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Khusid J A[1], Weiss J P[1], Carlsson M[2], Mangan E[2]
1. *SUNY Downstate College of Medicine,* ***2.*** *Pfizer Inc.*

FESOTERODINE FOR THE TREATMENT OF NOCTURNAL URGENCY IN PATIENTS WITH OVERACTIVE BLADDER SYNDROME: AN ANALYSIS OF RESPONDERS AND NON-RESPONDERS

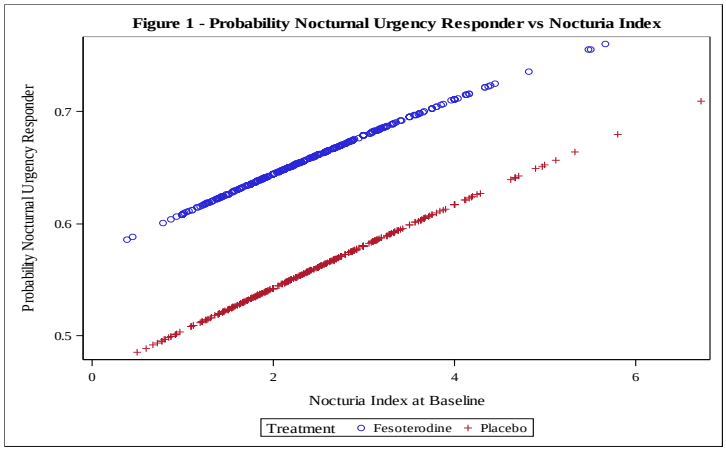
Hypothesis / aims of study
The International Continence Society (ICS) defines overactive bladder (OAB) as a syndrome consisting of "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency incontinence, in the absence of urinary tract infection or other obvious pathology [1].” Nocturnal urgency is a specific subset of urinary urgency occurring during the hours of sleep which plays a role in the genesis of nocturia, which is defined by the ICS as “the complaint of interruption of sleep one or more times because of the need to micturate, [with] each void preceded and followed by sleep [1].” A prior study demonstrated a statistically significant reduction in nocturnal urgency episodes in patients treated with the antimuscarinic medication fesoterodine (feso) as compared with placebo [2]. The purpose of the current study is to conduct a secondary analysis of this clinical trial data set to determine which nocturnal bladder indices derived from patient diary data inform and predict differences between responders and non-responders to both feso and placebo as well as to determine the mechanism by which pharmacotherapy may impact nocturnal urgency as a cause of nocturia.

Study design, materials and methods
Subjects with ≥2 but ≤8 nocturnal urgency episodes/24 hours began a 2-week, single-blind, placebo run-in, followed by 1:1 randomization to 12 weeks of double-blind treatment with fesoterodine (4 mg/day for 4 weeks with optional increase to 8 mg) or placebo using predefined criteria for nocturnal urgency episodes, nocturnal urine volume voided, and total 24-hour urine volume voided. The primary endpoint was the change from baseline to week 12 in mean number of micturition-related nocturnal urgency episodes/24 hours. Sample size calculation was performed using a t-test two-sided test at level = 0.05. Based on the primary end point, 426 subjects per treatment arm were required to achieve 80% power to detect a difference between treatments. Analyses were based on the full analysis set (i.e., all subjects who took ≥1 dose of study drug and had at least a baseline and a post-baseline efficacy assessment). Missing data were imputed using the last-observation-carried-forward method. Patients were stratified into two groups: those who experienced a decrease of at least one nocturnal urgency void per 24 hours “responders” and all others, considered “non-responders”. Descriptive summary statistics for change from baseline to week 12 of maximum voided volume (MVV), nocturnal bladder capacity (NBC), nocturnal bladder capacity index (NBCi), nocturnal urine volume (NUV), nocturia index (NUV/MVV, Ni), nocturnal polyuria index and (NUV/24 hour volume, NPi) in responders and non-responders at baseline and at week 12 was performed. A paired t-test was applied to each of the parameters for responders and non-responders, separately. Additionally, a logistic regression analysis relating the above variables, when collected at baseline, to responder status was performed.

