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The Association of Pharmacologic Treatment of Urgency Urinary Incontinence on Sleep Quality and Daytime Sleepiness

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Abstract

Objective—To evaluate the association between pharmacological therapy for urgency urinary incontinence (UUI) and sleep quality.

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Methods—It is a planned secondary data analysis of sleep outcomes in a previously conducted multicenter, double-blinded, 12-week randomized trial of pharmacologic therapy for urgency-predominant incontinence among community dwelling women self-diagnosed using the 3-Incontinence Questions (3-IQ) questionnaire. Participants (N = 645) were assigned randomly to antimuscarinic therapy 4–8 mg daily or placebo. At baseline and 12 weeks, participants completed a validated voiding diary to evaluate incontinence/voiding symptoms, the Pittsburgh Sleep Quality Index (PSQI) to evaluate sleep quality, and the Epworth Sleepiness Scale to evaluate daytime sleepiness.

Results—Mean (SD) age was 56 (±14) years, 68% were white race, and 57% had poor sleep quality (PSQI score > 5). Mean frequency of any UI and UUI was 4.6 and 3.9 episodes per day, respectively. After 12-weeks, women randomized to the antimuscarinic group reported greater decrease compared to the placebo group in UUI frequency (0.9 episodes per day; P<0.001) and diurnal and nocturnal voiding frequency (P<0.05). As compared to the placebo group, women in the antimuscarinic group also reported greater improvement in sleep quality (total PSQI score 0.48; p=0.02), with greater improvement in sleep duration and sleep efficiency subscales (P<0.05). The intervention did not affect daytime sleepiness.

Conclusions—Pharmacological treatment of UUI is associated with decreased incontinence frequency and nocturia and improvement in overall sleep quality, sleep duration, and sleep efficiency.

Clinical Trial Registration—Clinical Trials.gov, NCT00862745.

Introduction

Urinary incontinence is a common problem for women, with approximately one-third to one-half of women reporting urinary frequency, urgency, nocturia, and/or urgency urinary incontinence (UUI) (1, 2). Urinary incontinence (UI) adversely impacts quality of life and is associated with depression, limitations in daily functioning, falling and fractures (3). One potential adverse consequence of UUI is sleep disruption. Many women who experience UUI episodes at night may have difficulty getting to sleep or staying asleep even after they fall asleep. UI at nighttime and frequent voiding at night during sleep increases with age and is common in older women. Approximately 20–45% of reproductive age women experience at least 1 void per night and 4–18% report 2 or more voids per night. Among women over 70 years of age, approximately 75% report at least 1 and 28–62% report 2 or more voids per night (4). Women suffering from UUI report more disturbance of sleep, compared to the general population who do not suffer UUI (5). Women are also more likely to experience high quality-of-life impact if they have nighttime incontinence (6).

Despite the association of UUI and sleep disturbances, there are very limited data on whether interventions that are specifically directed at improving UUI are effective in improving sleep outcomes, or whether improvements in sleep experienced by women undergoing treatment for UUI are mediated by improvement in their incontinence symptoms. The goal of this analysis was to evaluate the association between pharmacological therapy for UUI and sleep quality.

Despite the association of UUI and sleep disturbances, there are very limited data on the effect of UUI therapy on sleep quality. The goals of the study were to evaluate whether a pharmacological intervention for UUI is effective in improving sleep outcomes, and, if so, are improvements in sleep quality mediated or explained by improvements in nighttime urinary tract symptoms.

