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DULOXETINE TREATMENT OF WOMEN WITH ONLY URODYNAMIC STRESS INCONTINENCE AWAITING CONTINENCE SURGERY

Aims of Study

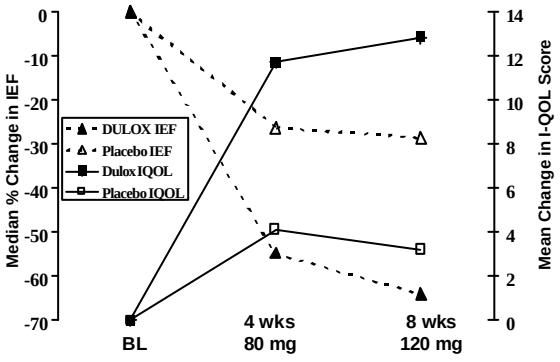
Duloxetine hydrochloride, a potent and selective inhibitor of serotonin (5-HT) and norepinephrine (NE) reuptake, is believed to increase efferent output from Onuf's nucleus via stimulation of pudendal motor neuron alpha-1 adrenergic and 5 HT-2 receptors, resulting in enhanced contractility of the rhabdosphincter [1]. One phase 2 and three phase 3 randomised placebo-controlled clinical trials have demonstrated significant efficacy for duloxetine for women with mild, moderate, and severe stress urinary incontinence (SUI) [2]. The primary aim of this randomised clinical trial was to assess the efficacy of duloxetine in the treatment of women with severe SUI symptoms due to urodynamic stress incontinence only and who were awaiting surgery for SUI.

Methods

109 women aged 33-75 years at 14 clinical centres in Canada (7 centres), the UK (4 centres), the Netherlands (2 centres), and Australia (1 centre), were enrolled into this double-blind, placebo-controlled study. The case definition was a predominant symptom of SUI with a weekly stress incontinence episode frequency (IEF) ≥14, the confirmation of urodynamic stress incontinence only within the 6 months preceding enrolment, the woman's decision to proceed with continence surgery, and the woman's having been scheduled for such surgery. After a 2-week placebo lead-in period, women were randomly assigned to receive placebo (N = 54) or duloxetine 80 mg/day (N = 55; 40 mg bid) for 4 weeks followed by a forced dose escalation to 120 mg/day (60 mg bid) for another 4 weeks. Assessment variables included IEF and continence pad use, both recorded real-time on paper diaries prior to each visit, the Incontinence Quality of Life (I-QOL) questionnaire total and subscale scores, the Patient Global Impression of Improvement (PGI-I) and Severity (PGI-S) ratings, and the Willingness to Consider Surgery (WCS) rating. Van Elteren's test was used to analyze the percent changes in IEF and pad use. Analysis of covariance was used to analyze mean changes in I-QOL scores. The PGI-I and WCS were analysed using the Cochran-Mantel-Haenszel test. All analysis was based on Intent-to-Treat principles.

Results

The mean baseline IEF was 22.3/wk; 89% of women rated their incontinence as moderate or severe. The table lists the changes in IEF, I-QOL total and subscale scores, and pad use by treatment. All variables showed significant improvements with duloxetine compared with placebo. 33.3% of these severely incontinent women taking duloxetine rated themselves as much better or very much better compared with 7.7% of those taking placebo (p = .006). There were some additional improvements in both IEF and I-QOL total score with duloxetine dose escalation (Figure), but the differences between the 40 mg bid and 60 mg bid responses were not statistically significant. Before enrolling in the trial, 39% of women were scheduled for retropubic urethropexies, 13% for slings, 46% for TVTs, and 2% for other procedures. After treatment, 10 of 49 (20%) women who were somewhat or very much not considered surgery before starting duloxetine said they



Changes in IEF and I-QOL by visit, duloxetine versus placebo; duloxetine dose was 40 mg twice daily at 4 weeks and 60 mg twice daily at 8 weeks.

interested in surgery after taking duloxetine, compared with none of 45 after taking placebo (p =.001). Side effects were more common with duloxetine and the profile was compatible with that described in previous larger studies. Most side effects had their onset prior to the duloxetine dose escalation.

	Median Weekly IEF Decrease	I-QOL Score Improvements				Median Weekly Pad Decrease
		Total	Social Embarrassment Subscale	Avoidance & Limiting Behavior Subscale	Psychosocial Impact Subscale	
Placebo	27%	2.4	3.6	2.0	2.1	4.8%
Duloxetine	60%	10.6	11.5	10.1	10.6	34.5%
p-value	<.001	.003	.008	.01	.002	.008

Conclusions

This study provides evidence for the efficacy of duloxetine in women with severe SUI due to urodynamic stress incontinence who have decided to proceed with continence surgery. The data suggest that some women may reconsider proceeding with their scheduled surgery after treatment with duloxetine. Increasing the duloxetine dose from 80- to 120-mg per day did not have a significant impact on either the efficacy or side effect profile of duloxetine, although some additional efficacy was observed.

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 for stress urinary incontinence: meta-analysis of worldwide efficacy. Presented at the Society for Urodynamics and Female Urology meeting, Chicago, April 2003