Immediate Switching of Antidepressant Therapy: Results from a Clinical Trial of Duloxetine

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Background. Approximately half of all treated depressed patients fail to show adequate response to their initially prescribed antidepressant medication. Switching to another medication represents one possible next-step approach for nonresponsive or partially responsive patients. However, specific techniques for switching between antidepressants have not been well studied. We examined the efficacy and tolerability associated with a switch from a selective serotonin reuptake inhibitor (SSRI) or venlafaxine to duloxetine.

Methods. All patients met criteria for major depressive disorder as defined in DSM-IV. Patients (N = 88) exhibiting suboptimal response or poor tolerability to their current antidepressant medication (citalopram 40 mg/d, escitalopram 20 mg/d, fluvoxamine 150 mg/d, paroxetine 40 mg/d, sertraline 150 mg/d, or venlafaxine 150 mg/d) were switched to duloxetine 60 mg once-daily (QD) without intermediate tapering or titration (“switching” group). A comparator group (N = 67), comprising patients not currently receiving antidepressant medication, initiated duloxetine therapy at 60 mg QD (“initiating” group). Safety assessments included comparisons of discontinuation rates, treatment-emergent adverse events, and changes in vital signs. Efficacy measures included the HAMD17, Hamilton Anxiety Scale (HAMA), and the Clinical Global Impression of Severity (CGI-S) scale.

Results. The efficacy of duloxetine in switched patients did not differ significantly from that observed in untreated patients initiating duloxetine therapy (mean changes: HAMD17 total score: 12.3 vs. 12.6; HAMA: 9.36 vs. 9.55, CGI-S: 1.94 vs. 2.12, respectively). However, the rate of discontinuation due to adverse events among patients switched to duloxetine was significantly lower than that in patients initiating duloxetine therapy (4.5% vs. 17.9%, p = .008). Treatment-emergent adverse events occurring in 10% of patients in both treatment groups were nausea, headache, dry mouth, insomnia, and diarrhea. Patients switched to duloxetine reported significantly lower rates of nausea and fatigue compared with patients initiating duloxetine.

Conclusions. In this study, the efficacy of duloxetine in switched patients was comparable to that observed in patients initiating duloxetine therapy. Immediate switching from an SSRI or venlafaxine to duloxetine (60 mg QD) was well tolerated.

Keywords  Duloxetine, Switching, SSRI, Safety
INTRODUCTION

Despite recent advances in the pharmacological treatment of major depressive disorder (MDD), a substantial proportion of depressed patients fail to achieve an adequate response to their initial antidepressant therapy. Typically, only one half to two-thirds of patients treated with antidepressant medications exhibit a response (defined as ≥50% improvement in HAMD$_{17}$ total score), and only one-third achieve remission (HAMD$_{17}$ total score ≤7) (1–3). Patients exhibiting only partial or no response have a poor prognosis, since the presence of residual depressive symptoms has been shown to increase the risk of relapse (4–6). Furthermore, partial responders have reduced physical and social function compared with patients who are in full remission (7,8).

Hence, the achievement of remission is increasingly emphasized as the goal of depression treatment (9,10).

Patients who fail to demonstrate an adequate response to an initial course of antidepressant therapy present the clinician with two important questions — (1) how long should the current therapy be continued? and (2) what alternative strategies may provide the greatest opportunity for future treatment success? With regard to the first question, the available data (11,12) suggest that patients showing no improvement in symptoms should have their treatment changed after 4–8 weeks, while those showing at least some symptom improvement (i.e., a partial response) should be considered for an alternative treatment approach after 6–12 weeks (13).

Once an initial trial of monotherapy has been deemed ineffective, several treatment options are available to the patient and clinician — (1) raise the dose of the current medication (14); (2) switch to another antidepressant (15); (3) add a second antidepressant to the current therapy (combination therapy) (16); or (4) augment the current therapy with an additional non-antidepressant agent (e.g., lithium, buspirone, or an atypical antipsychotic) (17,18).

