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Nocturia, nocturnal incontinence prevalence and response to anticholinergic and behavioral therapy

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Abstract

Objective—To determine whether participants in the Behavior Enhances Drug Reduction of Incontinence (BE-DRI) trial experienced reduction in the frequency of nocturia and/or nocturnal leakage during treatment with antimuscarinic pharmacotherapy with or without additional behavioral therapy.

Methods—We analyzed urinary diary data relating to nocturia and nocturnal incontinence before and after 8 weeks of study treatment in the BE-DRI trial, in which patients were randomly assigned to receive drug therapy with tolterodine tartrate extended-release capsules 4mg alone or in combination with behavioral training. Chi-square tests assessed whether nocturia and nocturnal incontinence prevalence varied by treatment arm and paired t tests assessed the change in mean frequency of nocturia and nocturnal leakage.

Results—Among 305 women, 210 (69%) had an average of at least one nocturia episode at baseline. There were small but statistically significant differences ($p < 0.001$) in mean nocturia frequency and nocturnal incontinence frequency with both treatments after 8 weeks, but no significant difference between study treatment groups.

Conclusion—Among these urge incontinent women, tolterodine with or without supervised behavioral therapy had little impact on either nocturic frequency or nocturnal incontinence.

Summary—In a sample of urge incontinent women, tolterodine with or without supervised behavioral therapy had little impact on either nocturic frequency or nocturnal incontinence.

Keywords

Lower Urinary Tract; Nocturia; Antimuscarinic Therapy; Behavioral Therapy; Urge Incontinence

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Introduction

Nocturia is the complaint of waking at night one or more times to void [1]. The prevalence of nocturia (once nightly) in American adults is 14–28%. [2,3] When nighttime voiding occurs twice or more nightly, quality of life is adversely impacted. [4] Nocturia is associated with sleep interruptions, can cause daytime sleepiness and impaired well-being [5], and is especially troubling in the elderly in whom the risk of injury from falls becomes a serious concern. [6,7] When nocturnal leakage occurs, the need to change pads and/or clothing and bedding is particularly troublesome and disruptive to sleep.

Overactive bladder (OAB) is a common condition characterized by urinary urgency, frequency, nocturia and sometimes urge incontinence. The mainstays of treatment for OAB include behavior modification and anticholinergic medication. Studies have demonstrated efficacy for the treatment of daytime symptoms, however the impact of these treatments on the nocturia component is less well described and there is little evidence to support a robust treatment effect on nocturia symptoms. Only modest improvements in nocturia have been noted during antimuscarinic pharmacotherapy [8] and during behavioral therapy [9] in OAB patients. Certainly the role of antimuscarinic therapy in the treatment of nocturia and nocturnal leakage remains to be established.

The behavior enhances drug reduction of incontinence (BE-DRI) trial was a randomized clinical trial that recruited women with urge incontinence and studied whether initial treatment with a combination of antimuscarinic drug with additional supervised behavioral training, was superior to drug treatment alone in allowing patients to discontinue the drug while sustaining significant long-term reduction of incontinence. [10] In that trial, we found that the addition of behavioral training to drug therapy did not improve women's ability to discontinue drug therapy while maintaining improvement in incontinence [11]. However we did show a beneficial effect of combined therapy on patient satisfaction, perceived improvement, and reduction in bladder symptoms. Outcomes relating to nocturia and nocturnal incontinence episodes were not included in that primary report. The objective of this analysis was to determine whether nocturia and nocturnal leakage severity were affected by treatment with antimuscarinic therapy with or without behavioral therapy in BE-DRI study participants.

Materials and methods

This analysis used data collected during the BE-DRI trial. The design, study methodology, and primary results of the trial, conducted by the Urinary Incontinence Treatment Network, have previously been published. [11] Briefly, the BE-DRI study was a two-stage randomized clinical trial conducted at nine clinical centers. Participants were community-dwelling women with urge urinary incontinence, randomly assigned to receive drug therapy alone or in combination with behavioral training. Drug therapy was open-label and provided free of charge. A permuted-block randomization schedule with stratification by type of incontinence (urge only vs. mixed), number of incontinence episodes per week (7–13 vs. 14+), and clinical site ensured concealment of the allocation sequence.