Materials and Methods

We conducted a planned secondary analysis of data from a randomized trial of pharmacological treatment for UUI to evaluate changes in quality of sleep, sleep duration, sleep efficiency, and daytime sleepiness. The parent study, Bringing Simple Urge Incontinence Diagnosis and Treatment to Providers (BRIDGES),was a 12-week randomized, double-blind, placebo-controlled clinical trial of fesoterodine (antimuscarinic) therapy in ambulatory women age 18 years or older who self-diagnosed as having UUI using the 3 Incontinence Questions (3IQ), a validated 3-item self-administered instrument to screen for and classify incontinence in women (7). Participants were enrolled in BRIDGES between February 2009 and January 2010. Eligibility criteria for BRIDGES have been described previously, 322 women were randomized to antimuscarinic medication and 323 to placebo. (7). Briefly, these ambulatory women were recruited from the general community surrounding 13 clinical sites in the United States. Women who initially reported clinically frequent incontinence during preliminary telephone screening (i.e., 7 or more incontinence episodes per week in the past 3 months) were asked to complete the 3IQ on paper during an in-person screening visit. Those who reported urgency-predominant urinary incontinence on the 3IQ measure were eligible to continue.

Women were excluded if they had urinary tract infection or hematuria on dipstick urinalysis, reported complex histories necessitating specialist referral, including anti-incontinence surgery in the past 5 years, other pelvic surgery in the past 6 months, more than 3 urinary tract infections in the past year, and other genitourinary disorders such as lower urinary tract or rectal fistula, interstitial cystitis, symptomatic pelvic organ prolapse, current or past urogenital cancer or radiation, congenital abnormality leading to incontinence, or major neurologic disorder such as stroke, Parkinson’s disease, spinal cord lesions, or multiple sclerosis. The study was approved by the institutional review board at each site and all participants provided written informed consent before enrollment.

Eligible women were randomly allocated in a 1:1 ratio to receive 12 weeks of pharmacological treatment with flexible-dose antimuscarinic 4 to 8 mg (i.e., fesoterodine group) or an identical placebo pill (placebo group) daily. Participants, clinical personnel, and statistical staff were masked to treatment assignment, and no unmasking occurred during the trial.

Participants were initially started either on antimuscarinic 4 mg or an identical placebo pill daily. At their 2-week telephone call and their 4-week follow-up visit, women were offered the option of increasing their dose to antimuscarinic 8 mg or an identical placebo daily. At their 8-week telephone call, they were invited to re-adjust their dose to a maximum of 8 mg or minimum of 4 mg daily.

All clinical efficacy outcomes were assessed at baseline and 12 weeks. For this analysis, the primary outcome was 12-week change in the quality of sleep assessed by the Pittsburg Sleep Quality Index (PSQI) (8) and daytime sleepiness assessed by Epworth Sleepiness Scale (ESS) (9). The PSQI is a 19-item self-rated questionnaire for the evaluation of subjective sleep quality over the last one month, which has 19 questions which are combined into 7 clinically-derived component scores, each weighted equally from 0–3, and the 7 component scores are added to obtain a global score ranging from 0–21, with higher scores indicating worse sleep quality (10). The clinical and psychometric properties of the PSQI have been formally evaluated by several research groups (11–13). The PSQI has a sensitivity of 89.6% and specificity of 86.5% for identifying sleep disorders using a cut-off score of 5 and the validity is further supported by similar differences between groups using PSQI or polysomnographic sleep measures (10). Sleep duration was defined as total hours of nocturnal sleep and sleep efficiency was calculated as a percentage of total hours slept/total time spent in bed * 100%. The ESS consists of 8 self-rated items, each scored from 0–3, that measure a participant's habitual “likelihood of dozing or falling asleep” in common situations of daily living, and this ESS score represents the sum of individual items, and ranges from 0–24. Values >10 are considered to indicate significant sleepiness (10).

Voiding frequency and urinary incontinence sub-types (urgency, stress, other) were assessed by a validated 3-day voiding diary (14). Participants recorded each time they voided in the toilet, leaked urine and rated the severity of urgency associated with each void or incontinence episode as none, mild, moderate, or severe. Data from the voiding diaries were abstracted by trained analysts who completed centralized training in diary abstraction, in order to calculate the average number of self-reported UUI, stress urinary incontinence (SUI), total incontinence, daytime voiding, and nighttime voiding episodes per day.

