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DULOXETINE VERSUS PLACEBO IN THE TREATMENT OF STRESS URINARY INCONTINENCE (SUI)

Aims
Duloxetine hydrochloride, a potent and selective inhibitor of serotonin (5-HT) and norepinephrine (NE) reuptake, is felt to increase efferent output from Onuf’s nucleus via stimulation of pudendal motor neuron alpha-1 adrenergic and 5 HT-2 receptors, resulting in enhanced contractility of the rhabdosphincter [1]. A phase II trial demonstrated dose proportional efficacy in treating SUI at doses of 40 and 80 mg/day [2]. The primary aims of this first Phase III study were to assess the efficacy (measured both by the decrease in incontinence episode frequency [IEF] and by the improvement in condition specific quality of life) and safety of duloxetine in women with a predominant symptom of SUI.

Methods
683 North American women aged 22-84 were enrolled in this double-blind, placebo-controlled study. The case definition was a predominant symptom of SUI with a weekly IEF $\geq 7$, the absence of predominant urge symptoms, normal diurnal and nocturnal frequencies, a bladder capacity $\geq 400$ mL, and positive cough stress and stress pad tests. After a 2-week observation period and a 2-week placebo lead in period, subjects were randomly assigned to receive placebo (N = 339) or duloxetine 80 mg/day (N = 344; 40 mg bid) for 12 weeks with three follow-up visits at 4-week intervals. Outcome variables included IEF, recorded real-time on diaries for one week prior to each visit, the Patient Global Impression of Improvement (PGI-I) Scale, and the Incontinence Quality of Life (I-QOL) questionnaire, a 22-item validated condition specific instrument, which evaluates the effects of UI in three domains (Avoidance and Limiting Behavior, Social Embarrassment, and Psychosocial Impact) [3]. Van Eltren’s test (a stratified Wilcoxon test) was used to analyze median percent changes in IEF where the stratification variable was weekly baseline IEF (<14 and 14 or greater). Analysis of covariance was used to analyze mean changes in average voiding interval and I-QOL. PGI-I was analysed using Cochran-Mantel-Haenszel test.

Results
The mean baseline IEF was 18/wk; 436 (64%) subjects had a baseline IEF $\geq 14$. The table lists the results for IEF and I-QOL for the entire study population and for the more severely incontinent strata and reveals a significant decrease in IEF and improvements in quality of life with duloxetine, independent of baseline incontinence severity. Based on the PGI-I results, 62% of duloxetine subjects considered their bladder condition to be better on treatment, compared to 39.6% of placebo subjects (p <.001). Duloxetine subjects demonstrated statistically significant improvements compared to placebo in all three I-QOL domains. These improvements with duloxetine were associated with significant increases in voiding intervals compared to placebo (20 versus 2 min, p < .001).

<table>
<thead>
<tr>
<th>Table 1.</th>
<th>All Subjects (N = 683)</th>
<th>More Severe Strata (≥14 IEF; N = 436)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Median IEF Decrease</td>
<td>Mean I-QOL Improvement</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>-50%</td>
<td>+11.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>-27%</td>
<td>+6.8</td>
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<tr>
<td>P</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
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</table>

Discontinuation rates for adverse events were 4% for placebo and 24% for duloxetine (p <.001), with nausea being the most common symptom leading to discontinuation of duloxetine (6.4%). The discontinuation rate for adverse events recognized as attributable to duloxetine was 16.8%. Nausea tended to be mild and transient with 36 of 58 (62%) women experiencing nausea completing the study. Of women completing the blinded study, 80% of duloxetine and 94% of placebo subjects elected to enter the open label extension.

Conclusions
These phase 3 data are consistent with phase 2 data and provide further evidence for the safety and efficacy of duloxetine as a pharmaceutical agent for the treatment of SUI, independent of severity.
References:


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