Additional Safety Outcomes

- Duloxetine was associated with a safe profile with no difference from placebo in adverse hepatic or cardiac events.

- Compared with placebo, duloxetine was associated with statistically significant mean changes in diastolic blood pressure and heart rate from baseline to endpoint, but not for systolic blood pressure.
  - Mean change systolic blood pressure mm Hg
    - placebo = -0.65; duloxetine 60 mg/day = 0.71 (P = .321); duloxetine 120 mg/day = 1.07 (P = .206)
  - Mean change diastolic blood pressure
    - placebo = -0.54; duloxetine 60 mg/day = 0.96 (P = .102); duloxetine 120 mg/day = 1.72 (P = .014)
  - Mean change heart rate beats per minute
    - placebo = -3.78; duloxetine 60 mg/day = 1.59 (P < .001); duloxetine 120 mg/day = 2.21 (P < .001)

- Groups differed in the occurrence of sustained EBP‡
  - placebo 0 patient; duloxetine 60 mg/day 5 patients (P = .027 vs placebo); duloxetine 120 mg/day 1 patient

- Duloxetine 60 mg/day and 120 mg/day were each effective in reducing the severity of anxiety and impairment associated with GAD. The improvements were clinically meaningful as indicated by the response, sustained improvement, and remission rates.

- Strengths of the study include the use of a geographically diverse sample; the use of the structured interview guide for the HAMA; and the use of an entry criteria (HADS) that was independent of the primary outcome measure (HAMA).

- The most common adverse event was nausea, which was tolerable for most patients as indicated by its low treatment discontinuation rate.

- The results of the present multicenter, placebo-controlled study demonstrate that duloxetine 60 mg/day and 120 mg/day are effective, safe, and well tolerated in the treatment of GAD.

REFERENCES


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CONCLUSIONS

- Duloxetine 60 mg/day and 120 mg/day were each effective in reducing the severity of anxiety and impairment associated with GAD.

A Fixed-dose Study of the Efficacy and Safety of Duloxetine for the Treatment of Generalized Anxiety Disorder

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ABSTRACT

Objective: Both serotonergic and noradrenergic medications have been used independently for the treatment of generalized anxiety disorder (GAD). This study examined the efficacy and safety of duloxetine, a balanced and potent dual reuptake-inhibitor of both serotonin and norepinephrine, for the treatment of GAD.

Methods: In a 9-week, double-blind, fixed-dose study, 513 patients [Mean age=43.8 yrs; 67.8% female] with a DSM-IV defined GAD diagnosis were randomly assigned to receive either duloxetine 60 mg/day (N=168), duloxetine 120 mg/day (N=170), or placebo (N=175). Primary efficacy outcome was change from baseline to endpoint in the Hamilton Anxiety Scale (HAMA) total score assessed via ANCOVA. Secondary measures included response, remission, and sustained improvement rates; mean change in Sheehan Disability Scale (SDS) Global Functional Impairment score; HAMA Psychic and Somatic Factor scores; and response, remission, and sustained improvement rates.

Results: Compared with placebo, both duloxetine groups demonstrated significantly greater reduction in HAMA scores (mean decrease duloxetine 60 mg/day=12.8, duloxetine 120 mg/day=12.5, vs placebo=8.4, P < .001), greater response rates (duloxetine 60 mg/day=58%, duloxetine 120 mg/day=56% vs placebo=31%, P < .001), greater remission rates (duloxetine 60 mg/day=31%, duloxetine 120 mg/day=38%, placebo=19%, P < .001, respectively), and greater sustained improvement rates (duloxetine 60 mg/day=63.6%, duloxetine 120 mg/day=66.9% vs placebo=42.8%, P < .001). Both duloxetine groups also had greater improvements in SDS global scores (P < .001), greater reductions in the HAMA psychic factor (P < .001) and HAMA somatic factor scores (P < .001). Discontinuation rates due to adverse events were 11.3% for duloxetine 60 mg/day, 15.3% for duloxetine 120 mg/day, vs. 2.3% for placebo (P < .001). The three most frequent adverse events associated with duloxetine were nausea, dizziness, and dry mouth.

