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The Effects of Drug and Behavior Therapy on Urgency and Voiding Frequency

Kathryn L. Burgio, PhD^{a,b}, Stephen R. Kraus, MD^c, Diane Borello-France, PT, PhD^d, Toby C. Chai, MD^e, Kimberly Kenton, MD, MS^f, Patricia S. Goode, MD^{a,b}, Yan Xu, MS^g, and John W. Kusek, PhD^h for the Urinary Incontinence Treatment Network

^aUniversity of Alabama at Birmingham, Birmingham, AL

^bDepartment of Veterans Affairs, Birmingham, AL

^cUniversity of Texas Health Sciences Center, San Antonio, TX

^dDuquesne University, Pittsburgh, PA

^eUniversity of Maryland, Baltimore, MD

^fLoyola University Medical Center, Maywood, IL

^gNew England Research Institutes, Watertown, MA

^hNational Institute of Diabetes & Digestive & Kidney Diseases, NIH, Bethesda, MD

Abstract

Introduction and Hypotheses—The objective of this study was to examine the effects of drug therapy alone and combined with behavioral therapy on urgency and 24-voiding frequency in women with urge-predominant incontinence and to identify predictors of change.

Methods—A planned analysis of data from a multi-site, randomized, controlled trial (N=307). Bladder diaries were used to document voids, incontinence, and urgency severity.

Results—Urgency scores decreased significantly within both treatment groups, but changes did not differ between groups ($p=0.30$). Improvement in urgency was associated with greater baseline urgency ($p<0.0001$) and black ethnicity ($p=0.03$). Voiding frequency increased with drug alone and decreased slightly with combined therapy ($p=0.009$), and improvement was associated with combined treatment ($p<0.0001$), higher baseline frequency ($p<0.0001$), and lower baseline incontinence episode frequency ($p=0.001$).

Conclusions—Although combined drug and behavioral therapy does not appear to improve urgency more than drug alone, it resulted in better outcomes on voiding frequency.

Corresponding author: Kathryn L. Burgio, PhD, University of Alabama at Birmingham, Birmingham VA Medical Center, 11G, 700 South 19th Street, Birmingham, AL, 35233, Telephone: (205) 558-7067, FAX: (205) 558-7068, kburgio@uab.edu.

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Keywords

Behavioral treatment; Drug therapy; Overactive bladder; Urge incontinence; Urinary frequency; Urinary urgency

Introduction

Urinary urgency is the defining symptom of overactive bladder (OAB), a bothersome condition that affects approximately 13% of adult women. [1,2] Primary interventions for OAB include pharmacotherapy and behavioral therapies. [3,4] While several drugs have demonstrated clinical efficacy in decreasing symptoms of OAB, they have not totally resolved symptoms in most patients. To address this limitation, behavioral interventions have been utilized in combination with drug therapy to manage these symptoms. Behavioral interventions have been shown to be effective for reducing urinary incontinence (UI) in women with stress, urge and mixed UI. [5–11] They can also improve the frequency of daytime urination and nocturia, [12,13] but little is known of their effects on the sensation of urgency.

Several previous studies have investigated whether combining behavioral and drug interventions would result in greater improvements in UI or voiding frequency compared to a single intervention. [14,15] We have reported the results of a multi-center, randomized, controlled trial, the Behavior Enhances Drug Reduction of Incontinence (BE-DRI) study, which showed that adding behavioral therapy to drug therapy did not enhance the ability of women with urge-predominant UI to discontinue their drug therapy and maintain clinically significant reductions in UI episodes. [16] However, women who received combined therapy reported greater perceived improvement, satisfaction, and better scores on several secondary outcomes.

The primary outcome for many OAB treatment trials is a reduction in episodes of urinary incontinence. Much less is known about the effectiveness of drug therapy, behavioral therapy or combined therapy on urgency and voiding frequency. In this secondary analysis of data from the BE-DRI Study, we examined the effects of drug therapy alone and combined drug and behavioral therapy on urgency and frequency of voiding and identified baseline predictors of change in urgency and voiding frequency in women.

