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DULOXETINE COMPARED WITH PLACEBO FOR THE TREATMENT OF WOMEN WITH SYMPTOMS OF BLADDER OVERACTIVITY

Hypothesis / aims of study

Duloxetine, a serotonin-noradrenalin reuptake inhibitor (SNRI), has been shown to significantly increase bladder capacity and sphincter tone without interfering with normal micturition in animal models. The mechanisms of action for these effects seem to be both central sensory afferent and central motor efferent modulation [1]. To date, duloxetine has demonstrated significant efficacy in 6 published randomized clinical trials enrolling women with predominant stress urinary incontinence (SUI). The aim of this study was to evaluate the efficacy and safety of duloxetine in the treatment of women with symptoms of bladder overactivity.

Study design, materials and methods

306 women, 21 to 84 years of age, were recruited at 30 continence centres in Australia, Canada, and the US and randomly assigned to placebo (N=153) or duloxetine (N=153) in this double-blind, placebo-controlled trial, conducted in accordance with CONSORT guidelines. Symptoms of overactive bladder were defined as either bothersome urinary urgency and/or urge urinary incontinence (UUI) for a minimum of 3 months prior to study entry. In addition, participants were required to have 1) an average, documented voiding interval of $\leq$2 hours during waking hours and, during multichannel urodynamic testing performed before randomisation, 2) no stress incontinence and 3) either detrusor overactivity or urgency forcing cessation of bladder filling at a bladder capacity of <400 mL. Following a 2-week blinded placebo lead-in, patients were randomized to duloxetine (40-mg twice daily for, escalated to 60-mg twice daily after 4 weeks) or placebo for 12 weeks. The main outcome measure was mean change from baseline to endpoint in the average number of micturition episodes (ME) per 24 hours, recorded on paper diaries. Secondary outcomes were changes in the number of incontinence episodes (IE) per 24 hours, in the Incontinence Quality of Life questionnaire (I-QOL) total and subscale scores, and in the daytime mean time between voids (MTBV). Overall improvement was also compared using the Patient Global Impression of Improvement (PGI-I) rating. Safety was assessed with vital signs, adverse event reporting, routine laboratory testing, ECGs, and the measurement of post-void residual urine volumes (PVR). The sample size provided 80% power for detecting an effect size of .33 in the mean change of number of micturitions per day (based on the effect size with anticholinergic agents) using a two-sided, .05 level t-test. The primary analyses of quantitative data used the Wilcoxon-Mann-Whitney Test; secondary analyses used an ANCOVA model. Categorical data were analyzed using the Cochran-Mantel-Haenszel statistic or Fisher exact test.

Results

EFFICACY: Patients randomized to duloxetine demonstrated significant improvements compared with patients randomized to placebo for decreases in micturition and incontinence episodes, for increases in the daytime MTBV, and for improvements in I-QOL scores (Table). The changes in urinary diary parameters were significant when patients were taking 80- and 120-mg of duloxetine per day. Similarly, duloxetine patients were more likely to consider themselves improved based on their PGI-I ratings at both doses (60% versus 43%, p = .005; and 62% versus 42%, p = .008 respectively). Treatment differences in improvements in I-QOL subscale scores were significant for the Avoidance and Limiting Behaviour and Psychosocial Impact subscales, but not for the Social Embarrassment subscale.

SAFETY: Treatment-emergent adverse events (TEAEs) were reported more commonly by duloxetine-treated than placebo-treated patients (79.1% versus 55.6%, p<.001). The most common TEAEs with duloxetine (nausea, dry mouth, dizziness, constipation, insomnia and fatigue) were the same as those reported by women with SUI. Most TEAEs were mild or moderate and nonprogressive in severity, occurred early and resolved within a month and did not tend to recur when the dose of duloxetine was escalated. Laboratory assessments, vital signs, and ECGs were stable relative to baseline and no clinically relevant differences were detected between groups. There was a significant difference in the change in PVR volumes with duloxetine (<5 mL mean change; Table) but no patient reported or discontinued due to hesitancy or retention.

Variable	Group	Baseline Value	Change at 80 mg/day	p-value	Change at 120 mg/day	p-value
Number ME	Dulox	10.76	-1.49	<.001	-1.90	<.001
	Pbo	10.49	-0.43		-0.82	
Daytime MTBV (minutes)	Dulox	113.6	+22.1	<.001		<.001
	Pbo	119.6	+2.8			
IE/24 hours	Dulox	1.70	-0.66	<.001	-0.87	=.002
	Pbo	1.44	-0.04		-0.18	
Variable	Group	Baseline	Change at endpoint	p-value		
I-QOL Score	Dulox	56.65	+8.37	=.035		
	Pbo	57.11	+4.87			
PVR (mL)	Dulox	18.40	+4.34	=.029		
	Pbo	17.56	-1.21			

Interpretation of results

In this trial, duloxetine was superior to placebo in the treatment of women with wet and dry symptoms of bladder overactivity associated with detrusor overactivity or a bladder capacity <400 mL. It is unlikely that these benefits resulted from the treatment of unrecognized SUI since patients with urodynamic stress incontinence were excluded.

Concluding message

Given the different central mode of action of SNRIs, Duloxetine could prove to be an effective alternative pharmacological platform to the antimuscarinic platform for the treatment of women with symptoms of bladder overactivity.

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CLINICAL TRIAL REGISTRATION: **Because the last patient visit was 9 Sept 2003 and pre-posting was not required unless LPV was after 13 Sept 2005, the trial was not pre-posted. Results will be posted in www.lillytrials.com (5308) after publication.**

HUMAN SUBJECTS: **This study was approved by the Approved by Ethics Committees at 34 study sites in Australia, UK and US and followed the Declaration of Helsinki Informed consent was obtained from the patients.**