The available data do not allow a clear distinction to be drawn between the relative efficacy of each of these treatment options, and the choice of a next-step strategy is typically made on a case-by-case basis. This is reflected in surveys that have attempted to establish a consensus among physicians regarding the next step following initial antidepressant treatment failure. In a 1991 study, 118 psychiatrists were asked to do next in the case of a patient who had failed to respond to 4 weeks of nortriptyline therapy. The most popular choices were to employ lithium augmentation (34% of respondents), continue nortriptyline for a further 2 weeks (18%), and switch to fluoxetine (16%) (19). In a more recent survey of psychiatrists regarding their next-step strategy for patients nonresponsive to 8 weeks of selective serotonin reuptake inhibitor (SSRI) treatment, the most popular choice (selected by 44% of respondents) was to switch to a non-SSRI medication (20).

Lack of response to antidepressant therapy represents only one possible factor that may necessitate a change in treatment. Patients encountering intolerable side effects may request a change in medication, even though the response to the initial treatment may have been favorable. Side effects requiring a change of antidepressant may be associated with either short-term (e.g., nausea, insomnia) or long-term treatment (e.g., weight gain, sexual dysfunction) (21). Treatment options for patients intolerant of their current medication include switching to another antidepressant, or utilizing an antidote to mitigate side effects (e.g., the use of sildenafil to mitigate treatment-emergent sexual dysfunction) (22) or an antidote with possible antidepressant augmentation benefit (e.g., bupropion for the same treatment-emergent sexual dysfunction).

One distinct advantage of switching as a treatment option is the abundance of clinical trial data, both acute and long term, supporting the efficacy and safety of approved antidepressant medications. In comparison, results from adequately controlled, double-blind studies of combination antidepressant or augmentation therapy are limited. Switching medications (i.e., maintaining monotherapy) may offer some additional advantages over combination or augmentation therapy. Treatment compliance may be higher in patients taking only a single medication, while the cost associated with monotherapy may be expected to be lower than that of polypharmacy. Furthermore, the use of a single medication is less likely to produce adverse events than multimodal therapy (23), while the potential for drug-drug interactions is also reduced. However, exceptions to these benefits of monotherapy occur when combination/augmentation provides greater efficacy that leads to improved compliance, or when the augmentation is carried out with generic medications which cost less. One concern that may be raised when switching medications, especially in partial responders, is the risk of losing whatever degree of symptom improvement has already been achieved. However, results from a small open-label study suggest that patients can switch antidepressants while in remission, without suffering relapse (24).

Once the decision has been made to switch a patient from one antidepressant to another, the clinician must next consider how to implement the change in medication. Although there are many reports in the literature describing the efficacy and tolerability associated with switching antidepressants, the details of exactly how the switch was accomplished are frequently omitted. There are a number of mechanisms by which the switch may be achieved:

1. The existing medication is abruptly discontinued, while the new antidepressant is initiated at full therapeutic dose (“immediate” or “direct” switch, Figure 1a). This technique presents the patient with the simplest dosing regimen, since dose tapering and/or titration are not required. Since discontinuation syndromes can occur with all classes of antidepressants (25,26), this switching strategy may put patients at risk for discontinuation-emergent symptoms if the switch is to an agent of a different class. On the other hand, immediate switches have been shown to be safe and well tolerated when they have occurred between antidepressants affecting similar neurotransmitter systems, such as switches from one...
SSRI to another (27), or from SSRIs to dual action antidepressants such as mirtazapine (28).

2. The new medication is gradually titrated upward while the current agent is gradually tapered downward (“1 up - 1 down,” Figure 1b). This method offers the advantage that the patient is never exposed to simultaneous full, therapeutic doses of both antidepressants, but maintains an adequate dose of “combination therapy” during the crossover period. The primary drawback to this approach is that the dosing regimen during the crossover period is more complicated than an immediate discontinuation of the first agent at the same time the expected therapeutic dose of the second agent is started. Complicated regimens adversely impact patient compliance. In addition, serotonin syndrome may be a complicating factor if both medications exhibit a strong serotonergic influence (25).

