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INTERACTION BETWEEN PLACEBO RESPONSE AND SUBJECTS' DECISION TO DOSE ESCALATE IN A TRIAL OF FLEXIBLE-DOSE ANTIMUSCARINIC TREATMENT FOR OVERACTIVE BLADDER SYMPTOMS

Hypothesis / aims of study

Substantial placebo (PBO) responses are commonly reported and are of increasing concern in clinical trials evaluating the efficacy and safety of fixed-dose antimuscarinic treatment for overactive bladder (OAB) symptoms. However, little is known regarding the extent and potential differences in placebo response in flexible-dose trials of antimuscarinic treatment for OAB symptoms. In such trials, subjects who are randomized to placebo can "elect" sham dose escalation (PBO escalators [PBO+E]) or maintain initial dosing (PBO nonescalators [PBO–NE]). Identifying the differences in responses between PBO+E and PBO–NE groups, and understanding the reasons for these differences, is critical for an accurate interpretation of study outcomes in the active-treatment arm in flexible-dose trials. In this post hoc analysis, we compared PBO responses in PBO+E and PBO–NE groups from a large, double-blind, flexible-dose trial [1].

Study design, materials and methods

We assessed placebo data from a randomized, double-blind, 12-week, placebo-controlled, flexible-dose fesoterodine study that enrolled subjects with OAB symptoms (1). At week 2, subjects chose to maintain initial dosing or increase to a higher dose (sham escalation for PBO group). Subjects completed 3-day bladder diaries, the Patient Perception of Bladder Condition (PPBC), and Urgency Perception Scale (UPS) at baseline and weeks 2 and 12. Subjects who discontinued the study before the week 2 visit and provided no post-baseline efficacy data were excluded from this analysis. Statistical comparisons between PBO+E and PBO–NE groups in diary variable and patient-reported outcomes (PROs) were conducted using an ANCOVA model (diary variables) or Cochran-Mantel-Haenszel test (PROs); $P<0.05$ was considered significant. Adverse events were monitored throughout the study.

Results

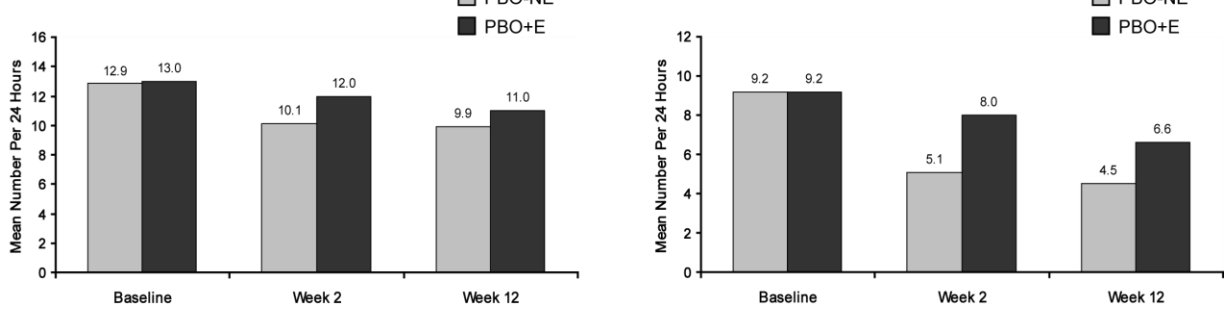
Of the 435 PBO subjects who continued to the week 2 visit, 325 (74.7%) opted for dose escalation. Mean values for bladder diary variables at baseline, week 2, and week 12 visits are shown in the **Figure**. Subjects in the PBO+E group appeared to have marginally more severe OAB symptoms and greater OAB symptom bother than subjects in the PBO–NE group at baseline, although these differences were generally not statistically significant ($P<0.05$ for UPS only). During the 2-week period preceding dose escalation, subjects in the PBO–NE group demonstrated statistically significantly greater LS mean improvement in micturitions/24 h (–2.9 vs –0.9; $P<0.0001$), urgency episodes/24 h (–4.2 vs –1.1; $P<0.0001$), and severe urgency episodes (–3.0 vs –1.2; $P<0.0001$) compared with subjects in the PBO+E group; furthermore, a greater percentage of subjects in the PBO–NE group showed improvement on the PPBC (64% vs 42%; $P=0.0003$) during the initial 2-week period. There was no significant difference between groups for the additional improvements in diary variables or PROs that occurred between weeks 2 and 12, though improvements in these outcomes were generally numerically greater in the PBO+E group. Across the overall study period (baseline to week 12), LS mean improvements in study outcomes were statistically significantly greater in the PBO–NE group for micturitions/24 h (–3.0 vs –2.0; $P=0.0016$), urgency episodes/24 h (–4.8 vs –2.5; $P<0.0001$), severe urgency episodes (–3.2 vs –2.1; $P=0.0038$), and PPBC score (74% vs 55% of subjects; $P=0.0021$). Improvements in urinary urgency incontinence episodes/24 h and UPS score during the initial 2-week period and overall 12-week period were numerically but not statistically significantly greater in the PBO–NE group. Rates of dry mouth (10% vs 7%), constipation (8% vs 5%), and study discontinuations resulting from any treatment-emergent adverse event (10% vs 3%) were higher in the PBO–NE group.