Drug therapy was with tolterodine tartrate extended-release capsules 4 mg daily. Combination therapy included drug and behavioral intervention that included teaching pelvic floor muscle control and exercises; behavioral strategies to diminish urgency, suppress bladder contractions, and prevent both stress and urge incontinence; timed voiding to increase voiding intervals; and individualized fluid management. During the first stage of the study, participants received 8 weeks of their assigned treatment. During the second

stage, immediately following the first, study interventions were discontinued in both groups. The primary study outcomes were measured 6 months after discontinuation of therapy.

For this analysis, we studied urinary diary records obtained at baseline and at the end of 8 weeks of active therapy. In each 7-day urinary diary, patients recorded every void and every urinary incontinence episode and also indicated the time they went to bed each night and the time they arose every morning. Diaries were considered to be evaluable if at least 5 days were complete. A Nocturia episode was defined as any recorded urinary incontinence episode and/or nighttime void; any accidents and/or voids were counted in this definition, but when incontinence occurred at the time of a recorded void, this episode was counted only once. Review of nighttime diary data indicated that some patients did not record a void when they awoke at night with a urinary incontinence episode, changed their pad and returned to sleep. In order to account for this, we defined nocturnal incontinence episodes as any recorded nighttime void accompanied by an incontinence episode, plus any incontinence episode recorded without an associated void; voids without associated incontinence episodes were not counted in this count. Events that occurred at precisely the same time as wake time or bed time were not considered nocturnal events. Information was averaged over any nights that a respondent recorded this information during the 7-day diary. Having information meant that on a given diary day, the respondent reported both wake and bed times as well as diary information. Of the 307 women randomized to the BE-DRI trial, nearly 70% (213) had usable information from 7 days for nocturnal assessment. Most (96%) had usable information from five or more days.

Frequencies were calculated to estimate the prevalence of nocturia and nocturnal incontinence events at baseline and after 8 weeks of study treatment overall and by treatment arm. These urinary events were presented by categories: an average of 0, > 0–0.99, 1–1.99, 2–2.99 and 3+ events per night. Chi-square tests were used to assess whether the distribution of nocturia and nocturnal incontinence varied by treatment arm.

Frequency of nocturia and nocturnal incontinence were also considered as continuous variables to measure severity. Paired t tests were used to assess the change in the mean number of nocturia and nocturnal incontinence episodes between baseline and the 8 week visit overall and by treatment group. Two sample t tests were used to ascertain whether the change in the mean number of these events from baseline to the 8 week visit differed by treatment group.

Logistic regression modeling was used to calculate the odds of any nocturia or nocturnal incontinence at the 8 week visit based on patient predictors. The nocturia event variable (comparing any nocturia episodes to none) was created by dichotomizing whether or not a woman experienced any nocturia. Similarly, models to calculate the odds of any nocturnal incontinence (comparing any incontinence with zero incontinence) at the 8 week visit were also fit. Each logistic regression model controlled for clinical site and study treatment regardless of significance. Other variables considered included fluid intake, patient reported diagnosis of congestive heart failure, patient reported diagnosis of diabetes, body mass index, age, urge and stress scores from the medical, epidemiological and social aspects of aging (MESA) urinary incontinence questionnaire, [12] and race/ethnicity. To start, each covariate was considered separately in a model controlling for study treatment. Covariates that reached statistical significance ($p < 0.05$) were then considered in multivariable modeling. The final multivariable model included only variables that reached statistical significance ($p < 0.05$) and was evaluated using the Hosmer-Lemeshow goodness of fit test. The final model fit controlling for baseline nocturnal incontinence frequency was also presented. Linear regression models where the mean number of nocturia and nocturnal incontinence episodes were the outcome variables were then fit for comparison.

There was a sizable amount of missing data from the diaries at the 8 week visit. Sensitivity analysis was performed on the final multivariable models where all missing variables were set to having a nocturia episode and vice versa. Similar sensitivity analyses were considered for nocturnal incontinence episodes.

Results

Table 1 details the demographics of this study population. Study groups were similar at baseline with respect to age, race, socioeconomic status, incontinence severity and other important predictor variables. No significant differences existed between the two treatment groups.