3. The new medication is initiated at full therapeutic dose and the current medication is subsequently tapered downward.
It is important to emphasize that if the patient is currently receiving a monoamine oxidase inhibitor (MAOI) medication an appropriate washout phase is required during the switching process, and therefore none of the above-mentioned strategies would be possible when patients are switched to or from MAOIs.

One previous study compared two methods of switching from one SSRI to another in a prospectively defined manner. Patients currently receiving fluoxetine were randomized under double-blind conditions to two treatment groups. One group was switched immediately to paroxetine, while the second group underwent a 2-week placebo-washout period before beginning paroxetine treatment. The proportion of patients discontinuing prematurely did not differ significantly between the two treatment groups (29).

One of the most common objectives of a switching strategy is to introduce a new medication with a neurochemical profile distinct from the one currently employed. Irrespective of the reason underlying the switching decision, that is, lack of efficacy or intolerance, an agent with a different mechanism of action may provide a greater opportunity for treatment benefit to the patient. A growing body of evidence suggests that antidepressant medications enhancing the neurotransmission of both serotonin (5-HT) and norepinephrine (NE) may have greater efficacy than those acting upon a single neurotransmitter, at least in more severe depressed populations (30–33). Thus, the combination of the SSRI fluoxetine with the selective NE reuptake inhibitor desipramine was found to be significantly more effective than desipramine alone, especially with regard to remission (34). Furthermore, venlafaxine, which inhibits the reuptake of both 5-HT and NE at higher doses, has also been shown to produce higher remission rates than SSRIs (35).

Duloxetine is a relatively balanced and potent dual reuptake inhibitor of 5-HT and NE. The efficacy of duloxetine has been demonstrated in double-blind, placebo-controlled clinical trials of up to 9 weeks duration (36–39). In this study, the efficacy and tolerability of a direct switch to duloxetine (60 mg QD) was examined in patients who were nonresponsive or only partially responsive to their current antidepressant medication (citalopram, escitalopram, fluvoxamine, paroxetine, sertraline, or venlafaxine). Comparisons were made with patients who were treatment naïve for this episode of depression, and initiated duloxetine therapy at 60 mg QD.

**METHODS**

**Study Design**

This was an open-label, multicenter trial involving 27 investigative sites. The current analyses utilized data from an interim data lock, covering the first 8 weeks of a 12-week study. The study protocol was reviewed and approved by the ethical review board at each site, in accordance with the principles of the Declaration of Helsinki, and all patients signed informed consent documents prior to the administration of any study procedures or study drug.

The objective of the present analysis was to compare the safety and efficacy of duloxetine in two treatment groups:

1. “Initiating” group — currently untreated patients who initiated duloxetine therapy at 60 mg once daily;
2. “Switching” group — patients exhibiting suboptimal response or poor tolerability to their current antidepressant medication who were switched directly to duloxetine (60 mg once daily) without intermediate tapering or titration.

All patients entered a 1 week screening period. Patients taking citalopram (≤40 mg/d), escitalopram (≤20 mg/d), fluvoxamine (≤150 mg/d), paroxetine (≤40 mg/d), sertraline (≤150 mg/d), or venlafaxine (≤150 mg/d) were allowed to continue their current medication during the screening period. Patients receiving doses above these levels were excluded. Patients who had received fluoxetine therapy within the last 30 days were also excluded (due to the long half-life of its active metabolites). Patients who had received SSRI treatment (other than fluoxetine) and discontinued the SSRI within 1 month of the screening visit were required to wash out from the SSRI treatment for a period of 21 days, and were then considered to be untreated. At the conclusion of the screening period, currently untreated patients and SSRI switch patients meeting study criteria were assigned to receive duloxetine treatment (60 mg QD). In the case of the “switching” group, the switch from the current medication to duloxetine was immediate — no intermediate tapering or titration was employed, and no combination or augmentation therapy was permitted. All patients were required to remain at the assigned duloxetine dose (60 mg QD) for a 1 week initial treatment phase. Patients unable to tolerate duloxetine treatment during this period were discontinued. During the remainder of the study period, each patient’s duloxetine dose could be titrated to efficacy within a range from 60 mg QD (minimum) to 120 mg QD (maximum), with 90 mg QD as an intermediate dose. The duloxetine dose could be increased or decreased only at scheduled visits, and could be increased only if the patient’s HAMD17 total score was >7 at the scheduled visit.