Materials and Methods

Overview

The BE-DRI study was a two-stage randomized clinical trial conducted by 9 clinical centers in the U.S. (See Appendix) Participants were women with urge-predominant UI randomly assigned to drug therapy alone or drug therapy combined with behavioral training. In Stage 1, both groups received 10 weeks of active treatment. In Stage 2, immediately following active treatment, drug and behavioral therapy were discontinued. Details of the study design and results of the trial have been described previously. [16,17] The primary outcome of the trial was successful discontinuation of drug. This paper reports on the secondary outcomes of urgency and frequency of voiding measured at the end of active therapy (10 weeks).

Participants

Participants were 307 community-dwelling women with urge-predominant UI, defined as urge symptom index score greater than stress symptom index score on the Medical, Epidemiological, and Social Aspects of Aging Questionnaire (MESA).[18] Clinical

evaluation included medical history, physical examination, and a 7-day bladder diary. Pelvic floor muscle strength was assessed using the Brink scale, [19] and prolapse was quantified using the pelvic organ prolapse quantification system (POP-Q). [20] To be included in the study, women had to report ≥ 7 episodes of incontinence on a 7-day baseline diary, persistent incontinence for ≥ 3 months, no current use of antimuscarinics or other medications that could impact UI, and no evidence that incontinence was secondary to neurologic or other systemic diseases.

Intervention

Participants were randomly assigned in equal numbers to either drug therapy alone or drug therapy combined with behavioral therapy. In both groups, treatment was implemented in 4 visits, at intervals of 2 to 3 weeks, over a period of 10 weeks.

Drug therapy was tolterodine tartrate (extended-release capsules) at a dose of 4 mg per day. If not well tolerated, the dose could be decreased to 2 mg or another antimuscarinic medication could be substituted. At the initial visit, all participants received written information about the drug and recommendations for fluid intake and managing common drug side-effects (dry mouth and constipation).

Combination therapy included drug therapy and behavioral training, implemented by a nurse practitioner, nurse specialist, and/or physical therapist. Behavioral therapy included pelvic floor muscle training (using vaginal palpation); behavioral strategies to diminish urgency, suppress bladder contractions, and prevent both stress and urge incontinence; delayed voiding to increase voiding intervals for those who voided >8 times per day; and individualized fluid management for those with excessive urine output ($> 2,100$ ml per day).

A central component of behavioral training was to teach women how to respond adaptively to the sensation of urgency by using urge suppression techniques. [10] They were instructed not to rush to the toilet, but instead to pause, to sit down if possible, to practice relaxing, and to contract the pelvic floor muscles several times to suppress urgency and detrusor contraction, as well as to prevent urine loss.

Training was supplemented with verbal and written instructions for daily home practice between clinic visits. Recommendations included 45 pelvic floor muscle contractions per day divided into 3 sessions of 15 contractions each. Contraction duration was initiated at 3 seconds duration with 6 seconds rest, but duration could be shorter for participants who could not sustain this in the first session. At each treatment visit, exercise technique was assessed by digital vaginal palpation and the results used to guide and progress the exercise prescription across visits to a maximum of 10 seconds. Participants were also encouraged to integrate the exercises into their daily activities.

Participants were evaluated at each treatment visit for adherence to pelvic floor muscle exercise (using a self-administered exercise questionnaire) and to behavioral strategies (using questions administered by the interventionist). To optimize adherence, barriers to the behavioral program were identified and possible solutions discussed with the participant.

To ensure standardized administration of the treatments across clinicians and clinical sites, all interventionists attended a 2-day, in-person, centralized training program and were certified on bladder diary interpretation, hands-on pelvic floor muscle training (with live models), and patient education skills related to teaching pelvic floor muscle exercise and behavioral strategies. This included counseling patients on fluid management and delayed voiding, as well as assisting them to solve exercise and behavioral adherence problems. To support maintenance of the interventionists' skills, the trainers held twice monthly

conference calls, in which they reviewed study procedures, precepted cases, and discussed specific situations that arose at the individual sites.

Measurements

Participants were assessed at baseline and the end of active therapy (10 weeks). At each time point, participants completed a 7-day bladder diary in which they recorded fluid intake and the time of each void and incontinence episode. To assess urgency, participants used the Indevus Urgency Severity Scale (IUSS) to rate the urgency associated with each void and incontinence episode on two days (Day 1 and Day 7). [21] Response options were none (0), mild (1), moderate (2) and severe (3). Mean urgency ratings were determined from reports on two days. If the reports from one day were missing, the mean was based on reports from a single day.

