients initially randomly assigned to placebo were rescued to active drug if they met blinded non-response criteria at any time after Week 8, and data from patients rescued from placebo to active drug were not included in the analyses presented herein. Only 15 patients completed the 8-month study on placebo, making comparisons of predictors of sustained remission in placebo-treated patients unfeasible due to lack of adequate sample size and selectivity of the sample.

Treatment group differences in patient demographics and baseline severity of illness were compared using analysis of variance (ANOVA) for continuous outcomes (age, baseline HAMD-17, and CGI-S) and with Fisher’s exact test for comparing percentages for categorical outcomes (sex and origin).

The HAMD-17 was used to monitor depressive symptom severity throughout the study.25,26 The a priori-specified primary efficacy measure for this study was the Maier subscale of the HAMD-17, which assesses core emotional symptoms of depression and includes HAMD-17 Items 1 (depressed mood), 2 (guilt), 7 (work and activities), 8 (retardation), 9 (agitation), and 10 (psychic anxiety).27 Additional HAMD-17 factor subscales selected to test the hypotheses—specifically, anxiety/somatization (Items 10–13, 15, and 17); retardation/somatization (Items 1, 7, 8, and 14); and sleep (Items 4, 5, and 6)—were used to assess improvement in specific MDD symptom domains. The Hamilton Rating Scale for Anxiety (HAMA) total score was also used to assess improvement in the anxiety facet of the disorder.29

Pearson correlations were used to assess the significance of the associations between baseline to endpoint change (using last observation carried forward [LOCF]) between the HAMD-17 total score and 2-week improvement (Week 1 values could be carried forward if Week 2 values were not available) on all HAMD-17 subscales and the HAMA total score. Remission of MDD was defined as a HAMD-17 total score ≤7. Successful treatment was defined as sustained remission (an achieved, then sustained HAMD-17 score ≤7 throughout the patient’s participation in the 8-month study). A patient who achieved remission at the 8-month study endpoint or at last observation was considered to have achieved sustained remission. Time to sustained remission was determined using a Kaplan-Meier survival analysis and compared between duloxetine and escitalopram using the log-rank test.
Within each treatment group (duloxetine or escitalopram), sustained remission was predicted using logistic regression. Models for remission included baseline score and a binary predictor for a 20% or 30% response on a subscale by Week 2. Literature has supported a 20% to 30% early improvement in depressive symptoms as clinically relevant and predictive of further improvement. We chose the 2-week time point to assess early response, since it is a typical time interval between initial antidepressant prescription and first subsequent clinic visit for patients. Odds ratios (ORs) with statistical significance for successful treatment in patients with versus without clinically detectible improvement in HAMD-17 subscales (20% or 30% decrease) from baseline to 2 weeks were determined along with associated positive predictive values (PPVs) and negative predictive values (NPVs). Individual symptom items of predictive subscales provided the capacity to identify potential changes associated with these clinical facets.

PPV is defined as the number of patients meeting early response criteria and later achieving sustained remission divided by the number of patients meeting early response criteria. In other words, for those patients who had an early response, the PPV is the proportion of patients who achieved sustained remission. NPV is defined as the number of patients not meeting early response criteria and later not achieving sustained remission divided by the number of patients not meeting early response criteria. In other words, for those patients who did not have an early treatment response, the NPV is the proportion of patients who did not achieve sustained remission. The early response criteria used were a 20% or 30% decrease from baseline to 2 weeks for a subscale.

For subscales that were significantly predictive of sustained remission for duloxetine or escitalopram, a test for interaction was conducted to determine whether a response at 2 weeks was a better predictor of sustained remission for 1 drug compared to the other using a logistic regression model as previously described with the inclusion of therapy and an interaction between therapy and a binary predictor for a 20% response on a subscale by Week 2.

In this paper, results described as “significantly” or “statistically significantly” different refer to pairwise comparisons with $p \leq 0.05$.

**RESULTS**

A total of 1049 patients were screened, 365 of whom failed to meet entry criteria. The remaining 684 patients were randomly assigned to duloxetine 60 mg once daily (QD) ($N = 273$), escitalopram 10 mg QD ($N = 274$), or placebo QD ($N = 137$). A total of 664 patients provided post-baseline data (262 duloxetine-treated patients, 267 escitalopram-treated patients, and 135 placebo-treated patients). The overall patient
cohort was predominantly female (65.2%) and Caucasian (77.6%). The mean age of patients in the duloxetine treatment group was significantly lower than that of the escitalopram group (41.1 years versus 43.3 years, respectively; p = 0.036). There were no other significant between-group differences in baseline demographics or psychiatric profile (Table 1).

