ABSTRACT

Background: Anxious depression, defined as Major Depressive Disorder (MDD) with high levels of anxiety symptoms, represents a relatively common depressive subtype with distinctive clinical features. This post-hoc analysis compared the safety, tolerability and efficacy of open-label treatment with duloxetine in outpatients with anxious vs. non-anxious depression.

Methods: All patients met criteria for MDD as defined in DSM-IV; patients (N=249) were treated with duloxetine 30- or 60-mg QD (once daily) for 12 weeks. Response was defined as ≥50% reduction in total Hamilton Depression Rating Scale (HAMD17), Hamilton Anxiety Scale (HAMA), and from 60 mg QD to 120 mg QD, with 90 mg QD as an intermediate dose. Efficacy outcomes were based on the mean change in HAMD17 total score from baseline. Analysis was two-tailed with α=0.05.

Results: Anxious (n=109) and non-anxious (n=140) patient groups differed significantly in demographic factors, treatment status at entry, discontinuation rates, overall rates of treatment-emergent adverse events and specific rates of treatment-emergent adverse events (except for a greater incidence of influenza in patients with anxious depression). At endpoint, open treatment with duloxetine was accompanied by a significantly greater reduction in total HAMD17 and HAMA total scores among anxious vs. non-anxious depressed patients. Differences in CGI-S and HAMA scores at endpoint between these two groups were not statistically significant. Although discontinuation and response rates were similar at endpoint between anxious and non-anxious patients, 11 yrs. as defined with anxious depression had a more rapid improvement, displaying a significantly shorter median time to response in anxious depression.

Conclusions: In this post-hoc subgroup analysis, duloxetine administered similar safety and tolerability in anxious and non-anxious depressed patients. However, the efficacy of duloxetine in anxious vs. non-anxious depression was somewhat superior to that observed in non-anxious depression. Further placebo-controlled studies are needed to confirm and extend these findings.

INTRODUCTION

Anxious depression, an important and common clinical subtype of major depression characterized by marked anxiety, has been associated with higher levels of suicidality. Additionally, anxious depressions have been less responsive to antidepressant treatment than non-anxious depressions in some, but not all, studies. Adequate treatment of anxious depression is clinically important, as treatment-resistant patients have been associated with a higher risk of relapse in patients with major depression. This post-hoc analysis compares the efficacy and tolerability of open-label treatment with duloxetine, a balanced neuroradulator inhibitor of serotonin and norepinephrine (NE) in adult outpatients with anxious vs. non-anxious depression

METHODS

Study Design

Post-hoc analysis of 12-week, open-label, 21-site duloxetine monotherapy trials.

Three study phases:

• Study Period I: 11-week duloxetine dosage period treatment
• Study Period II: 11-week open-label, flexible-dose period
• Two participant groups in main study
  • “Treatment-naive” (not on antidepressant treatment at entry)
  • “Treatment-switch” (on venlafaxine or SSRIs at study entry)
  • Two participants groups in post-hoc analysis
    • Anxious depression defined by a ≥7 on Hamilton Anxiety Scale/Somatization Factor score

Study Treatment

• “Treatment-naive” group
  • Study Period I: randomization to treatment with duloxetine 30- or 60 mg QD (once daily) for 11 weeks
  • Study Period II: fixed dose duloxetine 60, 90, or 120 mg QD for 11 weeks
  • Study Period III: fixed dose duloxetine 60, or 120 mg QD for up to 11 weeks

• “Treatment-switch” group
  • Study Period I: initial switch from SSRIs (except fluoxetine) or venlafaxine to duloxetine 30, 60, or 120 mg QD for 11 weeks
  • Study Period II: fixed dose duloxetine 60, 90, or 120 mg QD for up to 11 weeks

Inclusion criteria:
  • Adult outpatients with major depressive disorder per DSM-IV
  • Clinical Global Impression-Severity (CGI-S) score ≤4 at two consecutive screenings
  • Antidepressant-free (treatment-naive) or ongoing treatment with SSRIs (obtained: 60mg/day; paroxetine: 40 mg/day; sertraline: 150 mg/day; fluoxetine: 120 mg/day; escitalopram: 20 mg/day; venlafaxine: 150 mg/day).