In addition to the bladder diary, severity of symptom distress and bother were measured using the Urogenital Distress Inventory (UDI) [22] and the Overactive Bladder Questionnaire (OAB-q). [23] Condition-specific impact of incontinence was assessed using the Incontinence Impact Questionnaire (IIQ), [22] and impact on quality-of-life was measured using the Short-Form Health Survey (SF-12) [24] and Health Utility Index (HUI-2). [25]

Statistical Analysis

The first analysis compared the two treatment groups on change in mean score on the Indevus Urgency Severity Scale and change in 24-hour voiding frequency from baseline to the end of active treatment using parametric statistics.

To identify potential predictors of change in urgency and voiding frequency, several baseline variables were examined: demographic characteristics, urgency score, voiding frequency, characteristics of incontinence (MESA urge and stress scores, number of incontinence episodes on bladder diary, IIQ score, OAB-q score, duration of incontinence, prior treatment/surgery for incontinence), medical history and physical examination variables (self-assessment of overall health, smoking status, fluid intake, current estrogen use, diabetes, presence of fecal incontinence, body mass index (BMI), POP-Q scores, pelvic floor muscle strength, SF-12 score, and HUI-2 score).

Analyses were conducted separately for each outcome: change in urgency ratings and change in 24-hour voiding frequency from baseline to post-treatment. Potential predictors were explored in bivariate analyses to determine their relationship to change in urgency and frequency using least-squares regression analysis controlling for treatment group and site. For continuous variables we report the regression coefficient. For the categorical variables we report both the regression coefficient and the adjusted means (LSMEANS).

Variables significantly related to outcome in bivariate analyses at the 0.1 level or of clinical importance were entered into multivariable regression models to test their independent association with change in urgency and frequency. Treatment group (drug alone or combined drug + behavior), clinical site, and the corresponding baseline values (urgency or frequency) were included in all multivariable models whether statistically significant or not.

Results

Of the 561 women who signed informed consent and were evaluated for the BE-DRI study, 254 were excluded: 119 withdrew consent prior to randomization, one was erroneously excluded, and 134 were found to be ineligible (UI was not urge predominant, $n = 77$; fewer than 7 UI episodes per week on bladder diary, $n = 19$; other reason, $n = 38$). The 307 women

who were randomized ranged in age from 21 to 87 years (mean=56.9). Nearly all reported mixed stress and urge UI (96.7%). Participant characteristics are presented in Table 1.

Of the 307 women who were randomized, 242 women (79%) provided adequate urgency data at baseline and 183 (59%) at the 10-week visit. About half of the urgency data were based on a single day of diary (57% at baseline and 48% at 10 weeks). The subgroup of women who provided data on urgency had significantly lower frequency of incontinence episodes compared to the women with missing data ($P=0.003$ at baseline; $P < 0.0001$ at 10 weeks). They also had higher levels of education at baseline (80% vs. 66% had a high school or higher education, $P = .02$), but not at 10 weeks ($P = .72$). The groups did not differ on age at either time point. All 307 women provided adequate voiding frequency data at baseline and 269 at the 10-week visit.

At baseline, mean urgency ratings were in the mild to moderate range (1.55 in drug alone; 1.51 in combined). Mean scores on the urgency severity scale decreased significantly from baseline to 10 weeks within both the drug alone and combined drug plus behavior groups, but the magnitude of change between groups over this time period was not significantly different (Table 2). Because baseline urgency severity scores were within the mild to moderate range, we also examined changes in the subgroup of 52 women (33 with complete data) whose mean urgency severity score was ≥ 2 (at least moderate) at baseline. In the drug only group, mean urgency score decreased by 0.77, and in combined therapy, the mean urgency score decreased by 1.01, indicating larger changes compared to the group of women whose scores were in the normal range at baseline ($P < 0.0001$).