Interpretation of results

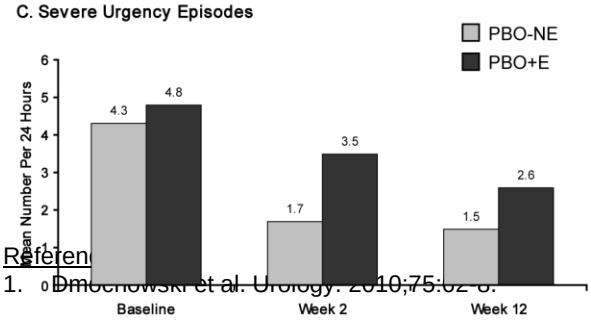
This analysis suggests that for an individual with OAB symptoms, the decision of whether to dose escalate may be driven by the magnitude of their PBO response, with a larger placebo response (as assessed via efficacy and safety endpoints) more likely corresponding with the decision to maintain (not escalate) treatment dosing. This is an important consideration in the analysis of the active agent, for which placebo is the primary comparator.

Concluding message

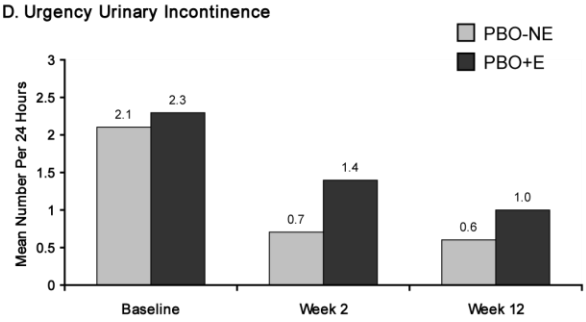
This is the first analysis of placebo response in trials evaluating flexible-dose antimuscarinic treatment for OAB symptoms. Our results suggest that there may be important differences between PBO–NE and PBO+E subjects, and that the decision of whether to dose escalate may be driven by the magnitude of the placebo response, a combination of placebo pharmacology and trial-induced behavioral changes. Most importantly, these data suggest that pooling PBO–NE and PBO+E data for comparison with dose-stratified active-treatment data may result in an underestimation of treatment response in subjects electing antimuscarinic dose escalation and overestimation of treatment response in subjects electing to maintain initial antimuscarinic dosing.



C. Severe Urgency Episodes



D. Urgency Urinary Incontinence



Note: Baseline means represent subjects with data at baseline and week 2.

References

1. Dmochowski et al. Urology. 2010;75:62-8.

Specify source of funding or grant	**Pfizer Inc**
Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**Yes**
Specify Name of Public Registry, Registration Number	**Clinicaltrials.gov** **NCT00536484**
Is this a Randomised Controlled Trial (RCT)?	**Yes**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Schulman Associates IRB, Inc.** **Human Investigation Committee** **Western Institutional Review Board** **Institutional Review Board of Human Research**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**