Annals of Internal Medicine | ARTICLE

Behavioral Therapy to Enable Women with Urge Incontinence to Discontinue Drug Treatment

A Randomized Trial

Kathryn L. Burgio, PhD; Stephen R. Kraus, MD; Shawn Menefee, MD; Diane Borello-France, PT, PhD; Marlene Corton, MD; Harry W. Johnson, MD; Veronica Mallett, MD; Peggy Norton, MD; Mary P. FitzGerald, MD; Kimberly J. Dandreo, MSc; Holly E. Richter, PhD, MD; Thomas Rozanski, MD; Michael Albo, MD; Halina M. Zyczynski, MD; Gary E. Lemack, MD; Toby C. Chai, MD; Salil Khandwala, MD; Jan Baker, APRN; Linda Brubaker, MD; Anne M. Stoddard, ScD; Patricia S. Goode, MD; Betsy Nielsen-Omeis, RN, BSN; Charles W. Nager, MD; Kimberly Kenton, MD; Sharon L. Tennstedt, PhD; John W. Kusek, PhD; T. Debuene Chang, MD; Leroy M. Nyberg, MD, PhD; and William Steers, MD, for the Urinary Incontinence Treatment Network*

Background: Women with urge urinary incontinence are commonly treated with antimuscarinic medications, but many discontinue therapy.

Objective: To determine whether combining antimuscarinic drug therapy with supervised behavioral training, compared with drug therapy alone, improves the ability of women with urge incontinence to achieve clinically important reductions in incontinence episodes and to sustain these improvements after discontinuing drug therapy.

Design: 2-stage, multicenter, randomized clinical trial conducted from July 2004 to January 2006.

Setting: 9 university-affiliated outpatient clinics.

Patients: 307 women with urge-predominant incontinence.

Intervention: 10 weeks of open-label, extended-release tolterodine alone (n = 153) or combined with behavioral training (n = 154), followed by discontinuation of therapy and follow-up at 8 months.

Measurements: The primary outcome, measured at 8 months, was no receipt of drugs or other therapy for urge incontinence and a 70% or greater reduction in frequency of incontinence episodes. Secondary outcomes were reduction in incontinence, self-reported satisfaction and improvement, and scores on validated questionnaires measuring symptom distress and bother and health-related quality of life. Study staff who performed outcome evaluations, but not participants and interventionists, were blinded to group assignment.

Results: 237 participants completed the trial. According to life-table estimates, the rate of successful discontinuation of therapy at 8 months was the same in the combination therapy and drug therapy alone groups (41% in both groups; difference, 0 percentage points [95% CI, −12 to 12 percentage points]). A higher proportion of participants who received combination therapy than drug therapy alone achieved a 70% or greater reduction in incontinence at 10 weeks (69% vs. 58%; difference, 11 percentage points [CI, −0.3 to 22.1 percentage points]). Combination therapy yielded better outcomes over time on the Urogenital Distress Inventory and the Overactive Bladder Questionnaire (both P <0.001) at both time points for patient satisfaction and perceived improvement but not health-related quality of life. Adverse events were uncommon (12 events in 6 participants [3 in each group]).

Limitations: Behavioral therapy components (daily bladder diary and recommendations for fluid management) in the group receiving drug therapy alone may have attenuated between-group differences. Assigned treatment was completed by 68% of participants, whereas 8-month outcome status was assessed on 77%.

Conclusion: The addition of behavioral training to drug therapy may reduce incontinence frequency during active treatment but does not improve the ability to discontinue drug therapy and maintain improvement in urinary incontinence. Combination therapy has a beneficial effect on patient satisfaction, perceived improvement, and reduction of other bladder symptoms.

Ann Intern Med. 2008;149:161-169. www.annals.org

For author affiliations, see end of text.

ClinicalTrials.gov registration number: NCT00090584.

* For a list of the Urinary Incontinence Treatment Network investigators, see **Appendix 1** (available at www.annals.org).

Urinary incontinence affects more than 10 million Americans, is common among women, and accounts for billions of dollars annually in societal costs (1, 2). Of the several types of incontinence, urge incontinence (involuntary urine loss associated with a strong desire to void) has the greatest impact on quality of life (3, 4).

Muscarinic-receptor antagonists and behavioral treatments, which teach participants new habits or continence skills, are both safe and effective first-line treatments for urge incontinence (1, 5–7). However, most patients do not achieve complete continence with either therapy alone. In addition, long-term medication adherence can be difficult to achieve.

See also:

Print
Editors' Notes 162

Web-Only
Appendixes
Appendix Table
Appendix Figure
Conversion of graphics into slides

Context

Does behavioral intervention help women to discontinue drug therapy for urge incontinence?

Contribution

In this multicenter trial, 307 women with urge-predominant incontinence were randomly assigned to 10 weeks of tolterodine plus behavioral training or tolterodine alone. Six months after the treatments were discontinued, 41% of women in both groups reported that they were still off drug therapy and still had at least 70% reduction in the frequency of incontinence episodes (compared with baseline) without additional treatment.