Exclusion criteria:
  • Treatment with fluoxetine within 30 days prior to IV or propranolol monoexposure within 14 days prior to IV
  • Lack of consent to ≥2 adequate antidepressant trials in current episode

Study outcome measures:
  • HAMD17 Total Score
  • CGI-Score
  • CGI-Impairment Score
  • CGI-Worsening Score
  • HAMA Total Score
  • HAMA Anxiety Subtotal
  • HAMD17 Anxiety Subtotal

Safety and tolerability assessments:

• Early study discontinuation reasons
• Treatment-emergent adverse events

Safety and tolerability outcomes:

Statistical Methods

• infield HAMD17 Anxiety Subtotal and HAMA Total, mean (SD)
  • Statistical Methods
    • Rates for reasons of early discontinuation and rates of treatment-emergent adverse events were assessed and compared among anxious and non-anxious participant groups using the Cochran-Armitage test for trend controlling for treatment status at entry (treatment-switch vs. treatment-naive).
    • Treatment-emergent adverse events were grouped into event categories, including central nervous system (CNSS), gastrointestinal, neuromuscular and skeletal, and CNS anxiety, and Kaplan-Meier survival analyses were performed on time to occurrence of treatment-emergent adverse event groupings comparing anxious and non-anxious patient groups.

RESULTS

Table 1: Stabilized Duloxetine Dose in “Treatment- Naive” and “Treatment-Switch” Participant Groups

<table>
<thead>
<tr>
<th>Participant Group</th>
<th>Anxious (n=109)</th>
<th>Non-anxious (n=140)</th>
<th>Total (n=249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine 60 mg QD, N (%)</td>
<td>29 (27)</td>
<td>34 (24.3)</td>
<td>63 (25.5)</td>
</tr>
<tr>
<td>Duloxetine 90 mg QD, N (%)</td>
<td>20 (18)</td>
<td>32 (23)</td>
<td>52 (21)</td>
</tr>
<tr>
<td>Duloxetine 120 mg QD, N (%)</td>
<td>34 (31)</td>
<td>36 (25.3)</td>
<td>70 (28)</td>
</tr>
</tbody>
</table>

Table 2: Baseline Participant Characteristics (All Randomized Participants)*

| Age, mean (SD) | 43.09 (12.19) | 43.39 (21.37) | 43.15 (17.91) | 0.011 |
| Gender, % | 73.4 (62.9) | 67.9 (67.9) | 65.8 (67.9) | .697 |
| Treatment naïve patients(%) | 52.3 | 57.1 | 55.0 | .521 |

Table 3: Early Discontinuation Rates

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Anxious (n=109)</th>
<th>Non-anxious (n=140)</th>
<th>Total (n=249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any reason, N (%)</td>
<td>35 (25)</td>
<td>33 (23)</td>
<td>68 (27)</td>
</tr>
<tr>
<td>Patient decision, N (%)</td>
<td>35 (25)</td>
<td>33 (23)</td>
<td>68 (27)</td>
</tr>
<tr>
<td>Any reason, N (%)</td>
<td>35 (25)</td>
<td>33 (23)</td>
<td>68 (27)</td>
</tr>
<tr>
<td>Patient decision, N (%)</td>
<td>35 (25)</td>
<td>33 (23)</td>
<td>68 (27)</td>
</tr>
</tbody>
</table>

Table 4: Treatment-Emergent Adverse Events Reported by ≥1%

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Anxious (n=109)</th>
<th>Non-anxious (n=140)</th>
<th>Total (n=249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>33 (30)</td>
<td>36 (26)</td>
<td>69 (28)</td>
</tr>
<tr>
<td>Headache</td>
<td>27 (25)</td>
<td>32 (23)</td>
<td>59 (24)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>21 (19)</td>
<td>35 (25)</td>
<td>56 (23)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>17 (16)</td>
<td>35 (25)</td>
<td>52 (21)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15 (14)</td>
<td>31 (22)</td>
<td>46 (19)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (14)</td>
<td>31 (22)</td>
<td>46 (19)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (11)</td>
<td>17 (12)</td>
<td>29 (12)</td>
</tr>
<tr>
<td>Constipation</td>
<td>15 (14)</td>
<td>26 (19)</td>
<td>41 (17)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (6)</td>
<td>12 (8)</td>
<td>19 (8)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>6 (6)</td>
<td>18 (12)</td>
<td>24 (10)</td>
</tr>
</tbody>
</table>

N=number of participants

When rates were adjusted for by treatment-switch vs. treatment-naive treatment status using the CMH test, no significant difference in the rates of specific treatment-emergent adverse events were noted between anxious and non-anxious groups with the exception of nausea (5.2% vs. 3.6%) p=0.09. Similar results were found when using Fisher’s exact test.

No significant differences were noted between anxious and non-anxious patients in the occurrence of treatment-emergent adverse events grouped (p<0.001) central nervous system (CNSS), gastrointestinal system, neuromuscular and skeletal system, and CNS anxiety symptoms.

CONCLUSIONS

Patients with anxious depression treated with up to 12 weeks of open-label duloxetine monotherapy, compared to those with non-anxious depression:

• Significantly greater reduction in depression and anxiety/somatization, as evidenced by the HAMD17 and the HAMA Anxiety/Somatization scores.
  • Similar improvements on CGI-S and HAMA scores
  • Similar remission and response rates, but more rapid improvement (significantly shorter median time to response and remission)
  • Similar safety and tolerability outcomes