For the duloxetine and escitalopram treatment groups, the change from baseline to endpoint in the HAMD-17 total score was statistically significantly correlated with 2-week improvement on all of the HAMD-17 subscales and the HAMA total score. As shown in Table 2, for duloxetine- and escitalopram-treated patients, there are highly significant relationships between the amount of improvement on several moods and behaviors at the end of 2 weeks with improvement on the HAMD-17 total score at the end of 8 months of treatment. Specifically, at 2 weeks, improvement in retardation, in the core depression factor (Maier subscale), and in anxiety were significantly associated with outcome at 8 months for duloxetine- and escitalopram-treated patients with numerically greater correlations for retardation and the Maier subscales for duloxetine. A similar proportion of patients in both active treatment

---

**TABLE 1**

**Baseline Patient Demographics and Psychiatric Profile**

<table>
<thead>
<tr>
<th></th>
<th>Duloxetine 60 mg QD</th>
<th>Escitalopram 10 mg QD</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>41.1 (11.6)*</td>
<td>43.3 (13.0)</td>
<td>42.5 (12.3)</td>
</tr>
<tr>
<td><strong>Age range, y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min – Max</td>
<td>18–66</td>
<td>18–79</td>
<td>20–73</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>173 (63.4)</td>
<td>186 (67.9)</td>
<td>87 (63.5)</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>83.0 (20.8)</td>
<td>83.4 (21.8)</td>
<td>87.5 (24.0)</td>
</tr>
<tr>
<td><strong>Ethnic origin, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>206 (75.5)</td>
<td>212 (77.4)</td>
<td>113 (82.5)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>22 (8.1)</td>
<td>26 (9.5)</td>
<td>8 (5.8)</td>
</tr>
<tr>
<td>African American</td>
<td>35 (12.8)</td>
<td>28 (10.2)</td>
<td>14 (10.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (0.7)</td>
<td>3 (1.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>East Asian</td>
<td>3 (1.1)</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (1.8)</td>
<td>4 (1.5)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td><strong>HAMD-17 total score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>17.6 (4.8)</td>
<td>17.8 (5.1)</td>
<td>17.7 (5.2)</td>
</tr>
<tr>
<td><strong>CGI-S score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>4.2 (0.7)</td>
<td>4.2 (0.7)</td>
<td>4.2 (0.7)</td>
</tr>
</tbody>
</table>

*p = 0.05 vs. escitalopram.

Abbreviations: QD, once daily; SD, standard deviation; HAMD-17, 17-item Hamilton Depression Rating Scale; CGI-S, Clinical Global Impressions of Severity.
### TABLE 2

**CORRELATION BETWEEN CHANGES IN 2-WEEK SYMPTOM SCORES AND 8-MONTH HAMD-17 TOTAL SCORE AND POSITIVE AND NEGATIVE PREDICTIVE VALUES FOR A 20% IMPROVEMENT IN THE HAMD-17 TOTAL SCORE, HAMD-17 SUBSCALES, AND HAMA TOTAL SCORE AT 2 WEEKS**

<table>
<thead>
<tr>
<th>ASSESSMENT</th>
<th>CORRELATION COEFFICIENT</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DULOXETINE</td>
<td>ESCITALOPRAM</td>
<td>DULOXETINE</td>
</tr>
<tr>
<td>HAMD-17 total score</td>
<td>NA</td>
<td>NA</td>
<td>53.4</td>
</tr>
<tr>
<td>HAMD-17 Maier subscale</td>
<td>0.47*</td>
<td>0.39*</td>
<td>57.0</td>
</tr>
<tr>
<td>HAMD-17 retardation/somatization subscale</td>
<td>0.42*</td>
<td>0.30*</td>
<td>55.4</td>
</tr>
<tr>
<td>HAMD-17 sleep subscale</td>
<td>0.28*</td>
<td>0.32*</td>
<td>41.9</td>
</tr>
<tr>
<td>HAMD-17 anxiety/somatization subscale</td>
<td>0.38*</td>
<td>0.40*</td>
<td>46.7</td>
</tr>
<tr>
<td>HAMA total score</td>
<td>0.44*</td>
<td>0.41*</td>
<td>47.8</td>
</tr>
</tbody>
</table>

*Correlation between change from baseline to endpoint (last observation or 8 months) in the HAMD-17 total score and 2-week improvement on the HAMD-17 subscales and the HAMA total score.

*P < 0.001.