Caution

Only 68% of the women completed the 10-week treatment (same as before).

Implication

Behavioral intervention was insufficient to help women stay off drug therapy and sustain treatment gains after short-term drug therapy.

—The Editors

Adding behavioral training to pharmacologic treatment is an appealing approach to improving outcomes and to possibly permitting discontinuation of drug therapy; however, evidence for the efficacy of combination therapy over either treatment alone is scarce and inconclusive (8–10). Our primary aim was to determine whether combining antimuscarinic drug therapy with supervised behavioral training improves the ability of women with urge incontinence to achieve clinically important reductions in incontinence episodes more than drug therapy alone and to sustain these improvements after discontinuing medication.

METHODS

The BE-DRI (Behavior Enhances Drug Reduction of Incontinence) study was a 2-stage, randomized trial conducted by 9 clinical centers in the United States. (See **Appendix 1**, available at www.annals.org, for a list of participating centers.) We randomly assigned patients to receive drug therapy alone or drug therapy combined with behavioral training. In stage 1, participants received 10 weeks of the assigned treatment. In stage 2, which immediately followed active treatment, we discontinued drug therapy in both groups. We measured outcomes at 6 months after discontinuation of therapy (month 8) as well as at the end of active therapy (week 10). We did not allow crossovers. Drug therapy was open-label, and we provided the drugs free of charge to all study participants. Study staff who performed outcome evaluations, but not participants and interventionists, were blinded to group assignment. Details of the study design (**Appendix Figure**, available at www.annals.org) and methodology are described elsewhere (11). We recruited participants between July 2004 and January 2006 and completed the last follow-up in November 2006.

The institutional review boards of the participating centers approved the study, and all participants provided written informed consent.

Settings and Participants

We conducted the trial in outpatient clinics at the 9 university-based clinical centers of the Urinary Incontinence Treatment Network. We recruited participants through the investigators' clinical practices and through study announcements, advertisements, and referrals. We evaluated community-dwelling women who had urge incontinence only or urge-predominant incontinence, defined as an urge symptom index score greater than stress symptom index score on the Medical, Epidemiological, and Social Aspects of Aging Questionnaire (12). Clinical evaluation of potential participants included medical history, physical examination (measurement of height and weight, pelvic and rectal examination, and targeted neurologic assessment), and a 7-day bladder diary. For study eligibility, women had to report at least 7 episodes of incontinence in the diary, persistent incontinence for at least 3 months, no current use of antimuscarinics or other medications that could affect urinary incontinence, and no evidence that incontinence was secondary to neurologic or other systemic diseases. The **Appendix Table** (available at www.annals.org) lists the exclusion criteria.

Randomization and Interventions

Eligible participants were randomly assigned to drug therapy alone or drug therapy combined with behavioral therapy. Randomization was done at the coordinating center through a proprietary Web-based automated randomization system. A permuted-block randomization schedule with stratification by type of incontinence (urge only vs. mixed), number of incontinence episodes per week (7 to 13 per week vs. ≥14 per week), and clinical site ensured concealment of the allocation sequence.

We conducted treatment in 4 visits over 10 weeks, at intervals of 2 to 3 weeks, for both study groups. We considered attendance complete if a participant attended at least 3 visits. For intervention purposes, both groups completed a daily bladder diary throughout the 10 weeks of active therapy.

Drug therapy consisted of tolterodine tartrate (extended-release capsules), 4 mg/d. At the first treatment visit, participants received a 30-day drug supply, drug information, and recommendations for fluid management. Patients were also given handouts with recommendations for managing dry mouth and constipation, the most common drug side effects. The dose could be decreased to 2 mg to minimize side effects, or another antimuscarinic medication could be prescribed if the first was not tolerated. We performed pill counts at each visit to monitor adherence and

considered drug therapy complete if a patient took at least 80% of the prescribed drug regimen.

Combination therapy included drug and behavioral training. A nurse practitioner, nurse specialist, or physical therapist provided the behavioral intervention, which included teaching pelvic floor muscle control and exercises (using vaginal palpation); behavioral strategies to diminish urgency, suppress bladder contractions, and prevent both stress and urge incontinence (13, 14); delayed voiding to increase voiding intervals for those who voided more than 8 times per day; and individualized fluid management for those with excessive urine output (>70 oz per day). To support the training, we gave participants a handout listing hints for pelvic floor muscle training (**Appendix 2**, available at www.annals.org).

At each treatment visit, we assessed pelvic floor muscle strength by digital palpation and used the results to guide the exercise prescription, in which the frequency and duration of the exercise regimen was specified for the patients.

We evaluated patients at each treatment visit for adherence to exercise prescriptions (by using a self-administered exercise questionnaire) and behavioral strategies (by using questions administered by the interventionist). To optimize adherence, we identified barriers to the behavioral program and discussed possible solutions with the participant. To standardize implementation of the treatments across clinical sites, all interventionists attended a 2-day, in-person, centralized training program and were certified on all treatment components.