As detailed in Table 2, there were 210 (69%) of women who had an average of at least one nocturia episodes per night. Table 3 shows that among 305 women with evaluable diaries at baseline the mean number of nocturia episodes was $1.68 (\pm 1.27)$ with no difference between the two study treatment groups ($p = 0.60$) at baseline. After 8 weeks of treatment, mean nocturic frequency in the drug plus behavioral therapy group was marginally lower than that of the drug-alone group ($p = 0.052$). Sixty-two percent of women had an average of at least 1 nocturia episode per night after treatment. There were significant decreases in mean nocturia episodes between baseline and the 8 week visit for both the drug-only ($p = 0.005$) and the drug-plus ($p < 0.001$) groups. The decrease in nocturic frequency between baseline and the 8 week visit was not significantly different for the drug-plus group compared with the drug-only group ($p = 0.08$).

As detailed in Table 4, the odds of any nocturia at the 8 week visit did not differ by treatment group: OR 1.35 95% CI (0.54, 3.36), $p = 0.52$. None of the covariates considered reached statistical significance after controlling for treatment group and site. The model fit was reasonable (Hosmer-Lemeshow lack of fit test, $p = 0.20$) and conclusions were similar after performing sensitivity analysis. Linear regression models predicting the frequency of nocturia at the 8 week visit were more sensitive and age was found to be a significant covariate. In this linear regression model, the number of nocturia episodes was not found to be statistically significantly decreased for the drug plus compared with the drug only group ($p = 0.074$).

As detailed in Table 5, at baseline only 85 (28%) women experienced no nocturnal incontinence events. Non-significant chi-square tests suggest there was again no significant difference between treatment groups with respect to nocturnal incontinence frequency at baseline or at 8 weeks following trial treatment.

In Table 3, the mean (standard deviation) frequency of nocturnal incontinence at baseline was $0.64 (\pm 0.78)$, range 0 to 4.7. There was little difference in nocturnal incontinence frequency when the two study treatment groups were compared ($p = 0.71$) at baseline. Similarly, after 8 weeks of study treatment, the frequency of nocturnal incontinence was similar for the two treatment groups ($p = 0.47$). However, there were statistically significant decreases in the frequency of nocturnal incontinence between baseline and the 8 week visit for both the drug alone ($p < 0.001$) and the drug-plus ($p < 0.001$) groups. There was no evidence that the decrease in nocturnal incontinence between baseline and the 8 week visit was larger for the drug-plus group compared with the drug-only group ($p = 0.11$).

In a simple logistic regression model controlling only for treatment group and site, the odds of any nocturnal incontinence at the 8 week visit did not differ by treatment group: OR 1.46 (95% CI 0.84, 2.55), $p = 0.18$. Table 6 shows the results of multivariable logistic regression modeling after controlling for treatment group, clinical site and age. The odds of any nocturnal incontinence being present increases nearly twofold for every 10 year increase in

age, while the odds does not vary according to treatment group. When controlling for average nocturnal incontinence frequency at baseline in the same model, the OR (95% CI) for treatment group is 1.68 (0.87, 3.21), $p = 0.12$ and average nocturnal incontinence at baseline is highly predictive ($p < 0.001$) of 8 week nocturnal incontinence. Linear regression models predicting average nocturnal incontinence at the 8 week visit also yielded similar results to the final model. The model fit was reasonable (Hosmer-Lemeshow lack of fit test, $p = 0.73$). Similar conclusions were drawn from the final multivariable model after sensitivity analysis was performed; this confirmed the robustness of the final multivariable model.

When considering the small group of patients that had baseline average nocturic frequency > 2 and/or nocturnal incontinence frequency of > 2 , findings for nocturnal incontinence events and nocturia episodes were similar.

Discussion

Among urinary symptoms reported by aging patients, nocturia is very bothersome and difficult to manage effectively. [13] A variety of etiological factors have been identified to contribute to increased nocturia, including nocturnal polyuria, sleep disturbances, and diminished bladder capacity. [14] Among younger women, lower urinary tract causes may play a larger role than among older women, in whom a relative nighttime polyuria appears to be more prevalent. This reality may underlie the relative lack of success achieved with the use of anti-muscarinic agents for treatment of the nocturia in populations of OAB patients that have not been selected for lower urinary tract causes of nocturia. [15]

The most important finding of the current study was that, among women with urge incontinence, neither treatment with tolterodine alone nor treatment with tolterodine and a regimented program of behavioral and pelvic floor therapy reduced nighttime voids in a clinically meaningful way. Although the reduction from baseline was statistically significant for both groups, patients still were voiding on the average over once per night. Similar to other studies using anti-muscarinic agents alone, the reduction in nighttime voids was rather subtle, [15,16] implying that factors other than OAB may be responsible for nocturnal voids in many women with urge incontinence. Data from some studies suggest that anti-muscarinic agents may offer the most benefit to OAB patients without nocturnal polyuria. [15]