**Patients**

Patients were adult males and females (≥18 years of age) meeting Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for MDD (40). Patients were
required to have a 17-item Hamilton Rating Scale for Depression (HAMD$_{17}$) total score $\geq 15$ and a Clinical Global Impression of Severity (CGI-S) score $\geq 4$ at two consecutive screening visits. As mentioned earlier, patients could have been either drug-free/treatment-naïve or nonresponsive to an ongoing treatment with either an SSRI or venlafaxine.

Exclusion criteria included: a diagnosis of bipolar disorder, schizophrenia, or other psychotic disorder; the presence of an Axis II disorder that would interfere with compliance with the study protocol; a serious medical illness (any cardiovascular, hepatic, respiratory, hematologic, endocrinologic, or neurologic disease, or clinically significant laboratory abnormality); subjects judged to be at serious suicidal risk; treatment with fluoxetine within 30 days prior to Visit 1; treatment with a monoamine oxidase inhibitor within 14 days prior to Visit 1; lack of response of the current episode to two or more adequate courses of antidepressant therapy at a clinically appropriate dose for a minimum of four weeks, or meeting criteria for treatment resistant depression; any anxiety disorder as a primary diagnosis within the past six months; a history of substance dependence within the past six months; or a positive urine drug screen.

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

**Efficacy Measures**

Efficacy measures included the HAMD$_{17}$ total score, the Hamilton Anxiety Scale (HAMA), and the CGI-S. The Montgomery-Asberg Depression Rating Scale (MADRS) is becoming widely utilized and may offer some advantages for outpatient studies. However, in previous placebo-controlled studies of duloxetine the HAMD$_{17}$ and MADRS scales yielded similar results, while data from the HAMD$_{17}$ exhibited an improved signal-to-noise ratio when compared with the MADRS. This led to the selection of the HAMD$_{17}$ in the present study. Response was defined as a $\geq 50\%$ improvement in HAMD$_{17}$ total score from baseline. Remission was defined as a HAMD$_{17}$ total score $\leq 7$. Response and remission were considered to be sustained if, once the appropriate criterion had been met, it was maintained at all subsequent visits.

**Safety Measures**

Safety was assessed by means of spontaneously reported adverse events, and changes in vital signs, weight, and laboratory tests (hematology, urinalysis, and clinical chemistry). Safety measures recorded at every visit included spontaneously reported treatment-emergent adverse events, supine blood pressure, and heart rate. Elevated blood pressure was defined as supine systolic blood pressure $\geq 140$ mm Hg and at least $10$ mm Hg greater than baseline, or supine diastolic blood pressure $\geq 90$ mm Hg and at least $10$ mm Hg greater than baseline. A patient was considered hypertensive if criteria for elevated systolic or diastolic blood pressure were met at 3 consecutive visits. Elevated heart rate was defined as $\geq 100$ beats per minute (bpm), and an increase $\geq 10$ bpm from baseline.

Significant weight change was defined as body weight increase or decrease $\geq 7\%$ from baseline.

**Statistical Methods**

Baseline scores for HAMD$_{17}$, HAMA, and CGI-S were compared for switch and initiating patients using a one-way analysis of variance (ANOVA). Patient demographics were compared using the ANOVA model for continuous outcomes (age) and with Fisher’s exact test for comparing percentages for categorical outcomes (gender, origin). Between-group comparisons of baseline demographics, response/remission rates, and times to response/remission utilized the Protected Least Significant Difference method.

