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DULOXETINE VS. PLACEBO IN THE TREATMENT OF STRESS URINARY INCONTINENCE: A GLOBAL PHASE 3 STUDY

Aims of Study

Duloxetine hydrochloride, a potent and selective inhibitor of serotonin (5-HT) and norepinephrine (NE) reuptake, is thought 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). Trials in North America and Europe have provided evidence for the safety and efficacy of duloxetine as a pharmacological agent for the treatment of stress urinary incontinence (SUI) (2,3). The aim of this study was to assess the efficacy and safety of duloxetine in women with SUI in diverse populations on four continents.

Methods

458 women aged 27-79 were enrolled in this double-blind, placebo-controlled study. The study was conducted at 38 study centres in Argentina, Australia, Brazil, Finland, Poland, South Africa and Spain. The case definition was a predominant symptom of SUI with a weekly incontinence episode frequency (IEF) ≥7, the absence of predominant urge symptoms, normal diurnal and nocturnal frequencies, a bladder capacity ≥400 mL, and both a positive cough and stress pad test. Women on stable pelvic floor muscle training (PFMT) and those with prior continence surgery were not excluded but no new PFMT was introduced. After a 2-week observation period and a 2-week placebo lead in period, subjects were randomly assigned to receive placebo (N=231) or duloxetine 40 mg bid (N=227) for 12 weeks with three follow-up visits at 4-week intervals. Outcome variables included IEF, recorded on real-time 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. Van Elteren'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. The PGI-I, which is a 7-point scale ranging from "very much better" to "very much worse." was analysed using Cochran-Mantel-Haenszel test. The responses "very much better", "much better", and "a little better" (scores 1, 2 and 3) were grouped into a single "better" category. Analyses were performed according to intent-to-treat principles.

Results

The mean baseline IEF was 18.4/wk for assessable subjects; 56% had a baseline IEF ≥14. Overall current use of pelvic floor muscle training (PFMT) was 9.0% (country range 2.6% to 27.3%). There was a significant decrease in IEF with duloxetine compared with placebo with comparable significant improvements in quality of life (table). These improvements with duloxetine were associated with significant increases in voiding intervals compared with placebo (change of 20.4 versus 8.5 min, $p < .001$), were reported within 4 weeks of commencing therapy, and persisted for the duration of therapy. Discontinuation rates for adverse events were 1.7% for placebo and 17.2% for duloxetine ($p < .001$) with nausea being the most common reason for discontinuation (3.1%). Nausea was also the most common adverse event, occurring in 25.1% of duloxetine subjects compared with 3.9% of placebo subjects ($p < .001$). Nausea was mild or moderate in most subjects (80.7%) and did not worsen in any subject. 88% of women who experienced nausea while taking duloxetine completed the trial. 60% of nausea resolved by 7 days, 86% by one month.

	IEF Decrease (all subjects)	IEF Decrease (more severe strata)	I-QOL Improvement	PGI-I "better" categories
Duloxetine	54%	55%	10.3	74%
Placebo	40%	42%	6.4	64%
P	.05	.022	.007	.03

Conclusions

The data demonstrate improvements in incontinence and quality of life with duloxetine that are consistent with those observed in two other phase 3 trials in Europe and North America. The placebo response was over 10% higher in this trial, possibly related to a greater number of treatment naïve subjects, as reflected by a 9% prevalence of current PFMT compared with 19.1% and 17.4% in the other phase 3 trials ($p<.001$).

References

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.

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