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BIOMECHANICAL AND ELECTROPHYSIOLOGICAL EFFECTS OF DULOXETINE IN WOMEN WITH STRESS URINARY INCONTINENCE

Hypothesis / aims of study
Duloxetine, a serotonin (5HT) and norepinephrine (NE) reuptake inhibitor, has been demonstrated to enhance striated urethral sphincter activity via stimulation of 5HT and NE receptors in the sacral cord pudendal motor nucleus during the filling phase in the cat. This action is the hypothesized mechanism by which duloxetine effects significant improvement in stress urinary incontinence (SUI) in women [1-4]. Our objective was to examine the effects of duloxetine on biomechanical and electrophysiological measures of urethral and bladder function in women with SUI.

Study design, materials and methods
Sixty-five women aged 22-73 years with urodynamic SUI, normal bladder compliance, and no detrusor overactivity were randomized at 8 study sites to receive placebo (31) or duloxetine (34) 40-mg twice daily for 4 weeks in this double blind study. After 4 weeks, all subjects were allowed to take duloxetine in an open-label extension to the study. The following assessments were made at 4 weeks and at 7 months: 1) Urethral Biomechanical (all sites): Valsalva Leak Point Pressure (VLPP); maximum urethral closure pressure (MUCP) from resting, Kegel, and Valsalva urethral pressure profiles (UPPs); and pressure transmission ratios (PTR) from cough UPPs. 2) Bladder Biomechanical (all sites): emptying function was evaluated with simple uroflowmetry and pressure-flow studies. 3) Urethral Electrophysiological (9 subjects, 1 site): peak-to-peak amplitude, mean rectified voltage (MRV), and root mean square voltage (RMS) at rest and with coughing, and multi-motor unit potential (MUP) analysis of resting continuous activity from urethral concentric needle EMG; three sacral reflexes, and a continence reflex study of coordination of sphincter and pelvic floor muscle activity.

Results
At 4 weeks, there was a numerical advantage for duloxetine over placebo for all five biomechanical urethral measurements but these differences did not attain statistical significance due to the small proportion of the study population that completed all testing. However, the consistency of the findings across all parameters supports a positive and clinically important impact of duloxetine on urethral closure function. A post-hoc analysis of all VLPP data revealed a clinically relevant and statistically significant superiority of duloxetine compared with placebo (duloxetine mean baseline VLPP 79.9 cm water, endpoint 95.0; placebo baseline 98.0, endpoint 81.9, $p = .006$). Analysis of uroflow data showed that duloxetine did not affect emptying phase function. For duloxetine responders, there were important increases in the electrical activity of the rhabdosphincter at rest and with coughing. A dramatic five-fold increase in cough activity observed in one duloxetine subject after 7 months of treatment suggested progressive enhancement of rhabdosphincter motor unit activity with chronic duloxetine use. EMG changes in six placebo subjects were random and unrelated to their responder status. Duloxetine was significantly superior to placebo as measured by percent change in weekly incontinence episodes, patient perceived improvement measured with a global rating scale, increases in the time between voids, and decreases in the number of continence pads used.

Interpretation of results
This study has generated data to support the hypothesis that duloxetine achieves its significant clinical benefits in women with SUI by improving urethral closure during the filling phase (especially during physical stress and with a pelvic floor muscle contraction) while

increasing the quantitative electromyographic activity of the striated urethral sphincter. The data also provide evidence that duloxetine has no measurable effect on lower urinary tract function during the emptying phase. These observations are compatible with those made with duloxetine in the *in vivo* cat animal model and provide evidence that the mode of action hypothesized using this model is applicable to women. The overall efficacy profile was consistent with that established in previous clinical trials that have enrolled over 1000 duloxetine-treated subjects and 1000 placebo-treated subjects.

Concluding message

The data from this study support the hypothesis that duloxetine improves SUI in women by enhancing urethral closure and electrical activity of the striated urethral sphincter.

References

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