Baseline characteristics of participants in each treatment group were compared using analysis of covariance (ANCOVA) models, adjusted for clinical site. Association of changes in overall quality of sleep and voiding outcomes over 12-weeks were also examined using analysis of covariance (ANCOVA), adjusting for baseline values as well as site. No additional covariates were included in the models, as no demographic baseline differences were observed between intervention groups. Analyses were conducted without regards to adherence or final medication dosage. The following covariates were tested as potential mediators of change in sleep quality: age, ethnicity, smoking, alcohol use, nighttime UUI, nighttime SUI, and nighttime voids. Mediators were tested by adding each individually to sleep quality change models and observing the percent change in the covariate for intervention in the revised model. All analyses were performed using SAS statistical software Version 9.4 (SAS Institute, NC).

Results

As previously reported, 322 women were randomized to antimuscarinic, and 323 to placebo (7) and were included in the analysis (Figure 1). All but one woman randomized to antimuscarinic and 2 women randomized to placebo took at least one dose of medication. Adherence to medication (assessed through pill counts) was similar in both treatment groups, with 86% of women in the antimuscarinic and 87% in the placebo group completing

80% of administrations (P=.82). Of those in the antimuscarinic group, final medication dosage was confirmed for 281 women who returned their unused pills. Ninety women (32.0%) remained at 4 mg dose for the entire study, 152 (54.1%) increased to 8 mg and remained at this dose throughout the study, and 39 (13.9%) increased to 8 mg but returned to 4 mg before the end of the study.

At baseline (in this and the original study), the randomized groups were similar in demographic, clinical, incontinence and sleep characteristics (P>.05; Table 1). The mean [SD] age of participants was 56 [±14] years, 68% were white women, the mean baseline frequency of any type UI episodes was 4.6 (±3.4) and UUI episodes was 3.9 (±3.0) per day. Mean (SD) PSQI scores for the placebo and antimuscarinic groups were similar at baseline (6.37 (3.26) and 6.63 (3.52), respectively; P >.05) (Table 2), as were ESS scores (6.71 (3.92) and 6.47 (3.99), respectively; P>.05; Table 2). Over half (57%) of participants reported poor sleep quality (PSQI score > 5) and 16% reported significant sleepiness (ESS score >10).

Follow-up data at 12 weeks were obtained for 303 (94.4%) women in the antimuscarinic group and 301 (93.2%) in the placebo group. Women who were missing follow-up data tended to be younger (mean [SD] age of 50 [18] versus 56 [14] years), non-white (58.5% versus 32.1%) and unmarried (77.0% versus 56.1%; all P<0.05), but did not differ from women contributing the follow-up data with respect to other characteristics, including baseline sleep variables, incontinence frequency, or bladder-specific questionnaire scores.

After 12 weeks, women randomized to the antimuscarinic group reported greater decrease in UUI frequency of 0.88 (95% confidence interval (CI) 0.56, 1.20; P<0.001) episodes per day compared to women in the placebo group (P<0.001), as well as reported greater decreases in total incontinence frequency (0.89 (95% CI 0.54, 1.24) episodes per day; P<0.001), daytime and nighttime incontinence (both P<0.001), diurnal and nocturnal voiding frequency (both P<0.05), and frequency of voids associated with moderate or severe urgency as compared to the placebo group (P<0.01; Table 3) (7).

At 12 weeks, the antimuscarinic group reported a lower PSQI score (improved) when compared to the placebo group (P=0.02; Table 2). Compared to the placebo group, women in the antimuscarinic group reported significantly greater improvement in sleep duration and sleep efficiency PSQI subscales (P<0.05). There was no significant difference in ESS score between groups. Post-hoc power analyses reveal that we had 80% power to detect a 0.68 change ESS sleep quality scores.

