Duloxetine as an Effective Treatment for Improving Painful Physical Symptoms and Functioning Associated with Generalized Anxiety Disorder

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ABSTRACT

Objectives: Painful physical symptoms are increasingly recognized as a significant morbidity associated with anxiety disorders. This study examined the efficacy and safety of duloxetine, a balanced and potent dual reuptake-inhibitor of serotonin and norepinephrine, for treatment of painful physical symptoms and functioning in GAD.

Methods: In a 9-week, double-blind, fixed-dose study, 513 patients [Mean age=43.78 yrs; 67.8% female] with a DSM-IV defined GAD diagnosis were randomly assigned to receive duloxetine 60 mg/day (N=168), duloxetine 120 mg/day (N=170), or placebo (N=175). Pain was assessed using Visual Analogue Scales for Pain. Other measures of patient functioning included the Sheehan Disability Scale (SDS), the Quality of Life Improvement and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) and European Quality of Life 5 Dimension (EQ-5D). Changes from baseline to endpoint in measures were analyzed using ANCOVA.

Results: Compared with placebo, both duloxetine groups demonstrated significantly greater reduction in ratings for each pain item: overall pain (P < .05), back pain (P < .01), shoulder pain (P < .02), and pain during waking (P < .001). The duloxetine groups also demonstrated greater improvement, compared with placebo group, in all domains of the SDS (P < .001), in the Q-LES-Q-SF total and maximum percent scores (P < .001) and EQ-5D Index (P < .01) and health state scores (P < .001).

Conclusions: Within patients with GAD, who were not selected for the occurrence of pain, treatment with duloxetine 60 mg/day and 120 mg/day resulted in significant improvement in painful physical symptoms. Duloxetine also enhanced patients’ quality of life and overall functioning.

REFERENCES

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CONCLUSIONS
• Duloxetine 60 mg/day and 120 mg/day were each effective treatments for reducing the severity and impairment associated with painful physical symptoms in GAD.
• Multiple painful physical symptoms are present within patients who have GAD, and the baseline mean values on the pain measures suggest that these symptoms are an important consideration for treatment.
• Duloxetine treatment also significantly enhanced role functioning, subjective well-being, and perceived health compared with placebo.
• As a relatively balanced dual reuptake inhibitor of serotonin and norepinephrine, duloxetine 60 mg/day and 120 mg/day were effective treatments for reducing painful physical symptoms and improving patient-reported functional outcomes in patients with GAD.

Other Functional Outcomes
Patients treated with duloxetine experienced greater improvement on their SDS global functional impairment score than patients who received placebo (both duloxetine groups, P < .001)
- On each specific domain of the SDS, the duloxetine-treated patients showed greater mean improvements than the placebo-treated patients (all P values < .001)
- Work/School: placebo = -1.15; duloxetine 60 mg/day = -2.64; duloxetine 120 mg/day = -2.39
- Social life: placebo = -1.29; duloxetine 60 mg/day = -2.54; duloxetine 120 mg/day = -2.40
- Family Life/Home: placebo = -1.21, duloxetine 60 mg/day = -2.58; duloxetine 120 mg/day = -2.33

Compared with the placebo group, duloxetine-treated patients showed greater mean improvement in life satisfaction and well-being on the Q-LES-Q-SF after treatment (both duloxetine groups, all P values < .001)
- Q-LES-Q-SF Total Score: placebo = 6.25; duloxetine 60 mg/day = 10.50; duloxetine 120 mg/day = 11.23
- Q-LES-Q-SF Maximum Percent: placebo = 12.47; duloxetine 60 mg/day = 19.69; duloxetine 120 mg/day = 20.98

Both duloxetine groups also had greater improvements in perceived health status as measured by the EQ-5D index score (both duloxetine groups, P < .01) and EQ-5D VAS score (both duloxetine groups, P < .001) compared with placebo group
- EQ-5D Index Score: placebo = 0.15; duloxetine 60 mg/day = 0.22; duloxetine 120 mg/day = 0.22
- EQ-5D VAS Health Score: placebo = 12.47; duloxetine 60 mg/day = 19.69; duloxetine 120 mg/day = 20.98
INTRODUCTION

Background
• Anxiety disorders and medical conditions are known to be frequently comorbid, but there is an increasing awareness that painful physical symptoms are also associated with anxiety disorders. 1,2
• Duloxetine is a relatively balanced reuptake inhibitor of both serotonin and norepinephrine and is efficacious in reducing painful physical symptoms in patients with major depressive disorder and in patients with diabetic peripheral neuropathic pain. 3,4

Hypothesis: Duloxetine 60 mg/day and 120 mg/day will be superior to placebo for improving painful physical symptoms and functioning in adults with DSM-IV defined General Anxiety Disorder (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 US).