Mean 24-hour voiding frequency at baseline was 7.33 per day in the drug only group and 7.07 in the drug plus behavior group. Voiding frequency increased from baseline to 10 weeks for the drug alone group ($P=0.02$) and decreased slightly for the drug plus behavior group ($P=0.2$). The difference between the amount of change for the two treatment groups was statistically significant ($P=0.009$) (Table 2). Because the mean baseline voiding frequency fell within the normal range (≤ 8 voids per 24 hours), we also examined the subset of 122 women who had reported greater than 8 voids per 24 hours. The drug only group showed a mean reduction of 1.31 voids per day (± 2.32), and the combined therapy group showed a mean reduction of 2.02 (± 1.56) voids per day, changes that were notably larger than those observed in the overall analysis, and significantly larger compared to the group of women whose scores were in the normal range at baseline ($P < 0.0001$).

In bivariate analyses, change in urgency score was significantly associated with ethnicity and education level. Table 3 shows results of the multivariate analysis for change in urgency scores, including statistically significant variables from bivariate analyses. Diabetes was also included for its clinical importance. Only baseline urgency severity was significantly associated with change in urgency ($P < 0.0001$). Those with greater urgency scores at baseline showed greater changes in urgency with treatment. Presence of diabetes was marginally significant. The model accounted for about 30% of the variability in change in urgency.

A second multivariable analysis was conducted adding baseline voiding frequency to the model. Baseline urgency severity remained a significant predictor while voiding frequency was marginally associated with change in urgency ($P = 0.09$). In addition, ethnicity was also associated with change in urgency in this model ($P = 0.03$). Non-Hispanic blacks had the greatest reduction in urgency scores compared to Non-Hispanic whites and other ethnic groups. This model accounted for about 32% of the variability in the change in urgency scores.

In the bivariate analyses of predictors of change in voiding frequency, the following four variables were significant and were entered into the multivariable model: age, number of incontinence episodes at baseline, current hormone therapy, and Brink score. Fluid intake was also included for its clinical importance. In multi-variable analysis, in addition to the covariate of treatment group, only baseline voiding frequency and number of incontinence episodes at baseline were significantly associated with change in voiding frequency after controlling for other variables (Table 4). Women with milder incontinence at baseline tended to have greater reductions in voiding frequency, compared to women with more baseline incontinence, who had smaller reductions or an increase in voiding frequency. Age was marginally associated with change in voiding frequency ($P = 0.051$). Younger women were more likely to have a reduction in voiding frequency, while older women tended to have increased voiding frequency. This model accounted for about 64% of the variability in the change in voiding frequency.

A second analysis was conducted that included baseline urgency severity in the model. In this analysis, baseline incontinence, baseline voiding frequency, and treatment remained significant, but age and baseline urgency severity were not significantly related to change in voiding frequency.

Discussion

Although drug therapy is a widely-used first-line therapy for urge UI and OAB, it is recognized that outcomes are not optimal and approximately two thirds of patients who are treated with an antimuscarinic medication discontinue its use within three to four months. [26] Combining behavioral and drug therapies has emerged as a promising approach to improving outcomes for women with these symptoms, based on the premise that they work by means of different mechanisms. [14]

In the BE-DRI study, women with urge UI who underwent behavioral training in addition to drug therapy were no more likely to discontinue drug therapy or sustain improvements in continence status than women treated with drug alone. However, women who received combined behavior and drug therapy reported greater improvements on several subjective secondary outcome measures, including patient's perception of improvement, patient satisfaction, and scores on validated questionnaires measuring symptom distress and bother (UDI and OAB-q). In this planned secondary analysis, we explored in more detail the impact of these treatments on urgency severity and 24-hour voiding frequency.

Although drug therapy alone and drug therapy combined with behavioral intervention each resulted in significant reductions in urgency severity scores, there was no added benefit of combined therapy. This finding may be explained in part by the fact that urgency scores were fairly low at baseline, with the means falling in the mild to moderate range. Further, at the end of active therapy, the mean score in the drug only group had decreased to 1.01, representing mild urgency. This value would be considered within the normal range for sensation associated with voiding. This may have created a "floor effect" in which drug therapy alone reduced urgency to a normal level with little opportunity for further improvement. It is also possible that behavioral treatment alone could also have achieved this effect in our population with mild urgency, but we cannot assess this in the present study because there was no behavioral treatment alone group.