Discussion

A 12-week pharmacological intervention for UUI was associated with improvement in overactive bladder symptoms (observed in the original study) and as well as improvements in overall sleep quality, sleep duration and sleep efficiency among ambulatory women with UUI as compared with a control group. We observed significant differences in sleep duration, sleep latency, sleep efficiency, and PSQI total scores. Those in the treatment group had improvements in their frequency of nocturnal voids and urge incontinence. Both fewer voids at night and decreased urge incontinence reduce the number of awakenings during the

night, which may be reflected in higher sleep efficiency, and longer sleep duration. It is also possible that participants in the treatment arm had increased ability to fall asleep more quickly at night (i.e. shorter sleep latency). These 3 components make up the overall PSQI score, thus it is not surprising there were significant improvements in overall PSQI scores. Interestingly, some PSQI domains were not significantly improved. The use of sleep medications did not differ between groups; their use is often a complex decision, can be used out of habit, and may not be directly impacted by improved sleep. Similarly, daytime sleepiness is not directly related to inability to sleep at night. We were unable to take napping behavior into account.

There are several reasons that treatment with antimuscarinic resulted in improved sleep quality. Antimuscarinic medications are known to improve incontinence and nocturia. This has been shown in other randomized clinical trials (15, 16). It is also possible that fesoterodine, like other antimuscarinic medications, may have a sedating effect resulting in overall improved quality of sleep (17). This study looked specifically at fesoterodine, but the results may be generalizable to other anticholinergic and antimuscarinic medications (7). While BRIDGES examined the impact of the antimuscarinic therapy fesoterodine on women with UUI, antimuscarinic medication has been shown to reduce nighttime voiding as well as improves sleep quality in patients with nocturia (18).

A clinically meaningful change in PSQI is 3 or more points (19). In a community-based sample of participants aged 45–75 years old, 50.5% had PSQI scores > 5, indicating poor sleep quality and 25.7% had ESS scores > 10, indicating daytime sleepiness. Our sample, therefore, had a somewhat higher proportion of participants who met criteria for poor sleep quality (57%) and lower proportion of daytime sleepiness (16%) than other studies (10).

In BRIDGES, serious adverse events were uncommon and unrelated to treatment, and no woman was found to have a concerning elevation in post-treatment post void residual (PVR) volume of ≥250 mL, suggesting that empiric therapy for UUI is a safe treatment for both UUI and its associated sleep disturbance (7). In mediation analysis, improvement in nighttime voiding frequency had the largest association with sleep quality, yet explained only 13% of the treatment association on sleep quality. No other strong mediators were identified, leaving the mechanism for most of the treatment association unexplained. Women were excluded in this study if they reported major comorbidities since the 3IQ was developed for use in non-specialist settings.

Several limitations of this study should be noted. This study included generally well-functioning women who would be most appropriate for evaluation in primary care or general gynecology setting, and results should not be extrapolated to women with more complicated histories or to men with UUI. Second, our study did not include women with urinary urgency in the absence of incontinence. Therefore, results cannot be extrapolated to patients with “dry” overactive bladder symptoms. While we did measure and control for some medical comorbidities associated with poor sleep (e.g., obesity, alcohol use) in the analyses, we did not measure or control for others (e.g., specific sleep disorders such as obstructive sleep apnea and restless leg syndrome, or levels of physical activity and hypnotic use which

may also impact sleep quality). Measured variables were similarly distributed between groups but we don't know the association of unmeasured variables on the results.

Our results suggest is that the improvement in sleep quality may be another benefit to treatment of UUI for women. As both incontinence and sleep disturbance are prevalent and bothersome conditions in middle-age and older women, a treatment that may improve both conditions may provide clinical value. This analysis provides new data that indicate initiating pharmacologic treatment for UUI in ambulatory women is associated with improvement in important domains of sleep. Among community-dwelling women with UUI, flexible-dose antimuscarinic therapy not only resulted in improvement in incontinence measures, but was also associated with significant improvements in overall quality of sleep, sleep duration, and sleep efficiency.