The lack of profound impact of supervised behavioral therapy further supports the idea that, in this group of women with urge incontinence, factors beyond the bladder and pelvic floor may be responsible for nocturic episodes. Our findings are in contrast to those of Johnson et al who studied a slightly more symptomatic group of older women (mean age of 68 years and mean nocturnal voids of 1.9, vs. 56 years and 1.7 voids/night in the current study) and found that behavioral training was superior to both drug treatment (oxybutynin) and placebo. [9] Interestingly they found approximately the same reduction using behavioral therapy alone as we saw in the current study during treatment with behavioral therapy and tolterodine (median reduction of 0.5 per night). They also found results with oxybutynin to be statistically inferior to those of behavioral therapy, somewhat in contrast to our finding that results of treatment with tolterodine alone were similar to results of combined therapy. Participants in the study by Johnson et al started at a relatively low dose of oxybutynin (2.5 mg t.i.d.) and were allowed to self-titrate; it is possible that with maximum anticholinergic dosing the drug treatment arm would have achieved treatment effects similar to the behavioral treatment arm in that study. It is also possible that a sustained release formulation used in this trial may have had different effect on nocturnal symptoms than an immediate release formulation of the drug.

Our analysis has some limitations. The BE-DRI study was not designed to study patients with troublesome nocturia, and so overall the severity of nocturia was mild, limiting our abilities to observe improvements with treatment. It is also possible that among patients with unknown or suboptimally controlled concomitant medical conditions such as diabetes or congestive heart failure might have affected some patients' ability to respond to therapy.

In summary, among women with urge incontinence but relatively little nocturia, tolterodine with or without supervised behavioral therapy did not dramatically reduce nocturnal incontinence events. It is certainly possible that among a more symptomatic group of women either therapy alone or in combination would have a more profound impact. Our data suggest that factors beyond the bladder and pelvic floor contribute to the modest levels of nocturia reported by patients enrolled in BE-DRI.

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Table 1

Characteristics of BEDRI study participants (n = 307) by treatment group. Treatment groups were similar with regard to all demographic variables at baseline.

Characteristic	Combined (n = 154)	Drug Only (n = 153)
Age (mean (SD))	55.8 (14.2)	58.0 (13.5)
Racial group (n, (%))		
Hispanic	13 (9)	17 (11)
Non-Hispanic White	105 (69)	85 (56)
Non-Hispanic Black	22 (14)	35 (23)
Non-Hispanic Other	13 (9)	15 (10)
Level of Education (n, (%))		
High School or less	40 (26)	31 (20)
Some College/Associate Degree	58 (38)	60 (39)
Completed 4 Years of College	32 (21)	40 (26)
Graduate/Professional Degree	24 (16)	22 (14)
Occupation Status (Nam Powers) (mean (SD))	57.5 (23.3)	64.0 (24.3)
Duration of Urge Urinary Incontinence in years (mean (SD))	9.8 (9.5)	9.1 (10.3)
Previous nonsurgical treatment for Urinary Incontinence (n (%))	59 (38)	46 (30)
Prior Urinary Incontinence surgery (n (%))	19 (12)	22 (14)
Diuretic Use (n (%))	15 (10)	14 (9)
Diagnosis of Diabetes Mellitus (n (%))	19 (12)	20 (13)
BMI (mean (SD))	33.2 (9.5)	32.3 (7.6)
Fluid intake (average volume in oz per diary day)	64.0 (28.5)	67.3 (27.9)
Urge symptom score (MESA)	11.3 (3.5)	10.8 (3.2)
Stress symptom score (MESA)	11.0 (6.3)	10.3 (6.0)

Table 2a

Nocturic frequency at baseline and after 8 weeks of study treatment, according to study groups. Study groups were statistically similar with respect to nocturic frequency (chi-square test, baseline: $p = 0.39$, after 8 weeks of study treatment: $p = 0.66$). Figures represent number of patients (%).

