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Title: DULOXETINE VERSUS PLACEBO IN THE TREATMENT OF STRESS URINARY INCONTINENCE

Aims of the Study: Two pilot studies in humans have suggested that duloxetine, a potent selective inhibitor of 5-HT and NE reuptake, demonstrates efficacy in treating stress urinary incontinence (SUI). The primary aim of this Phase II study was to compare the efficacy, as determined by incontinence episode frequency (IEF), of 20, 40, or 80 mg/day duloxetine with that of placebo in the treatment of SUI. The secondary aim was to compare changes in quality of life of duloxetine-treated patients with those of placebo patients.

Methods:

553 women aged 18-65 with urinary incontinence (UI) of at least 3 months duration were enrolled in this double-blind, placebo-controlled, randomized study. The case definition included a predominant symptom of SUI with a weekly IEF $\geq$4, the absence of predominant symptoms of enuresis or urge UI, diurnal and nocturnal frequencies $\leq$7 and $\leq$2 respectively, negative funnel infusion cystometry with a first sensation >100 mL and a bladder capacity $\geq$400 mL, and a positive fixed volume cough stress test and stress pad test (>2g). 86 women also had multi-channel urodynamics with GSI being confirmed in 79 (92%). Subjects were excluded if they had prolapse $\geq$ stage II, had a postvoid residual volume $\geq$ 50 mL, were using any pharmacological agent or device for UI, had adopted or changed behavioral management for UI within three months, or had a history of prior continence surgery. After a two week placebo lead in, subjects were randomly assigned to receive placebo (N=138) or duloxetine at one of three doses (20 mg /day {N=138; 20 mg qd}, 40 mg/day {N=137; 20 mg bid}, or 80 mg/day {N=140; 40 mg bid}) for 12 weeks with three follow-up visits at 4 week intervals. Outcome variables included the IEF, recorded prospectively on daily diaries for one week prior to each baseline and treatment visit, the Patient Global Impression Improvement (PGI-I) Scale, and the Incontinence Quality of Life Questionnaire (I-QOL), a 22-item validated questionnaire, which evaluates the effects of UI in three domains (Avoidance and Limiting Behavior, Social Embarrassment, and Psychosocial Impact). [1,2]. Analysis of variance (ANOVA) was used to analyze ranked percent changes in IEF, ranked changes in number of voids, ranked changes in average voiding interval, and changes in I-QOL and its domains. Least Squares means from the ANOVA models were used to compute p-values for comparing each duloxetine arm to placebo. Categorical variables (such as PGI-I) were analyzed using Pearson's Chi-Square test.

Results:

Table 1 lists the results for IEF, I-QOL, and PGI-I. Despite a high placebo response rate, analysis reveals a significant and dose dependent response to duloxetine for IEF which parallels the improvement observed in the I-QOL and PGI-I. Half of subjects at the 80 mg dose level had at least a 64% reduction in IEF while 65% had at least a 50% reduction. The improvement in IEF was observed despite concurrent dose dependent increases in average voiding interval in the duloxetine groups (16, 19, 24 minutes) which were significantly greater than that observed with placebo (7 minutes; $p = 0.004$, <0.001, and <0.001 for 20, 40, and 80 mg duloxetine respectively). Similar improvements were demonstrated in a subgroup of 148 subjects with the

most severe SUI (≥14 IEF/wk; Table 2). Subjects in this subgroup also demonstrated statistically significant improvements in all three domains of the I-QOL at the 80 mg/day dose. Discontinuation rates for adverse events were 5% for placebo, 10% for duloxetine 20 mg, 12% for 40 mg, and 16% for 80 mg (P = 0.04) with nausea being the most common symptom leading to discontinuation.

TABLE 1.

All Subjects	Median Percent Change in IEF (p)	Mean Improvement in I-QOL (p)	**PGI-I Percent "Much" or "Very Much Better" (p)**
Placebo	-41%	5.8	27%
Dulox 20mg	-54% (=0.059)	5.3 (=0.61)	31% (=0.50)
Dulox 40mg	-59% (=0.002)	7.8 (=0.16)	37% (=0.09)
Dulox 80mg	-64% (<0.001)	9.3 (=0.03)	44% (=0.005)

TABLE 2.

Subjects with ≥14 IE/wk at baseline	Median Percent Change in IEF (p)	Mean Improvement in I-QOL (p)	**PGI-I Percent "Much" or "Very Much Better" (p)**
Placebo	-29%	3.8	26%
Dulox 20mg	-52% (=0.231)	3.4 (=0.95)	23% (=0.73)
Dulox 40mg	-63% (=0.004)	9.4 (=0.071)	39% (=0.26)
Dulox 80mg	-65% (<0.001)	13.4 (=0.005)	48% (=0.06)

Conclusions:

The results of this trial provide further evidence for the efficacy of duloxetine 80 mg/day as a pharmacological agent for the treatment of SUI, with significant improvements demonstrated in both IEF and quality of life. Large scale Phase III clinical trials to further establish efficacy, tolerability, and safety are ongoing.

References:

1 Quality of life of persons with urinary incontinence: development of a new measure. Urology 1996;47:67-72.

2 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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