Results
The probability of being a nocturnal urgency responder increases linearly with both NBCi and Ni (Figures 1,2). Additionally, we observed that responders had a significant decrease in NUV relative to baseline whereas non-responders did not (-181.7mL [p<0.01] vs. +11.4mL [p=0.55] respectively, Table). While there was no significant change in overall bladder capacity (MVV) relative to baseline of responders or non-responders (-6.2 mL [p=0.24] vs. -1.8 mL [p=0.78] respectively, Table), responders experienced a significant drop in both NBCi and Ni vs non-responders (-0.82 [p<0.01] vs -0.05 [p=0.43] and -0.61 [p<0.01] vs 0.06 [p=0.35], respectively, Table).

Interpretation of results
The probability of being a responder was greater in patients treated with fesoterodine as compared to placebo. Additionally, responders experienced significant decrease of both NBCi and NUV compared with non-responders. The significant decrease in NBCi amongst responders and lack of significant change in NBC in either group indicates that response is more related to usual as opposed to maximum nocturnal voided volumes. Further, the probability of being a responder was linearly related to baseline NBCi. This data suggests that the patients most likely to be responders are those with small nocturnal voided volumes relative to their bladder capacity (MVV). The significantly increased responder rate in the feso group relative to placebo and the significant difference in NBCi between responders and non-responders suggests that feso may have a role in increasing nocturnal voided volumes.

Concluding message
We conclude that the ideal therapy in treating nocturia in patients with nocturnal urgency secondary to OAB should include strategies to decrease nocturnal urgency and nocturnal urine production, and increase nocturnal bladder capacity. Anticholinergic medications such as feso may have a role in increasing nocturnal bladder capacity in such patients.



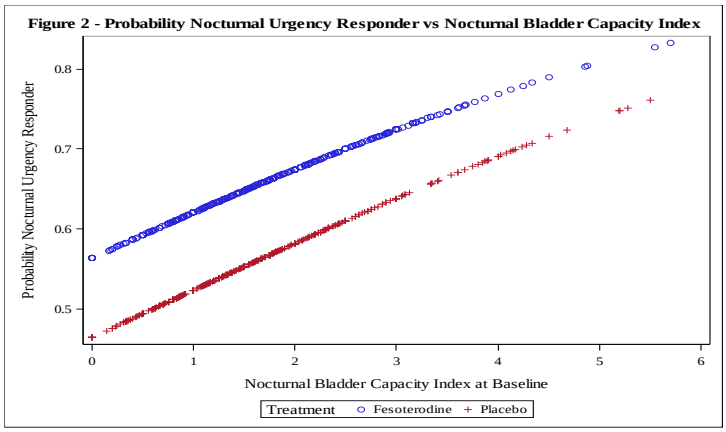


Table: Change in FVC Parameters at Week 12 Relative to Baseline				
Variable	**Mean Responder Baseline Value**	**Mean Non-Responder Baseline Value**	**Mean Responder Change in Value (p-value)**	**Mean Non-Responder Change in Value (p-value)**
MVV (mL)	290.56	295.54	-6.26 (0.24)	-1.80 (0.78)
NBC (mL)	248.50	264.75	+3.91(0.47)	-5.12 (0.49)
NBCi	1.75	1.53	-0.82 (<0.01)	-0.05 (0.43)
NUV (mL)	666.57	668.70	-181.67 (<0.01)	+11.41 (0.55)
Ni	2.46	2.36	-0.61 (<0.01)	+0.06 (0.35)
NPi	0.34	0.33	-0.02 (<0.01)	+0.02 (<0.05)

References

1. Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn. 2010;29(1):4-20.
2. Efficacy and safety of flexible dose fesoterodine in men and women with overactive bladder symptoms including nocturnal urinary urgency. J Urol. 2013;189(4):1396-401.

Disclosures

Funding: This study was sponsored by Pfizer Inc. **Clinical Trial:** Yes **Registration Number:** clinicaltrials.gov Registration # NCT00911937 **RCT:** Yes **Subjects:** HUMAN **Ethics Committee:** The study was approved by the appropriate institutional review boards and independent ethics committees and subjects provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guideline on Good Clinical Practice. The central IRB approving the protocol was Schulman Associates Institutional Review Board, Inc. 4290 Glendale-Milford Rd., Cincinnati, OH 45242 **Helsinki:** Yes **Informed Consent:** Yes