Abbreviations: HAMD-17, 17-item Hamilton Depression Rating Scale; HAMA, Hamilton Rating Scale for Anxiety; NA, not applicable; PPV, positive predictive value; NPV, negative predictive value; GI, gastrointestinal.
groups achieved sustained remission over the 8-month course of the study (36% [98/273] for duloxetine and 36% [98/274] for escitalopram). The median time to sustained remission was not significantly different between duloxetine (175 days) and escitalopram (196 days).

Statistically significant ORs for remission in patients with versus without 20% reduction in scores at 2 weeks for the HAMD-17 total score, HAMD-17 subscale scores, and HAMA total score ranged from 2.0 (anxiety/somatization subscale for duloxetine-treated patients) to 9.4 (Maier subscale for duloxetine-treated patients) (Figure 1). A 20% improvement from baseline to 2 weeks in the HAMD-17 and HAMA total scores, as well as the HAMD-17 subscales (with the exception of the HAMD-17 sleep subscale in duloxetine-treated patients) was a significant predictor of sustained remission for both drugs. Using a 30% improvement from baseline to 2 weeks did not substantially yield a better set of predictors of sustained remission.

PPVs and NPVs for a 20% improvement in the HAMD-17 total score, HAMD-17 subscales, and HAMA total score at 2 weeks are shown in Table 2. For both duloxetine- and escitalopram-treated patients, failure to reach an improvement of at least 20% on the HAMD-17 total score, subscale scores, or HAMA total score after 2 weeks of treatment was predictive of lack of subsequent sustained remission in >65% of patients (NPV > 65%). Further, for duloxetine-treated patients, failure to reach an improvement of at least 20% on the HAMD-17 Maier or retardation/somatization subscales after 2 weeks of treatment was predictive of lack of subsequent sustained remission in ≥80% of patients (NPV ≥ 80%). Using a 30% improvement from baseline to 2 weeks did not substantially improve PPV or NPVs.

For subscales that were significantly predictive of sustained remission for duloxetine or escitalopram, a test for interaction was conducted to determine whether a response at 2 weeks was a better predictor of sustained remission for 1 drug compared to the other. For the subscales that were significant predictors of sustained remission for duloxetine, only the Maier subscale was a significantly better predictor of sustained remission for duloxetine compared with escitalopram. For the subscales that were significant predictors of sustained remission for escitalopram, there were no subscales that were significantly better predictors of sustained remission for escitalopram compared with duloxetine.

**DISCUSSION**

As hypothesized, early predictors of eventual sustained remission included improvement in the core depression factor (Maier subscale) and psychic anxiety for duloxetine and escitalopram, as well as psychomotor retardation for duloxetine. Early response on the HAMD-17 and HAMA total scores
HAMD-17, HAMD-17 Subscales, and HAMA ≥20% Improvement at Week 2 as a Predictor of Successful Treatment Outcome

*significant (p < 0.05) predictor of sustained remission.

Abbreviations: CI, confidence interval; HAMD-17, 17-item Hamilton Depression Rating Scale; Ret/Som, retardation/somatization subscale; Anx/Som, anxiety/somatization subscale; HAMA, Hamilton Rating Scale for Anxiety.
as well as all HAMD-17 symptom factor subscales with the exception of the sleep subscale for duloxetine was predictive of sustained remission for both duloxetine and escitalopram. Prior support for these findings was evidenced in the correlation analysis demonstrating that the amount of “early” improvement in a symptom factor following 2 weeks of drug treatment was significantly associated with the amount of overall improvement in the disorder (i.e., on the HAMD-17 total score) achieved at 8 months.

For duloxetine-treated patients, the best predictors of failure to achieve sustained remission (those assessments with the largest NPVs) were the HAMD-17 Maier and retardation/somatization subscales. Of particular interest were the high ORs for duloxetine on the HAMD-17 Maier subscale (OR = 9.4; 95% confidence interval (CI), 4.8 to 19.6) and retardation/somatization subscale (OR = 5.4; 95% CI, 3.0 to 9.9) in comparison to other ORs. Consistent with a model in which early lack of positive clinical effects on presumed neurochemical targets predicts lack of sustained remission, failure to achieve a 20% improvement in the Maier or retardation/somatization subscales by the second week of treatment predicted failure to achieve sustained remission for ≥80% of duloxetine-treated patients.

For escitalopram-treated patients, the best predictors of failure to achieve sustained remission were the HAMD-17 total score and the HAMD-17 sleep and anxiety/somatization subscales. Failure to achieve a 20% improvement in the HAMD-17 total score or the HAMD-17 sleep or anxiety/somatization subscales by the second week of treatment predicted failure to achieve sustained remission for ≥75% of escitalopram-treated patients. Again, failure to show early minimal improvement indicates a high likelihood (75%) that patients will not achieve sustained remission.