Mean number of nocturia episodes	Drug-only cohort (N = 153)				Drug plus behavioral therapy cohort (N = 154)				Total (N = 307)	
	Baseline	After 8 Weeks	Study	Treatment	Baseline	After 8 Weeks	Study	Treatment	Baseline	After 8 Weeks
0	8 (5%)	9 (6%)			5 (3%)	12 (8%)			13 (4%)	21 (7%)
> 0-0.99	36 (24%)	42 (27%)			46 (30%)	41 (27%)			82 (27%)	83 (27%)
1-1.99	56 (37%)	54 (35%)			45 (29%)	55 (36%)			101 (33%)	109 (36%)
2-2.99	32 (21%)	18 (12%)			33 (21%)	19 (12%)			65 (21%)	37 (12%)
3+	21 (14%)	14 (9%)			23 (15%)	7 (5%)			44 (14%)	21 (7%)
Missing	0 (0%)	16 (10%)			2 (1%)	20 (13%)			2 (< 1%)	36 (12%)

Table 3

Nocturic frequency according to study group, at the end of 8 weeks of active treatment and before discontinuation of drug therapy.

	Drug alone	Drug plus behavioral therapy	Total	p-value
Nocturia episodes				
Mean (SD) number at baseline	1.72 (1.31) (n = 153)	1.64 (1.24) (n = 152)	1.68 (1.27) (n = 305)	0.60 *
Mean (SD) after 8 weeks study treatment	1.45 (1.22) (n = 137)	1.19 (0.95) (n = 134)	1.32 (1.10) (n = 271)	0.052 *
Mean (SD) difference between baseline and 8 weeks	0.28 (1.15) (n = 137)	0.51 (1.01) (n = 132)	0.39 (1.09) (n = 269)	0.08 *
	P = 0.005 **	P < 0.001 **		
Nocturnal incontinence episodes				
Mean (SD) number at baseline	0.62 (0.79) (n = 153)	0.65 (0.78) (n = 152)	0.64 (0.78) (n = 305)	0.71 *
Mean (SD) after 8 weeks study treatment	0.37 (0.57) (n = 113)	0.31 (0.48) (n = 105)	0.34 (0.53) (n = 218)	0.47 *
Mean (SD) difference between baseline and 8 weeks	0.26 (0.80) (n = 113)	0.43 (0.73) (n = 104)	0.34 (0.77) (n = 217)	0.11 *
	P < 0.001 **	P < 0.001 **		

* P-value is from testing whether the drug-alone group has the same mean number of episodes as the drug-plus group.

** P-value is from testing whether the mean number of episodes differs between baseline and 8 weeks for each treatment group.

Table 4

Results of a multivariable logistic regression model predicting the odds of any nocturia controlling for clinical site, and treatment group.

Variable	OR (95% CI)	p-value
Clinical site	Not presented	0.74
Treatment group		0.52
Drug-only	1.35 (0.54, 3.36)	
Drugplus behavioral therapy	1 Reference	

Table 5

Nocturnal incontinence frequency at baseline and after 8 weeks of study treatment, according to study groups. Study groups were statistically similar with respect to nocturnal incontinence frequency (chi-square test, baseline: $p = 0.73$, after 8 weeks of study treatment: $p = 0.07$). Figures represent number of patients (%).

Mean number of nocturnal incontinence events	Drug-only cohort (N = 153)		Drug plus behavioral therapy cohort (N = 154)		Total (N = 307)	
	Baseline	After 8 Weeks Study Treatment	Baseline	After 8 Weeks Study Treatment	Baseline	After 8 Weeks Study Treatment
0	45 (29%)	55 (36%)	40 (26%)	61 (40%)	85 (28%)	116 (38%)
> 0-0.99	69 (45%)	45 (29%)	70 (45%)	27 (18%)	139 (45%)	72 (23%)
1-1.99	29 (19%)	9 (6%)	29 (19%)	16 (10%)	58 (19%)	25 (8%)
2-2.99	7 (5%)	2 (1%)	10 (6%)	1 (< 1%)	17 (6%)	3 (1%)
3+	3 (2%)	2 (1%)	3 (2%)	0 (0%)	6 (2%)	2 (< 1%)
Missing	0 (0%)	40 (26%)	2 (1%)	49 (32%)	2 (< 1%)	89 (29%)

Table 6

Results of a multivariable logistic regression model predicting the odds of any nocturnal incontinence controlling for clinical site, treatment group and age.

Variable	OR (95% CI)	p-value
Treatment group		0.34
Drug-only	1.33 (0.74, 2.41)	
Drugplus behavioral therapy	1 Reference	
Age (for each 10 year interval)	1.87 (1.43, 2.44)	< 0.001