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WHEN DOES A DECREASE IN STRESS INCONTINENCE EPISODE FREQUENCY BECOME CLINICALLY IMPORTANT: THE PLACEBO RESPONSE IN PERSPECTIVE

Hypothesis / aims of study

Recent randomized, placebo-controlled duloxetine clinical trials enrolling women with stress urinary incontinence (SUI) report high but variable placebo responses, with placebo-associated decreases in incontinence episode frequency (IEF) of 27% to 40%. While mild incontinence and no prior incontinence treatment (that is no prior surgery or pelvic floor muscle training) increase the placebo response, the clinical importance of the observed range of placebo responses is unclear [1]. We hypothesized that these average changes in IEF reported by placebo-treated patients were not perceived as important by the patients. The aim of this analysis was to evaluate the clinical relevance of this range of placebo IEF responses by examining the relationship between the range of IEF improvements and parallel improvements in condition-specific quality-of-life using the validated Incontinence Quality of Life (I-QOL) questionnaire.

Study design, materials and methods

1913 women with SUI in Africa, Australia, Europe, and North and South America, were enrolled in 4 ethical committee approved, randomized, controlled 12-week trials comparing duloxetine 80 mg/day and placebo. The primary results of these studies have been published previously. Subjects completed 7-day urinary diaries before each baseline and treatment visit and I-QOL questionnaires at each of these visits. The percent change in IEF from baseline to endpoint was calculated from the diaries for all subjects regardless of their treatment assignment. The decreases in IEF were grouped by decile (for example $\leq$10%, >10% to $\leq$20%, >20% to $\leq$30%, etc.). Then, the mean change in I-QOL scores for the subjects in each decile was calculated. The clinical importance of the various levels of IEF improvement was assessed using the minimal clinically important difference (MCID) values established for I-QOL [2]. A within-group MCID was defined as the minimum improvement in mean I-QOL score required within a single group of subjects to be regarded clinically important. A between-group MCID was defined as the minimum difference in I-QOL scores required between two groups to be regarded as clinically important. The within- and between- group MCIDs for I-QOL have been determined to be 6.3 and 2.5 points, respectively [2]. In our assessment, we assumed that an IEF improvement level was important (had an important impact on quality of life as perceived by the patient) only when the mean I-QOL for that decile exceeded the within-group MCID of 6.3 points. We also considered that two IEF decile improvement levels were importantly different clinically only when the difference in mean I-QOL scores between the two deciles exceeded the between-group MCID of 2.5 points.

Results

The table compares the percent decrease in IEF by decile to improvements in I-QOL scores. It demonstrates that improvements in condition-specific quality-of-life are not clinically important until a 40 to 50% reduction in IEF is reached (decile 5). This is the first level of improvement at which the within-treatment MCID is exceeded and the first level of improvement that demonstrates a difference from the preceding level that exceeded the between-treatment MCID. The I-QOL improvements at all IEF reduction levels up to and including a 40% IEF reduction are essentially the same. The I-QOL differences between deciles 7 and 8 and deciles 8 and 10 were also judged clinically important because they exceeded the between treatment MCID value of 2.5.

Upper limit of IEF decrease decile	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Mean I-QOL increase	5.1	5.0	4.7	4.5	8.7*	8.8	8.5	13.2	15.3	16.7
Change from prior decile		-0.1	-0.3	-0.2	4.2#	0.1	-0.3	4.7#	2.1~	1.4~

*First decile to exceed within-treatment MCID of 6.3; #Difference in score from prior decile exceeds between-treatment MCID of 2.5; ~Total difference from decile 8 to 10 exceeds between treatment MCID

Interpretation of results

Clinically important thresholds for decreases in IEF appear to be around 50%, 80%, and 100%. Within the observed range of placebo IEF responses (27% to 40%) in women with SUI enrolled in duloxetine controlled clinical trials, the impact on condition-specific quality-of-life is not clinically important and does not differ across the range.

Concluding message

While the placebo reduction in incontinence episode frequency in these randomized controlled trials may seem appreciable and high to clinicians, they were not perceived as impactful or important by patients.

1. The effect of prior treatment experience and incontinence severity on the placebo response of stress urinary incontinence. Am J Obstet Gynecol 2004;191:194-7
2. The minimum clinically important difference in Incontinence Quality of Life Questionnaire (I-QOL) total and subscale scores in women with stress urinary incontinence. Neurouol Urodynam 2004;23:568-70

FUNDING: Eli Lilly and Company and Boehringer Ingelheim