Inclusion criteria
• DSM-IV GAD 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

Main 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 pain measure
The Visual Analogue Scales (VAS) for Pain 2 were administered at each visit
• The VAS consists of a scale from 0="None" to 100="extremely"
• Separate VAS ratings were obtained for overall pain, headaches, back pain, shoulder pain, proportion of day while awake with pain, and daily interference due to pain.

Secondary outcome measures
• Sheehan Disability Scale global functional and work, social life, and family/ home impairment scores
• Quality of Life Enjoyment and Satisfaction Scale Short Form (Q-LES-Q-SF)
— Total score and Maximum Percent score
— Community norms for the Q-LES-Q-SF are reported as mean total = 58.1 or 83.6%. 6
— Questionnaire was administered at baseline and treatment endpoint.
• European Quality of Life – 5 Dimensions (EQ-5D)
— Index score and a Visual Analogue Scale (0-100) score; higher scores indicate greater perceived health and well-being
— Community norms for EQ-5D Index = 0.86; VAS Health = 79.3.7
— Questionnaire was administered at baseline and treatment endpoint

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 60 mg/day; a dose decrease was allowed, but patients had to be taking their randomized dose by 2 weeks
• Study visits were conducted at weeks 1, 2, 4, 6, and 9 of treatment

Statistical Methods
• Primary pain outcome analysis: Visual Analogue Scales
— Primary analysis was performed with intent-to-treat (ITT) sample using ANCOVA with baseline severity as the covariate and investigator site and treatment group as fixed effects (LOCF)
— A mixed effects repeated measures model (MMRM) was conducted secondarily

Secondary functional outcome analysis:
• For SDS scales, primary analysis was performed with ITT sample using ANCOVA with baseline severity as the covariate and investigator site and treatment group as fixed effects (LOCF)
• Q-LES-Q-SF and EQ-5D score: A priori-defined analysis was performed with completer sample using ANCOVA with baseline severity as the covariate and investigator site and treatment group as fixed effects
• An LOCF analysis with the ITT sample was conducted secondarily

RESULTS

TABLE 1. Patient Characteristics and Baseline Values

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (N = 178)</th>
<th>Duloxetine 60 mg/day (N = 168)</th>
<th>Duloxetine 120 mg/day (N = 173)</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>
</tr>
<tr>
<td>Sex: n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>117 (66.9)</td>
<td>108 (64.3)</td>
<td>123 (72.3)</td>
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<tr>
<td>Racial origin: n (%)</td>
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<td></td>
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<tr>
<td>Caucasian</td>
<td>173 (98.9)</td>
<td>163 (97.0)</td>
<td>169 (99.4)</td>
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<tr>
<td>African descent</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (0.6)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Asian</td>
<td>0</td>
<td>4 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>Prior benzodiazepine Rx: n (%)</td>
<td>42 (24.0)</td>
<td>29 (17.3)</td>
<td>32 (18.8)</td>
</tr>
<tr>
<td>Baseline measures: mean (SD)</td>
<td></td>
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<td></td>
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<tr>
<td>VAS overall pain</td>
<td>34.3 (25.8)</td>
<td>34.3 (26.0)</td>
<td>30.3 (26.2)</td>
</tr>
<tr>
<td>VAS headaches</td>
<td>22.6 (24.9)</td>
<td>23.7 (25.2)</td>
<td>25.9 (27.5)</td>
</tr>
<tr>
<td>VAS back pain</td>
<td>24.6 (25.2)</td>
<td>25.5 (26.8)</td>
<td>25.1 (27.5)</td>
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<tr>
<td>VAS shoulder pain</td>
<td>24.8 (28.4)</td>
<td>22.1 (27.2)</td>
<td>23.1 (27.5)</td>
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<tr>
<td>VAS interference with daily activities</td>
<td>29.1 (25.8)</td>
<td>25.1 (25.2)</td>
<td>25.4 (25.7)</td>
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<tr>
<td>VAS pain while awake</td>
<td>37.6 (29.6)</td>
<td>35.6 (28.2)</td>
<td>33.3 (30.3)</td>
</tr>
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<td>Sheehan global impairment</td>
<td>15.1 (7.5)</td>
<td>15.2 (7.4)</td>
<td>15.1 (7.5)</td>
</tr>
</tbody>
</table>

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