**Differences in Predictive Indices for Both Antidepressants**

For the clinician, clinical change or lack of change in a major symptom subscale or factor may be the most easily determined measure to predict remission. Assuming an improvement of 20% on one of the HAMD-17 subscales to be a clinically detectible change, our results suggest some practical usefulness for predicting remission based on observation of early clinical improvement in symptoms that are drug-specific. Furthermore, the negative predictive values for symptom improvement, which are greater than the positive predictive values, suggest that non-improvement in specific subscales early (i.e., at 2 weeks) has particular clinical significance for limited long-term prognosis.

Since the HAMD-17 factors were complex in their composition, e.g., the retardation factor combining motor retardation and depressed mood, it was of interest to determine whether a reduction in the first
2 weeks in the specific symptom items of retardation and anxiety were predictive of outcome response for duloxetine and escitalopram, respectively. The OR results (using the criterion of a ≥1-point reduction from baseline to 2 weeks) were significant for the symptom items of motor retardation (OR = 2.4) and psychic anxiety (OR = 2.0), while reduction in somatic anxiety (OR = 1.6) was not a significant predictor for duloxetine. The results were, in part, contrary for escitalopram with significant ORs for psychic (OR = 2.3) and somatic (OR = 2.2) anxiety but not motor retardation (OR = 1.9). The findings for these items were in general accord with the primary analysis of the HAMD-17 factors.

Finally, there was interest for clinical reasons, in whether a significant reduction in the (less frequently recorded but highly important) item of “suicidal ideation” during the first 2 weeks was associated with outcome at 8 months. The OR of 7.1 for duloxetine was strikingly high and significant; the OR of 1.8 was not significant for escitalopram. The finding implies that early reduction of the intensity of such ideas is a very good predictor of later response to duloxetine, a finding that warrants testing in a future clinical study.

Study Limitations

These results should be interpreted with respect to several limitations. First, the only assessments of early symptom improvement used in this analysis were the HAMD-17 and HAMA. Therefore, it is likely that certain core depressive symptoms, such as hostility, irritability, and anger, were not specifically or adequately assessed. Second, this was a post-hoc analysis, and the results cannot be interpreted with the same degree of confidence as an a priori-specified analysis. However, these analyses were based on data from a study specifically designed to assess onset of antidepressant efficacy. Third, the study excluded patients with primary Axis I disorders other than MDD, those with a previous diagnosis of bipolar disorder or other psychotic disorders, patients at serious suicidal risk, and patients with an Axis II disorder that may have interfered with compliance with the study protocol. This limits the generalizability of the present results to a more typical unipolar depressed outpatient population. Finally, regarding the 4 symptom-item analyses, only the subset of patients with a given symptom was evaluated for ORs for eventual remission. For some symptoms, such as suicidality, this may represent a small minority of patients in the study.

Conclusion

Results of this analysis are consistent with the view that antidepressants, in this case SSRIs and SNRIs, initially act clinically in the first
2 weeks of treatment. In this first assessment of the association of successful treatment outcome over 8 months with early response, lack of early response in depressive symptoms at 2 weeks was predictive of failure to achieve sustained remission. Specifically, failure to show improvement in anxiety and depressed mood for both drugs and motor retardation for duloxetine in the first 2 weeks, in accord with hypotheses, was highly predictive of limited long-term response to treatment. The association of early symptom improvement with sustained remission, while significant, was less predictive of sustained remission. Early changes in specific symptom factors as measured by HAMD-17 subscales along with their associated predictive values and ORs were consistent with previous reports of antidepressant response specific to drug treatment, with early response in the core depression factor, anxiety, and motor activity for the SNRI duloxetine and the core depression factor and anxiety for the SSRI escitalopram. Based on the results of this analysis and this first demonstration that early (within 2 weeks) improvement is significantly associated with long-term (8 months) outcome of antidepressant drug treatment, a prospectively designed study that utilizes sound measures of the major components of MDD—specifically, anxiety, hostility, and motor activity—can be expected to provide guidelines for developing algorithms based on combining early symptom changes to predict treatment outcome with pharmacologically different antidepressants.

ACKNOWLEDGMENTS

This work was sponsored by Eli Lilly and Company. Martin Katz reports no conflicts of interest. Adam Meyers, Apurva Prakash, Paula Gaynor, and John Houston are stock shareholders and full-time employees of Eli Lilly and Company.

REFERENCES