Conclusion: Duloxetine 60 mg/day and 120 mg/day once daily was a safe, effective treatment that resulted in clinically significant improvement in symptom severity and disability associated with GAD.
BACKGROUND

• Generalized anxiety disorder (GAD) is one of the most common psychiatric illnesses, with recent findings from the National Comorbidity Survey Replication (NCS-R) study suggesting a lifetime risk estimate of approximately 8% for GAD.\(^1\)

• Duloxetine is a relatively balanced reuptake inhibitor of both serotonin and norepinephrine. Preclinical and clinical studies suggest that it is effective in reducing anxiety symptoms.\(^2\-^3\)

• Hypothesis: Duloxetine 60 mg/day and 120 mg/day will be superior to placebo for the treatment of DSM-IV defined GAD during a 9-week, double-blind, acute therapy trial.

METHODS

• Patients were ≥ 18 years of age and recruited from 42 outpatient treatment centers across 7 countries (Finland, France, Germany, South Africa, Spain, Sweden, and USA)

Inclusion Criteria

• DSM-IV GAD as determined by the Mini International Neuropsychiatric Interview and confirmed by study psychiatrist

• Clinical Global Impression Severity (CGI-S) Score of ≥ 4 (moderate)

• Hospital Anxiety and Depression Scale (HADS) anxiety subscale score ≥ 10

• Covi Anxiety Scale (CAS) total score ≥ 9

• Raskin Depression Scale (RDS) with no item > 3; CAS total > RDS total

• Medically healthy as determined by physical exam, electrocardiogram, and laboratory blood and urine analyses

Exclusion Criteria

• Recent (6 mo) diagnosis of major depression or substance abuse/dependence

• Past year history of panic, post-traumatic stress or eating disorders

• Lifetime history of obsessive-compulsive disorder, bipolar disorder or psychotic illness

• Concomitant psychotropic or excluded medication use

Primary outcome measure

• Hamilton Anxiety Scale (HAMA) total score using the Structured Interview Guide for HAMA (SIGH-A)\(^4\)

Secondary outcome measures

• Sheehan Disability Scale (SDS) global and specific functional impairment scores

• HAMA Psychic and Somatic Anxiety Factor, HAMA items anxious mood and tension (items 1 and 2)

• Hospital Anxiety and Depression Scale (HADS) subscale scores

• Clinical and Patient Global Impressions Improvement ratings (CGI-I, CGI-II)

• Treatment outcome status based on HAMA total score changes at end of treatment

  - Response: ≥ 50% reduction from baseline to endpoint

  - Sustained improvement: 30% reduction at any visit after baseline that was sustained at all subsequent visits

  - Remission: HAMA total score ≤ 7 at endpoint

Safety measures

• Vital signs, weight, and spontaneously reported adverse reports were recorded at each visit

• ECgS, blood chemistry, urinalysis (includes drug screen) at pre- and post-treatment

Study Design

• 9-week, acute, double-blind, randomized, fixed-dose, placebo-controlled study

• Patients were assigned to either duloxetine 60 mg/day, duloxetine 120 mg/day, or placebo

• Starting dose was duloxetine 60 mg/day; a dose decrease was allowed, but patients had to be taking their randomized dose by week 2

• Study visits were conducted at weeks 1, 2, 4, 6, and 9 of treatment

Statistical Methods

• All analyses were conducted on the intent-to-treat sample, which included patients who had a baseline observation and ≥ 1 post-randomization observation

• Primary analysis model was an ANCOVA based on LOCF with baseline severity as the covariate and investigator site and treatment group as fixed effects

• The mixed effects repeated measures model (MMRM) was also conducted secondarily