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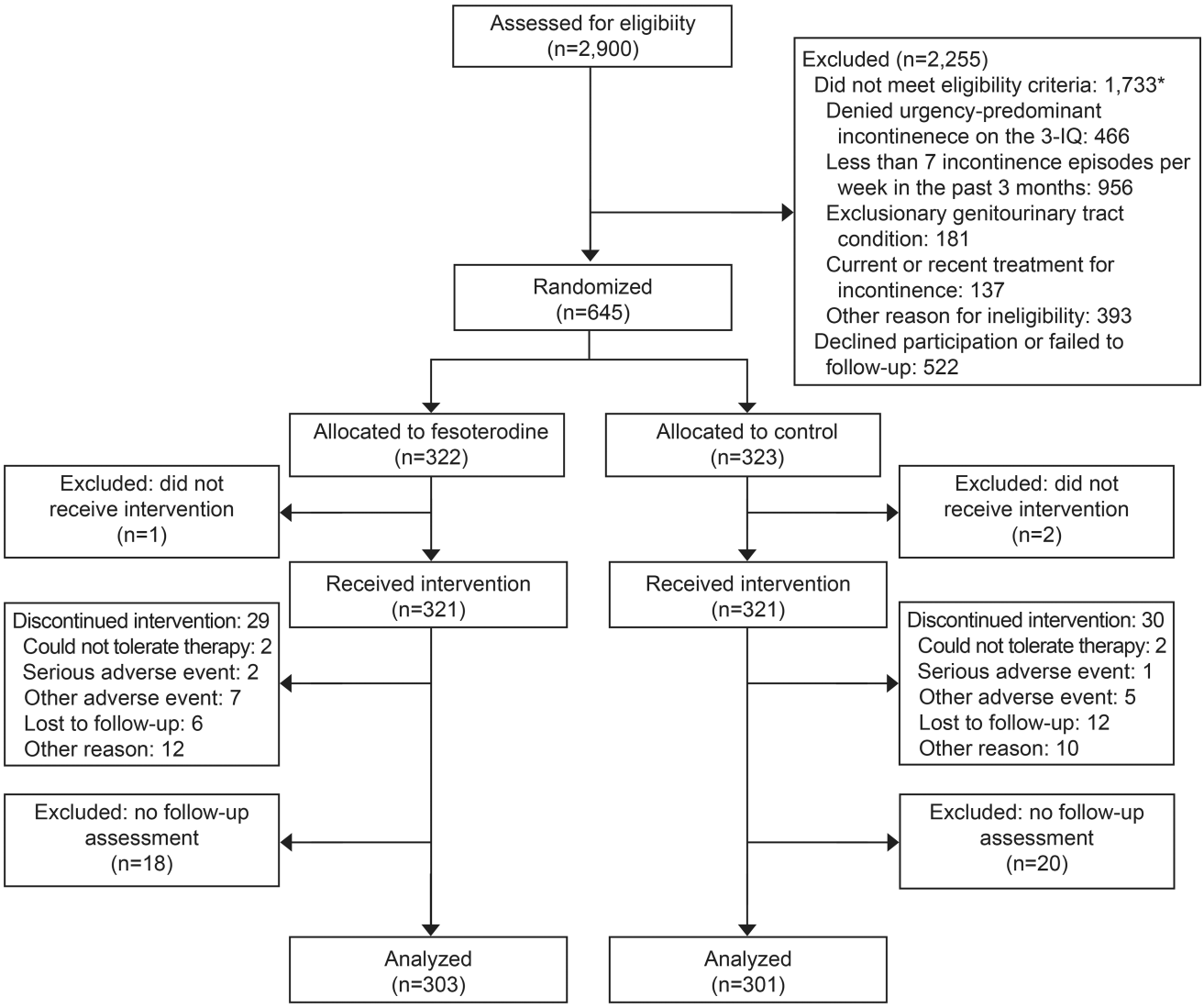

Figure 1. Recruitment, randomization, and retention in the BRIDGES trial

Recruitment, randomization, and retention in the Bringing Simple Urge Incontinence Diagnosis and Treatment to Providers (BRIDGES) trial. 3-IQ-3, 3-Incontinence Questions. *Not mutually exclusive.