Longitudinal changes in efficacy outcomes were assessed using a likelihood-based, mixed-effects model repeated measures approach. The model included the fixed categorical effects of group and investigator. Time of assessment was modeled as a continuous effect by including linear and quadratic terms for days on therapy, as well as the interaction of the linear and quadratic terms with group. Time was included as a continuous effect because the visit intervals have more flexibility than often seen in acute phase trials. Modeling time as continuous accounted for the unequal visit timing. Baseline HAMD$_{17}$ score was also included as a continuous covariate to account for severity of depression at entry. Within-patient error terms were modeled using an unstructured covariance matrix. The Kenward-Roger method was used to estimate denominator degrees of freedom.

The incidence of serious adverse events, discontinuations due to adverse events, and treatment-emergent adverse events were compared using Fisher’s exact test.

Mean changes from baseline to last observation in efficacy measures were compared using ANOVA with a model that includes group, investigator and baseline HAMD$_{17}$ score. Response and remission rates were compared using Fisher’s exact test.

Mean changes from baseline to last observation in blood pressure and pulse were compared using ANOVA with a model that includes group, investigator, and baseline HAMD$_{17}$ score. The percentage of the patients who had abnormal values at endpoint for vital signs were compared using Fisher’s exact test.
RESULTS

Patients

A total of 155 patients were included in this analysis, of whom 88 were switched directly from SSRI (or venlafaxine) therapy and 67 were currently untreated. The medications utilized prior to switching were citalopram (18 patients), fluvoxamine (1), paroxetine (12), sertraline (22), venlafaxine (21), other (14). There were no significant between-group differences in baseline demographics or psychiatric profile (Table 1).

Efficacy

There were no significant between-group differences in baseline-to-endpoint mean change in HAMD17, HAMA or CGI-S scores (Table 2). Furthermore, the rates of endpoint or sustained response and remission did not differ significantly in patients switching to duloxetine when compared with those initiating duloxetine (Table 3).

Mean time to response for switch patients was 34.3 days, compared with 31.8 days for patients initiating duloxetine, while mean times to achieve remission were 42.5 days versus 40.3 days for switch and initiating patients, respectively. Mean time to achieve sustained response for switch patients was 42.6 days, compared with 38.3 days for those initiating duloxetine therapy, while mean times to achieve sustained remission were 51.1 days versus 46.8 days for switch and initiating patients, respectively. None of the between-group differences in times to response or remission reached statistical significance.

Safety

Adverse Events

Five patients, of whom 3 were switched from SSRI/venlafaxine and 2 were initiating duloxetine, reported a total of 8 serious adverse events (one case each of appendicitis, atrial fibrillation, staphylococcal cellulitis, dyspepsia, increased heart rate, pharyngitis, superficial thrombophlebitis, and varicose veins).

The rate of discontinuation due to adverse events was significantly higher among patients initiating duloxetine therapy when compared with the switching group (17.9% vs. 4.5%, respectively; p = .008). The only adverse event leading to discontinuation in more than one patient initiating duloxetine was nausea (2 patients). Events leading to discontinuation in individual patients initiating duloxetine included headache, insomnia, diarrhea, and fatigue. No adverse event led to discontinuation in more than one switch patient.

During the acute therapy phase, the most frequently reported treatment-emergent adverse events in both treatment groups were nausea, headache, dry mouth, insomnia and diarrhea (Table 4a). Compared with patients initiating duloxetine therapy, switch patients reported significantly lower rates of nausea (22.7% vs. 38.8%, p = .034) and fatigue (6.8% vs. 17.9%, p = .043), and a significantly higher rate of upper abdominal pain (6.8% vs. 0.0%, p = .037).

In the first week of therapy, patients switched from SSRI/venlafaxine to duloxetine (60 mg QD) reported significantly lower rates of nausea and fatigue when compared with patients initiating duloxetine therapy (60 mg QD) (Table 4b).

There were no spontaneous reports of treatment-emergent mania or hypomania in either treatment group during the course of the study. However, patients with any diagnosis of bipolar disorder, schizophrenia, or other psychotic disorders were excluded from the study.