Efficacy outcomes

• The duloxetine 60 mg/day group significantly improved on the HAMA Psychiatric Factor score (P < .001), HAMA Somatic scores (P < .01), and HAMA anxious mood and tension items (P < .001) compared with the placebo group; the duloxetine 120 mg/day group also significantly improved more than the placebo group on the HAMA Psychiatric and Somatic scales and HAMA anxious mood and tension items (all P values < .001)

• Compared with the placebo group, duloxetine-treated patients were rated as more improved at study endpoint by clinician (CGI-I, both duloxetine groups, P < .001) and self-report (PGI-I, both duloxetine groups, P < .001)

• Patients who received duloxetine also had greater improvements in self-reported anxiety (HADS Anxiety scale, both duloxetine groups, P < .001) and depression (HADS Depression scale, both duloxetine groups, P < .001) than the placebo group

• At treatment endpoint, patients who were treated with duloxetine had greater response (both duloxetine groups, P < .001), sustained improvement (both groups P < .001), and remission rates (duloxetine 60 mg/day, P < .01, duloxetine 120 mg/day P < .001) compared with placebo

  - Responder percent: placebo = 31%; duloxetine 60 mg/day = 58%; duloxetine 120 mg/day = 56%

  - Sustained improvement percent: placebo = 42.8%; duloxetine 60 mg/day = 63.6%; duloxetine 120 mg/day = 66.9%

  - Remission percent: placebo = 19%; duloxetine 60 mg/day = 31%; duloxetine 120 mg/day = 38%

TABLE 1. Patient Characteristics and Baseline Values

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N=175)</th>
<th>Duloxetine 60 mg/day (N=168)</th>
<th>Duloxetine 120 mg/day (N=170)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: years, mean (SD)</td>
<td>44.1(13.4)</td>
<td>43.1 (12.9)</td>
<td>44.1 (12.6)</td>
<td>0.718</td>
</tr>
<tr>
<td>Sex: n, (%)</td>
<td>117 (66.9)</td>
<td>108 (64.3)</td>
<td>123 (72.3)</td>
<td>0.269</td>
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<tr>
<td>Racial origin: n, (%)</td>
<td>173 (98.9)</td>
<td>163 (97.0)</td>
<td>169 (99.4)</td>
<td>0.239</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (0.6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0)</td>
<td>4 (2.4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Prior benzodiazepine Rx: n, (%)</td>
<td>42 (24)</td>
<td>29 (17.3)</td>
<td>32 (18.8)</td>
<td></td>
</tr>
<tr>
<td>Baseline measures: mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAMA total</td>
<td>25.8 (7.6)</td>
<td>25.0 (7.1)</td>
<td>25.2 (7.3)</td>
<td>0.599</td>
</tr>
<tr>
<td>HAMA psychic anxiety factor</td>
<td>14.1 (4.0)</td>
<td>13.9 (3.6)</td>
<td>14.1 (3.8)</td>
<td>0.880</td>
</tr>
<tr>
<td>HAMA somatic anxiety factor</td>
<td>11.7 (4.5)</td>
<td>11.1 (4.5)</td>
<td>(11.1) (4.4)</td>
<td>0.426</td>
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<tr>
<td>CGI-S Severity score</td>
<td>4.8 (0.6)</td>
<td>4.8 (0.6)</td>
<td>4.8 (0.6)</td>
<td>0.569</td>
</tr>
<tr>
<td>HADS anxiety subscale</td>
<td>13.3 (3.9)</td>
<td>13.1 (3.7)</td>
<td>12.9 (3.5)</td>
<td>0.571</td>
</tr>
<tr>
<td>SDS global improvement</td>
<td>15.1 (7.5)</td>
<td>15.2 (7.4)</td>
<td>15.1 (7.5)</td>
<td>0.993</td>
</tr>
</tbody>
</table>

SAFETY OUTCOMES