Significant improvements in incontinence can be achieved through behavioral changes and/or skills without observing physiologic changes such as increased bladder capacity. [12] Similarly, while behavioral training can reduce the occurrence and/or severity of urgency, it may not be necessary to totally eliminate the sensation of urgency for a successful outcome

to occur. From a behavioral perspective, any urge sensation functions as a sensory cue to the patient to use her continence skills to avoid urine loss. Thus, even mild urge sensation has a clear role in maintaining bladder control.

In contrast to the lack of group differences for change in urgency severity, the treatment groups were significantly different on change in 24-hour voiding frequency, with an increase observed with drug therapy only and a slight decrease in combined therapy. Though group differences were statistically significant, the changes in voiding frequency were quite small. As was observed for urgency severity, this may be due to the mean 24-hour voiding frequency being in the normal range at baseline, and many women likely did not need to reduce their number of daily voids. The primary goal of the BE-DRI behavioral training program was to teach participants strategies to suppress urgency and maintain bladder control until urgency subsided and they could reach the bathroom without urine loss. Urge suppression aims to decrease incontinence episodes, but does not target voiding frequency or attempt to change voiding habits. In our combined therapy protocol, delayed voiding to reduce voiding frequency was utilized only for those women who had greater than 8 voids per 24 hours. When we examined changes in voiding frequency in the subgroup of women who voided more than 8 times per day (who comprised only 40% of the sample), we found that voiding frequency decreased by 2.0 voids per day in the combined group compared to 1.3 voids per day in the drug only group ($P=.07$).

Few clinical trials of combination interventions for OAB have been conducted. Mattiasson and colleagues attempted to improve outcomes of drug therapy for overactive bladder using simple written bladder training instructions, which focused specifically on expanding the voiding interval. [15] Patients who received drug therapy plus bladder training showed greater reduction in voiding frequency (they did not report on urgency), as well as greater increases in voided volumes compared to those who received drug therapy alone.

Our study examined various factors associated with decreased urgency and frequency in women in both treatment arms. A higher voiding frequency at baseline was associated with a smaller treatment effect. Voiding frequency in itself may be a chronic behavioral response in order to avoid incontinent episodes and such a response may not be modified in a 10-week treatment period. Our observation that older age was marginally associated with a lesser change in voiding frequency is consistent with prior studies showing increased age to be associated with greater incidence of detrusor overactivity and decreased bladder capacity. Such alterations in bladder function may contribute to greater symptoms of OAB in the elderly and make it more difficult to respond to therapy. [27]

There were several limitations to our study. First, although women in this study had significant urge incontinence, the subsample with urgency scores reported on average only mild urgency at baseline. Only half of the participants completed usable urgency ratings at both time points and this subgroup had milder incontinence at baseline compared to the women with missing data. Thus, it is possible that the women in our analyses had milder urgency as well. In this context, drug therapy alone may have improved urgency to the degree that further reduction by adding behavioral therapy was not possible. In addition, patients in the drug only group received components of the behavioral treatment program (bladder diary, written instructions for fluid management), which may have minimized differences in treatment effects between the groups.

In summary, drug therapy alone and combined therapy each improved urgency in women with predominant urge incontinence. However, in this group of women with fairly mild urgency severity scores, no added benefit for combined therapy was observed on the

magnitude of change over time. Small changes were seen for voiding frequency, and women with milder incontinence and those in combined therapy tended to have better outcomes.

