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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 ≥7, the absence of predominant urge symptoms, normal diurnal and nocturnal frequencies, a bladder capacity ≥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 ≥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 1.** | All Subjects (N = 683) | | More Severe Strata (≥14 IEF; N = 436) | |
|---|---|---|---|---|
| | Median IEF Decrease | Mean I-QOL Improvement | Median IEF Decrease | Mean I-QOL Improvement |
| Duloxetine | -50% | +11.0 | -52% | +12.8 |
| Placebo | -27% | +6.8 | -25% | +7.4 |
| P | <.001 | <.001 | <.001 | <.001 |

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 16.6%. Nausea tended to be mild and transient with 36 of 58 (62%) women experiencing nausea completing the study. Of women completing the blinded study, 90% 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 pharmacological agent for the treatment of SUI, independent of severity.

**References:**


1. Effects of duloxetine, a combined serotonin and norepinephrine reuptake inhibitor, on central neural control of lower urinary tract function in the chloralose-anesthetized female cat. J Pharmacol Exp Ther 1995;274:1014-24
2. Duloxetine versus placebo in the treatment of stress urinary incontinence. Am J Obstet Gynecol 2002; in press
3. Quality of life for women with urinary incontinence: further development of the incontinence quality of life instrument. Urology 1999;53:71-76.


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