Table 1 Baseline Demographics and Psychiatric Profile†

<table>
<thead>
<tr>
<th></th>
<th>Switching to Duloxetine (N = 88)</th>
<th>Initiating Duloxetine (N = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>44.1 (9.9)</td>
<td>41.3 (11.8)</td>
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<tr>
<td>Age, min – max</td>
<td>19–62</td>
<td>18–71</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>Female 67 (76.1)</td>
<td>42 (62.7)</td>
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<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>7 (8.0)</td>
<td>5 (7.5)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>75 (85.2)</td>
<td>56 (83.6)</td>
</tr>
<tr>
<td>East Asian</td>
<td>0 (0.0)</td>
<td>2 (3.0)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>6 (6.8)</td>
<td>4 (6.0)</td>
</tr>
<tr>
<td>HAMD17 total, mean (SD)</td>
<td>20.9 (4.2)</td>
<td>20.2 (3.3)</td>
</tr>
<tr>
<td>HAMA total, mean (SD)</td>
<td>6.2 (2.0)</td>
<td>6.1 (1.8)</td>
</tr>
<tr>
<td>CGI-S Severity, mean (SD)</td>
<td>4.5 (0.6)</td>
<td>4.3 (0.5)</td>
</tr>
</tbody>
</table>

†There were no significant between-group differences.

Table 2 Summary of Efficacy Measures

<table>
<thead>
<tr>
<th></th>
<th>Switching to Duloxetine (N = 84)</th>
<th>Initiating Duloxetine (N = 61)</th>
<th>p-value</th>
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<tr>
<td>HAMD17 Total</td>
<td>−12.3 (0.6)</td>
<td>−12.6 (0.7)</td>
<td>.791</td>
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<tr>
<td>HAMA Total</td>
<td>−9.36 (0.58)</td>
<td>−9.55 (0.66)</td>
<td>.832</td>
</tr>
<tr>
<td>CGI-S Severity</td>
<td>−1.94 (0.12)</td>
<td>−2.12 (0.14)</td>
<td>.341</td>
</tr>
</tbody>
</table>

Table 3 Summary of Response and Remission Rates†

<table>
<thead>
<tr>
<th></th>
<th>Switching to Duloxetine (N = 84)</th>
<th>Initiating Duloxetine (N = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response (any time)</td>
<td>76.2%</td>
<td>77.0%</td>
</tr>
<tr>
<td>Response (endpoint)</td>
<td>67.9%</td>
<td>63.9%</td>
</tr>
<tr>
<td>Response (sustained)</td>
<td>59.5%</td>
<td>54.1%</td>
</tr>
<tr>
<td>Remission (endpoint)</td>
<td>48.8%</td>
<td>55.7%</td>
</tr>
<tr>
<td>Remission (sustained)</td>
<td>44.0%</td>
<td>39.3%</td>
</tr>
</tbody>
</table>

†There were no significant between-group differences.
Mean changes in weight and vital signs are summarized in Table 5a. During acute phase treatment, both switching and initiating patients had small mean changes (≤1 mm Hg) in supine systolic and diastolic blood pressure, with no significant differences between treatment groups. Both patient groups also had mean increases in supine heart rate and mean decreases in body weight, with no significant between-group differences observed.

During the first week of treatment, switch patients had a mean increase in supine heart rate of 2.2 bpm, compared with a mean decrease of 1.3 bpm in patients initiating duloxetine (p = .002; Table 5b). There were no other significant between-group differences in vital sign mean changes during Week 1.

The incidence of treatment emergent elevated vital sign values at endpoint did not differ significantly between initiating and switching patients (high supine pulse: initiating 1.6% vs. switch 0.0%, p = .421; high supine systolic BP: initiating 5.8% vs. switch 1.2%, p = .299; high supine diastolic BP: initiating 3.9% vs. switch 0.0%, p = .154).

The incidence of abnormal weight gain (increase in body weight of ≥7% from baseline) or weight loss (decrease of ≥7% from baseline) did not differ significantly between initiating and switch patients (weight gain: initiating 1.6% vs. switch 1.2%, p = 1.00; weight loss: initiating 3.3% vs. switch 1.2%, p = .573).