Table 1

Baseline Characteristics by Treatment Group

	Fesoterodine (n = 322)	Placebo (n = 323)
Demographic		
Age in years, mean (SD)	56.2 (14.7)	55.9 (14.2)
Race/ethnicity, No. (%)*		
White	215 (66.8)	212 (65.6)
Black	73 (22.7)	71 (22.0)
Latina	18 (5.6)	28 (8.7)
Asian/Pacific Islander	9 (3.0)	6 (1.9)
Multiethnic/Other	7 (2.3)	6 (1.9)
Married, No. (%)	141 (43.8)	133 (41.2)
Clinical		
Excellent or very good overall health, No. (%)†	255 (79.2)	252 (78.0)
Previous childbirth (parity ≥ 1), No. (%)	256 (79.5)	256 (79.3)
Menopausal, No. (%)	229 (71.3)	229 (71.1)
Prior hysterectomy, No. (%)	99 (30.7)	95 (29.4)
Self-reported urinary tract infection in the past year, No. (%)	50 (15.5)	50 (15.5)
Current cigarette smoking, No. (%)	48 (14.9)	44 (13.7)
Current weekly alcohol consumption, No. (%)	96 (29.9)	99 (30.7)
Current systemic hormone therapy, No. (%)	35 (7.8)	27 (8.4)
Incontinence/micturition episodes per day		
Total incontinence episodes, Mean (SD)	4.5 (3.4)	4.8 (3.4)
Urgency incontinence episodes, Mean (SD)	3.8 (2.9)	4.0 (3.0)
Diurnal voiding episodes, Mean (SD)	8.6 (2.7)	8.8 (3.1)
Nocturnal voiding episodes, Mean (SD)	1.3 (1.3)	1.2 (1.2)
Moderate urgency-associated voids, Mean (SD)‡	7.5 (4.1)	7.8 (4.5)
Severe urgency-associated voids, Mean (SD)§	3.5 (3.3)	3.7 (3.6)

P>0.05 for comparison of fesoterodine and placebo groups for all variables listed in the table

*Participants self-reported their primary racial/ethnic group as White/Caucasian, Black/African-American, Latina/Hispanic, Asian, Pacific Islander, Native American/American Indian, or multiethnic.

†Overall health was assessed by asking women to rate their overall health as excellent, very good, good, fair, or poor.

‡Moderate urgency-associated voids were defined as voiding episodes associated with at least a “moderate” sensation of urgency on voiding diary.

§Severe urgency-associated voids were defined as voiding episodes associated with a “severe” sensation of urgency on voiding diary.

