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DULOXETINE FOR STRESS URINARY INCONTINENCE: A META-ANALYSIS OF SAFETY

Aims of Study

Duloxetine is a serotonin/norepinephrine reuptake inhibitor with demonstrated efficacy and safety in the treatment of stress urinary incontinence (SUI) {1,2}. This meta-analysis assesses combined data from 4 double-blind studies examining the safety 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, placebo-controlled studies performed in 16 countries in Africa, Australia, Europe, and North and South America. SUI was diagnosed using a clinical algorithm demonstrated to be 90.2% predictive for urodynamic stress incontinence. Subjects were randomly assigned to receive placebo (n = 955) or duloxetine (n = 958) for 12 weeks. Safety was assessed by the evaluation of treatment-emergent adverse events (TEAE), discontinuations for adverse events, vital signs, ECGs, and laboratory tests. TEAEs were elicited by non-probing inquiry and were recorded regardless of perceived causality. An event was considered treatment-emergent if it occurred for the first time or worsened during the double-blind treatment period.

Results

Nausea, dry mouth, fatigue, insomnia, constipation, headache, dizziness, somnolence, and diarrhea were significantly more common with duloxetine compared with placebo and occurred in at least 5% of subjects on duloxetine. Although nausea was the most common side effect (23.2%), it typically occurred within a few days of starting duloxetine (64% within 2 days, 94% within 4 weeks) and was mild or moderate in severity (82% was mild or moderate at onset; severity worsened in only 1 of 181 subjects). 80% of subjects who experienced nausea completed the study; 52% reported resolution of the nausea within one week (81% within one month). The discontinuation rate due to adverse events was significantly higher for duloxetine than for placebo (20.5% vs 3.9%, $p < .001$). Nausea, dizziness, insomnia, fatigue, and somnolence had a ≥1% discontinuation rate for duloxetine and were significantly more common with duloxetine compared with placebo. There was no difference in the incidence of sustained hypertension between the duloxetine-treated (0.2%) and placebo-treated groups (0.7%). A comprehensive analysis of corrected QT intervals revealed no arrhythmogenic tendencies with duloxetine. There were increases, within the normal range, in the duloxetine group compared with the placebo group for several hepatic enzymes, probably indicating transient enzyme induction. Significant individual elevations of hepatic enzymes were rare and transient, indicating an idiosyncratic response and not intrinsic hepatotoxicity or severe liver damage. 18 subjects (1.9%) in the duloxetine group reported 30 serious adverse events (SAEs) compared with 10 subjects (1.0%) in the placebo group who reported 13 SAEs. This difference was not statistically significant (p=.182). There was a single death reported; a 70 year-old woman randomized to duloxetine 40 mg bid died from a multifocal cerebrovascular accident not attributed to duloxetine.

Conclusions

This meta-analysis showed that duloxetine was safe and well-tolerated at a dose of 40 mg bid. The most commonly reported side effects were consistent with the known pharmacology of the molecule, namely, its principal action on both serotonergic and noradrenergic neurotransmission. In general, side effects were mild to moderate, occurred early, and were non-progressive and transient.

References

1. Duloxetine versus placebo in the treatment of stress urinary incontinence (SUI). Neurourology and Urodynamics 2002;21(4):383-4.

2. Duloxetine vs. placebo in the treatment of European and Canadian women with stress urinary incontinence. Oral Presentation, EAU, March 12-15, 2003, Madrid.