337

Bump R[1], Hooper C[1], Koke S[1], Yalcin I[1]
1. Lilly Research Laboratories

WORLDWIDE EFFICACY OF DULOXETINE AFTER 12 WEEKS AND 1 YEAR IN WOMEN WITH STRESS URINARY INCONTINENCE (SUI): A 4-STUDY META-ANALYSIS

Aims of Study

Duloxetine hydrochloride, a potent and balanced inhibitor of serotonin (5-HT) and norepinephrine (NE) reuptake, is believed 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]. The aim of this meta-analysis is to assess combined data from 4 randomized clinical trials examining the efficacy of duloxetine 40 mg bid versus placebo for the treatment of women with SUI.

Methods

1913 women aged 22-83 (mean 52.5) years with predominant SUI were enrolled in one phase 2 and three phase 3 double-blind, randomized, placebo-controlled clinical trials at 186 study sites in Africa, Australia, Europe, North America, and South America. Predominant SUI was diagnosed using a clinical algorithm demonstrated to be 90.2% predictive of urodynamic stress incontinence. Subjects were randomly assigned to receive placebo (n = 955) or duloxetine (n = 958) for 12 weeks. Outcome variables in the double-blind portion of the trial included incontinence episode frequency (IEF), mean time between voids (MTBV) (both calculated from patient-completed real-time paper diaries), the Patient Global Impression of Improvement (PGI-I) Scale rating, and the Incontinence Quality of Life (I-QOL) questionnaire total and three subscale scores. After the 12-week double-blind treatment period, subjects in the three Phase 3 studies entered long-term open-label extension studies, during which efficacy was assessed every three months using the PGI-I rating only. Van Elteren's test was used to analyze the median percent changes in IEF and change in MTBV. Analysis of covariance was used to analyze mean changes in I-QOL scores. The PGI-I was analysed using the Cochran-Mantel-Haenszel test. All analyses were based on Intent-to-Treat principles with every subject who provided any outcome data after randomization included in the analysis.

Results

For assessable subjects, the mean baseline IEF was 16.9/wk; 55% had a weekly IEF $\geq$14. At baseline, 65.9% of randomized subjects rated their incontinence as moderate or severe, 11.3% had undergone prior continence surgery, and 16.0% currently performed pelvic floor muscle training. The data in the table demonstrate that there were significant improvements for duloxetine compared with placebo as measured by median percent decrease in IEF, improvements in I-QOL scores, feeling better on the PGI-I, and increases in MTBV. Women with SUI began to consider themselves better when their decreases in IEF were at least 43.4%, and when their improvements in I-QOL scores were at least 6.4. Duloxetine-associated median reductions in IEF and mean improvements in I-QOL were well above these threshold levels (52% and 9.2 points, respectively) but the changes associated with placebo were not (33% and 5.9 points, respectively). Decreases in IEF and improvements in I-QOL were evident at the first post-randomization visit (4 weeks after randomization) and were maintained throughout the 12 weeks of the double-blind treatment period. In the combined double-blind and open-label PGI-I analysis, 74% of subjects considered themselves better at 3 months, 78% at 6 months, 79% at 9 months, and 82% at 12 months. Improvement rates were better at three months for subjects who first received duloxetine in an open-label extension (79%) compared with those who first received duloxetine in the double-blind study (71%).

	IEF Median Decrease	MTBV Increase	I-QOL Total	I-QOL Subscale (a)	I-QOL Subscale (b)	I-QOL Subscale (c)	PGI-I better
Dulox	52%	18.5 min	+9.2	+9.7	+8.2	+10.3	65%
Placebo	33%	4.3 min	+5.9	+6.4	+4.8	+7.0	50%
P	<.001	<.001	<.001	<.001	<.001	<.001	<.001

(a)Avoidance/Limiting Behavior; (b) Psychological Impact; (c) Social Embarrassment

Conclusions

These meta-analysis results reflect the consistent findings of the individual studies and provide strong evidence for the efficacy of duloxetine in the treatment of women with SUI as determined by outcome variables in several domains. The favorable treatment response with duloxetine was apparent within 4 weeks and was maintained for 3-months in the double-blind trials and for one year in the open-label trials.

Reference

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.