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TABLE 2

Measures of baseline and change in sleep variables, by treatment group

	Placebo Group (N=270)			Fesoterodine Group (N=277)			Between Groups	
Variable	**Baseline Mean (SD)**	**Change (95% CI)**	**P**	**Baseline Mean (SD)**	**Change (95% CI)***	**P**	**Difference (95% CI)***	**P**
PSQI total score**	6.37 (3.26)	−0.09 (−0.41, 0.23)	0.57	6.63 (3.52)	−0.58 (−0.89, −0.26)	<.001	0.48 (0.08, 0.89)	0.02
Daytime sleepiness	0.83 (0.70)	−0.02 (−0.10, 0.06)	0.63	0.83 (0.75)	−0.02 (−0.10, 0.06)	0.63	−0.00 (−0.10, 0.10)	0.99
Sleep disturbance	1.36 (0.53)	−0.02 (−0.09, 0.04)	0.50	1.33 (0.59)	−0.03 (−0.09, 0.03)	0.35	0.01 (−0.07, 0.09)	0.85
Duration of sleep	0.86 (0.70)	0.00 (−0.08, 0.08)	0.98	0.90 (0.71)	−0.14 (−0.22, −0.06)	<.001	0.14 (0.03, 0.24)	0.009
Sleep efficiency	0.57 (0.88)	0.06 (−0.05, 0.17)	0.27	0.75 (1.01)	−0.11 (−0.22, 0.00)	0.05	0.17 (0.03, 0.31)	0.02
Sleep latency	1.12 (0.98)	−0.05 (−0.14, 0.04)	0.24	1.14 (0.96)	−0.15 (−0.24, −0.06)	<.001	0.09 (−0.02, 0.21)	0.11
Need meds to sleep	0.65 (1.08)	0.00 (−0.11, 0.10)	0.96	0.63 (1.08)	−0.06 (−0.17, 0.04)	0.24	0.06 (−0.08, 0.20)	0.39
Overall sleep quality	0.98 (0.72)	−0.10 (−0.18, −0.02)	0.02	1.05 (0.74)	−0.06 (−0.14, 0.01)	0.11	−0.03 (−0.13, 0.07)	0.52
ESS***	6.71 (3.92)	0.16 (−0.19, 0.51)	0.36	6.47 (3.99)	−0.03 (−0.38, 0.31)	0.85	0.19 (−0.25, 0.64)	0.39

* Least square mean differences and p-values were derived from analysis of covariance models, adjusted for baseline level of symptoms as well as clinical site.

** Pittsburg Sleep Quality Index (PSQI) is a self-reported questionnaire that assesses sleep quality over a one month period and consists of 19-items weighted on a 0–3 interval scale. A global score is calculated by totaling the seven component scores providing an overall score ranging from 0 to 21 with lower scores indicative of better sleep quality.

*** Epworth Sleepiness Scale (ESS) is a self-reported questionnaire that assesses daytime sleepiness in eight different situations on a sale from 0–3 with a total score from 0 to 24, with lower scores indicative of better sleep quality.

Table 3

Measures of baseline and change in incontinence, by treatment group

	Placebo Group (N=270)			Fesoterodine Group (N=277)			Between Groups	
Variable	**Baseline Mean (SD)**	**Change (95% CI)**	**P**	**Baseline Mean (SD)**	**Change (95% CI)***	**P**	**Difference (95% CI)***	**P**
VOIDING/INCONTINENCE EPISODES PER 24 HOURS								
Total Incontinence	4.73 (3.24)	−2.04 (−2.31, −1.76)	<.001	4.49 (3.41)	−2.93 (−3.20, −2.66)	<.001	0.89 (0.54, 1.24)	<.001
Urgency Incontinence	3.96 (2.86)	−1.69 (−1.94, −1.44)	<.001	3.81 (2.87)	−2.57 (−2.82, −2.32)	<.001	0.88 (0.56, 1.20)	<.001
Diurnal Incontinence								
Nighttime Incontinence	0.64 (0.94)	−0.25 (−0.33, −0.18)	<.001	0.61 (1.01)	−0.42 (−0.50, −0.34)	<.001	0.17 (0.07, 0.26)	<.001
Diurnal Voids								
Nocturnal Voids	1.20 (1.16)	−0.23 (−0.35, −0.11)	<.001	1.30 (1.31)	−0.43 (−0.54, −0.31)	<.001	0.20 (0.05, 0.35)	0.01
Voids associated with moderate or severe urgency								

*Least square mean differences and p-values were derived from analysis of covariance models, adjusted for baseline level of symptoms as well as clinical site.

**Pittsburg Sleep Quality Index (PSQI) is a self-reported questionnaire that assesses sleep quality over a one month period and consists of 19-items weighted on a 0–3 interval scale. A global score is calculated by totaling the seven component scores providing an overall score ranging from 0 to 21 with lower scores indicative of better sleep quality.

***Epworth Sleepiness Scale (ESS) is a self-reported questionnaire that assesses daytime sleepiness in eight different situations on a sale from 0–3 with a total score from 0 to 24, with lower scores indicative of better sleep quality.