**DISCUSSION**

In this 8-week, open-label study, nonresponsive patients who were switched directly from an SSRI to duloxetine demonstrated an improvement in depressive symptoms similar in magnitude to that observed in currently untreated patients initiating duloxetine therapy. The switch to duloxetine was well tolerated, with only 4.5% of patients discontinuing treatment due to an adverse event. Furthermore, in the first week following a switch to duloxetine, patients reported significantly lower rates of nausea and fatigue when compared with the first week following initiation of duloxetine in untreated patients. These findings may be explained by the fact that switch patients had already been exposed to medications that are associated with nausea as a potential adverse event (SSRIs). This suggests that a switch from an SSRI to duloxetine should be well tolerated by most patients.
Within the switch group, a total of 68% of patients demonstrated a response to duloxetine therapy at the study endpoint, with 49% achieving remission. These results are consistent with those of previous studies reporting fairly high response rates following the switch to a serotonin and norepinephrine reuptake inhibitor (SNRI) such as venlafaxine. Thus, a large open-label study found that, among 152 patients with MDD and a documented history of unsatisfactory improvement after a minimum of 8 weeks of treatment with an adequate dose of an antidepressant, treatment with venlafaxine was followed by a response (50% improvement from baseline) in 58% of the patients (41). Similarly, 53% of 312 depressed patients with either “absolute” or “relative” treatment resistance responded to open-label venlafaxine treatment (42), while 69% of 69 SSRI-resistant depressed patients were considered as responders after venlafaxine treatment (43). Interestingly, a subset of patients in the present study were venlafaxine non-responders, suggesting that the switch within the class of SNRIs may be helpful.

A small, but statistically significant, increase in heart rate was observed at Week 1 among switching patients. This may be a result of discontinuing SSRI treatment, previously found to be associated with bradycardia (44). Mean changes in supine systolic and diastolic blood pressure were ≤1 mm Hg in both treatment groups. These data are consistent with those obtained from pooled duloxetine studies, in which mean changes in supine systolic and diastolic blood pressure for duloxetine-treated patients were approximately 1.5 mm Hg, and not considered to be clinically relevant (39). Furthermore, the small (ca. 0.5 kg) mean decreases in weight observed in both switching and initiating treatment groups are very similar to those reported previously in acute-phase studies of duloxetine (39).

A number of limitations of the current study should be noted. Firstly, this was an open-label study. In the absence of a placebo group, interpretation of efficacy results should be approached with a degree of caution. For this reason, the discussion of efficacy has been limited to a comparison of overall magnitude of improvement between switching and initiating treatment groups. Secondly, the study focused on patients currently receiving relatively low doses of SSRIs (≤20 mg/d escitalopram, ≤40 mg/d paroxetine or citalopram, ≤150 mg/d sertraline or fluvoxamine) or venlafaxine (≤150 mg/d) and excluded patients treated with fluoxetine. Since this was the first study to investigate direct switching from SSRI/venlafaxine to duloxetine, we elected to adopt a conservative approach toward dosing in order to minimize the risk of discontinuation symptoms and ensure patient safety. Additional studies will be required to extend the current results to patients who switch directly to duloxetine from higher doses of SSRIs, fluoxetine, and other agents. Thirdly, the study design allowed flexible dosing of duloxetine after the first week of therapy (in a range from 60–120 mg/d), and thus the two study groups were not receiving identical treatment after Week 1. However, a flexible dosing regimen may provide a more naturalistic setting in which to assess treatment effects, and provide a more accurate reflection of results typically encountered in day-to-day clinical practice. Furthermore, during the first week of therapy, which is perhaps the most important period with regard to treatment-emergent adverse events, both switching and initiating patients received the same fixed dose of duloxetine (60 mg once-daily).

**CONCLUSIONS**

In patients failing to respond to SSRI or venlafaxine therapy, an immediate switch to duloxetine (60 mg QD) appears to be effective and well-tolerated. The efficacy of duloxetine in switched patients was comparable to that observed in patients initiating duloxetine therapy. Furthermore, switching to duloxetine may be achieved using an immediate switch strategy, presenting the patient with a straightforward dosing schedule.

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