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APPENDIX

STEERING COMMITTEE

William Steers, MD, Chair (University of Virginia Charlottesville, VA); Ananias Diokno, MD, Veronica Mallett, MD, Salil Khandwala, MD (William Beaumont Hospital, Royal Oak, MI and Oakwood Hospital, Dearborn MI; U01 DK58231); Linda Brubaker, MD, MaryPat FitzGerald, MD (Loyola University Medical Center, Maywood, IL; U01 DK60379); Holly E. Richter, PhD, MD, L. Keith Lloyd, MD (University of Alabama, Birmingham, AL; U01 DK60380); Michael Albo, MD, Charles Nager, MD (University of California, San Diego, CA; U01 DK60401); Toby C. Chai, MD, Harry W. Johnson, MD (University of Maryland, Baltimore, MD; U01 DK60397); Halina M. Zyczynski, MD, Wendy Leng, MD (University of Pittsburgh, Pittsburgh, PA; U01 DK 58225); Philippe Zimmern, MD, Gary Lemack, MD (University of Texas Southwestern, Dallas, TX; U01 DK60395); Stephen Kraus, MD, Thomas Rozanski, MD (University of Texas Health Sciences Center, San Antonio, TX; U01 DK58234); Peggy Norton, MD, Lindsey Kerr, MD (University of Utah, Salt Lake City, UT; U01 DK60393); Sharon Tennstedt, PhD, Anne Stoddard, ScD (New England Research Institutes, Watertown, MA; U01 DK58229); Debuene Chang, MD, John W. Kusek, PhD, Leroy M. Nyberg, MD, PhD (National Institute of Diabetes & Digestive & Kidney Diseases); Anne M. Weber, MD (National Institute of Child Health and Human Development).

CO-INVESTIGATORS

Diane Borello-France, PT, PhD; Kathryn L. Burgio, PhD; Seine Chiang, MD; Ash Dabbous, MD; Chiara Ghetti, MD; Patricia S. Goode, MD; Lee N. Hammontree, MD; Kimberly Kenton, MD; Karl Lubner, MD; Emily Lukacz, MD; Alayne Markland, DO, MSc; Shawn

Menefee, MD; Pamela Moalli, MD; Kenneth Peters, MD; Joseph Schaffer, MD; Amanda Simsiman, MD; Larry Sirls, MD; Robert Starr, MD; R. Edward Varner, MD.

STUDY COORDINATORS

Rosemary Bradt, RNC; Laura Burr, RN; Karen Debes, RN; Tamara Dickinson, RN; Rosanna Dinh, RN, CCRC; Judy Gruss, RN; Alice Howell, RN, BSN, CCRC; Kathy Jesse, RN; D. Lynn Kalinoski, PhD; Kristen Mangus; Karen Mislanovich, RN; Judy Murray, CCRC; Shelly O'Meara, RN; Janese Parent, RN; Norma Pope, RN; Caren Prather, RN; Sylvia Sluder, CCRP; Mary Tulke, RN; Robin Willingham, RN, BSN; Gisselle Zazueta-Damian.

INTERVENTIONISTS

Dorothy Atkins, CRNP, MS; Jan Baker, APRN; Karen Debes, RN; Kathy Jesse, RN; Ryanne R. Johnson, BSN, RNC, WHNP; Kathryn Koches, RN; R. Jeannine McCormick, RN, MSN, CRNP; Karen Mislanovich, RN; Christy Moore, RN, BSN; Elva Kelly Moore, RN; Amy Mutch, CRNP; Betsy Nielsen-Omeis, RN, BSN; Lisa Radebaugh, MScN, CRNP; Patsy Riley, RN; Karen VandeVegt, PT.

BIostatistical COORDINATING CENTER

Kimberly J. Dandreo, MSc; Corinne J. Leifer, BA; Heather Litman, PhD, Susan M. McDermott, MPH, GNP; Anne Stoddard, ScD (Co-PI); Sharon Tennstedt, PhD (PI); Liane Tinsley, MPH; Yan Xu, MS.

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Elizabeth A. Gormley MD (Chair), Dartmouth-Hitchcock Medical Center, Lebanon NH; Paul Abrams MD, Bristol Urological Institute, Bristol UK; Diedre Bland MD, Blue Ridge Medical Associates, Winston Salem NC; J. Quentin Clemens MD, Northwestern University Medical School, Chicago IL; John Connett PhD, University of Minnesota, Minneapolis MN; William Henderson PhD, University of Colorado, Aurora CO; Dee Fenner MD, University of Michigan, Ann Arbor MI; Sheryl Kelsey PhD, University of Pittsburgh, Pittsburgh PA; Deborah Myers MD, Brown University School of Medicine, Providence RI; Jacek Mostwin MD, Johns Hopkins Hospital, Baltimore MD; Bassem Wadie MBBCh, MSc, MD, Mansoura Urology and Nephrology Center, Mansoura, Egypt.

Table 1

Participant Characteristics by Treatment Group

Variable	Treatment Group	
	Drug Only (n=153)	Drug + Behavior (n=154)
Ethnicity		
Hispanic	17 (11%)	13 (8%)
Non-Hispanic White	85 (56%)	105 (69%)
Non-Hispanic Black	35 (23%)	22 (14%)
Non-Hispanic Other	15 (10%)	13 (8%)
Missing	1	1
Marital status		
NotMarried	85 (56%)	84 (55%)
Married/Live as Married	68 (44%)	70 (45%)
Education		
≤ High School/GED	31 (20%)	40 (26%)
> High School	122 (80%)	114 (74%)
Menopause status		
Post-menopausal on HRT	27 (18%)	27 (18%)
Post-menopausal on no HRT	79 (52%)	72 (47%)
Pre-menopausal	47 (31%)	55 (36%)
Type of incontinence		
Mixed	147 (96%)	150 (97%)
Pure urge	6 (4%)	4 (3%)
Frequency of incontinence		
< 14 episodes/wk	47 (31%)	47 (31%)
≥ 14episodes/wk	106 (69%)	107 (69%)
Age – mean (sd)	58.0 (13.5)	55.8 (14.21)
BMI– mean (sd)	32.32 (7.59)	33.17 (9.52)

Table 2
Changes in Urgency Severity Scores and Voiding Frequency from Baseline to Post-treatment (10 weeks) by Group

	Drug Only		Drug + Behavior		P-Value (between group)
	n	Mean (SD)	n	Mean (SD)	
Urgency Score					0.30
Baseline	121	1.55 (0.52)	121	1.51 (0.55)	
Post-treatment	90	1.01 (0.60)	93	1.00 (0.63)	
Change (baseline to 10 weeks)	78	-0.54 (0.62)	76	-0.43 (0.63)	
P-Value (within group)		< .0001 *		< .0001 *	
24-Hour Voiding Frequency					0.009
Baseline	153	7.33 (3.42)	154	7.07 (3.03)	
Post-treatment	136	7.74 (2.45)	133	6.94 (1.69)	
Change (baseline to 10 weeks)	136	+0.55 (2.67)	133	-0.27 (2.44)	
P-Value (within group)		0.02 *		0.20 *	

* Paired t-test

Table 3

Multivariable Regression Analysis Predicting Change in Urgency Severity Scores Controlling for Treatment Group, Site and Baseline Urgency Severity

	Regression coefficient	Standard Error	Adjusted Means	P-value
Treatment				0.61
Drug alone	0.05	0.09	0.45	
Drug and behavioral intervention			0.40	
Clinical site	Not presented			0.88
Urgency severity at baseline	0.56	0.09	6.18	<.0001
Ethnicity				0.06
Hispanic	0.02	0.21	0.43	
Non-Hispanic Black	0.28	0.14	0.69	
Non-Hispanic Other	-0.24	0.17	0.17	
Non-Hispanic White (Ref)*			0.41	
Education				0.08
>HS	-0.20	0.11	0.33	
<=HS/GED (Ref)*			0.53	
Diabetes				0.052
Yes	-0.31	0.16	0.27	
No (Ref)*			0.58	

Ref = reference group

Table 4

Multivariable Regression Analysis Predicting Change in Voiding Frequency Controlling for Treatment Group, Site and Baseline Voids

	Regression Coefficient	Standard Error	Adjusted Means	P-value
Treatment				<.0001
Drug alone	−0.80	0.20	−0.53	
Drug and behavioral intervention			0.27	
Clinical site	Not presented			0.21
Number of voids at baseline	0.55	0.04		<.0001
Age (per 10 years)	−0.22	0.11		0.05
Number of Incontinence Episodes on Bladder Diary at Baseline	−0.15	0.05		0.001
Current HRT Use				0.71
Post-menopausal on HRT	0.29	0.35	0.01	
Post-menopausal on No HRT	0.17	0.32	−0.11	
Pre-menopausal (Ref)*			−0.28	
Fluid Intake	0.01	0.004		0.19
Brink Score	0.09	0.06		0.15

Ref = reference group