We discontinued both drug and behavioral training sessions at the end of stage 1 (10 weeks), a point at which most improvement has been achieved in previous trials (13, 14). We instructed participants receiving combination therapy to continue their behavioral program after discontinuation of drug therapy to maintain treatment effects.

During stage 2, we provided participants with a 2-month supply of the drug at no cost if they requested to resume drug therapy and did not have a urinary tract infection. We presented the option of receiving free drugs only after a patient requested to resume drug therapy to avoid introducing potential bias because of the "benefit" of free drugs.

Measurements, Outcomes, and Follow-up Procedures

We assessed patients at baseline, at the end of stage 1 (10 weeks), and at the end of stage 2 (8 months). We evaluated the primary outcome at the end of stage 2 (8 months) and defined it as not receiving drugs or any other therapy for urge incontinence and a 70% or greater reduction in frequency of incontinence episodes from baseline to end of stage 2, as recorded on the bladder diary. Our criterion of 70% reduction in incontinence episodes was based on data (15) indicating that this was a critical threshold for patient satisfaction.

Secondary outcomes included changes in frequency of incontinence episodes and voids, as recorded in the bladder diary. We measured severity of symptom distress and bother by using the Urogenital Distress Inventory (UDI) (16) and the Overactive Bladder Questionnaire (OAB-q) (17). We measured global ratings of patient satisfaction and perceived improvement by using 2 validated questions (13, 15): "How satisfied are you with your progress?" and "Overall, do you feel that you are much better, better, about the same, worse, or much worse?" We assessed condition-specific symptom impact by using the Incontinence Impact Questionnaire (16) and impact on quality of life by using the OAB-q health-related quality-of-life scale (17) and the Short-Form Health Survey (SF-12) (18).

We monitored patients for adverse events after the start of therapy by using information reported to the interventionist or clinician by the participant and from medical records. Clinicians reported adverse events by using a standard adverse event case report form. Consistent with labeling information, the following adverse events were precoded: urinary retention requiring catheterization, gastric retention, glaucoma or other sudden vision changes, anaphylactic reaction (including angioedema), peripheral edema, tachycardia or other cardiac arrhythmia, syncope, hallucinations, and small-bowel obstruction. Other adverse events were reported in an open-ended format. We considered known side effects of the study drug to be expected events and treated other events as unexpected. The clinical investigator reviewed events, assigned a severity level in accordance with U.S. Food and Drug Administration definitions, and decided whether to attribute each event to study treatment. A data and safety monitoring board (**Appendix 1**, available at www.annals.org) reviewed all events twice a year. We reported serious adverse events to the coordinating center, the sponsor, and the chair of the data and safety monitoring board within 72 hours.

Statistical Analysis

For the purposes of sample size estimation, we assumed that approximately 50% of patients would achieve success by our definition. A sample of 242 participants (121 per group) provided 85% power to detect a difference of 20 percentage points between treatments for the primary outcome at the 5% significance level by using a 2-sided test of difference in proportions. We increased the sample size to accommodate missing data and dropouts, resulting in a total target sample size of 300.

The primary end point analysis compared success rates between the 2 treatment groups at the end of stage 2 (8 months). We used life-table methods to estimate success rates in the 2 groups. For each observation interval, we computed the conditional probability of success. At 4 months and 6 months, we computed the conditional probability of success as the number of observed participants who had not used drugs or other therapy divided by those who had not returned to drugs before that time. At the 8-month visit, the conditional probability of success was calculated as the number of observed participants who did

not return to drug or other therapy and who achieved at least 70% reduction in the frequency of incontinence episodes divided by those who had not returned to drug therapy. If a woman requested or returned to drug use between visits, we counted her therapy as a failure beginning with the next visit. We then computed the cumulative probability of success at 8 months as the product of the interval-specific conditional estimates. We computed a 95% CI on the difference in success rates by using the standard errors of the estimates and assuming an asymptotically normal sampling distribution. We computed a sensitivity analysis to evaluate the robustness of the findings. One analysis was a complete case analysis in which we estimated the 8-month success rates only for women with complete follow-up data. The second analysis included all participants; we assumed that a patient's therapy had failed if her success status was unknown at 8 months. For these analyses, we used cross-classification and the Mantel–Haenszel method to control for randomization stratum.

As planned in the protocol, we computed 2 interim analyses: one when 50% of therapy failures had occurred and one when 72% had occurred. We used life-table methods to estimate the 8-month success rates and tested the hypothesis of no difference between treatment groups by using the log-rank hypothesis test. We used O'Brien–Fleming stopping rules (19), and the stopping boundary was not crossed in either analysis. After we adjusted for sequential analyses by using the method of Lan and DeMets (20), the significance level for the final analysis of the primary outcome was 0.033.

We conducted secondary analyses to examine outcomes at the end of active therapy (10 weeks) and at the end of stage 2 (8 months). To evaluate the changes in UDI, OAB-q, and average incontinence episodes per day, we compared mean differences between groups by using mixed-effect repeated measures analysis of variance, controlling for site and randomization stratum. We included all women who completed baseline or follow-up assessment or both. We performed all analyses by using SAS, version 9.1 (SAS Institute, Cary, North Carolina).

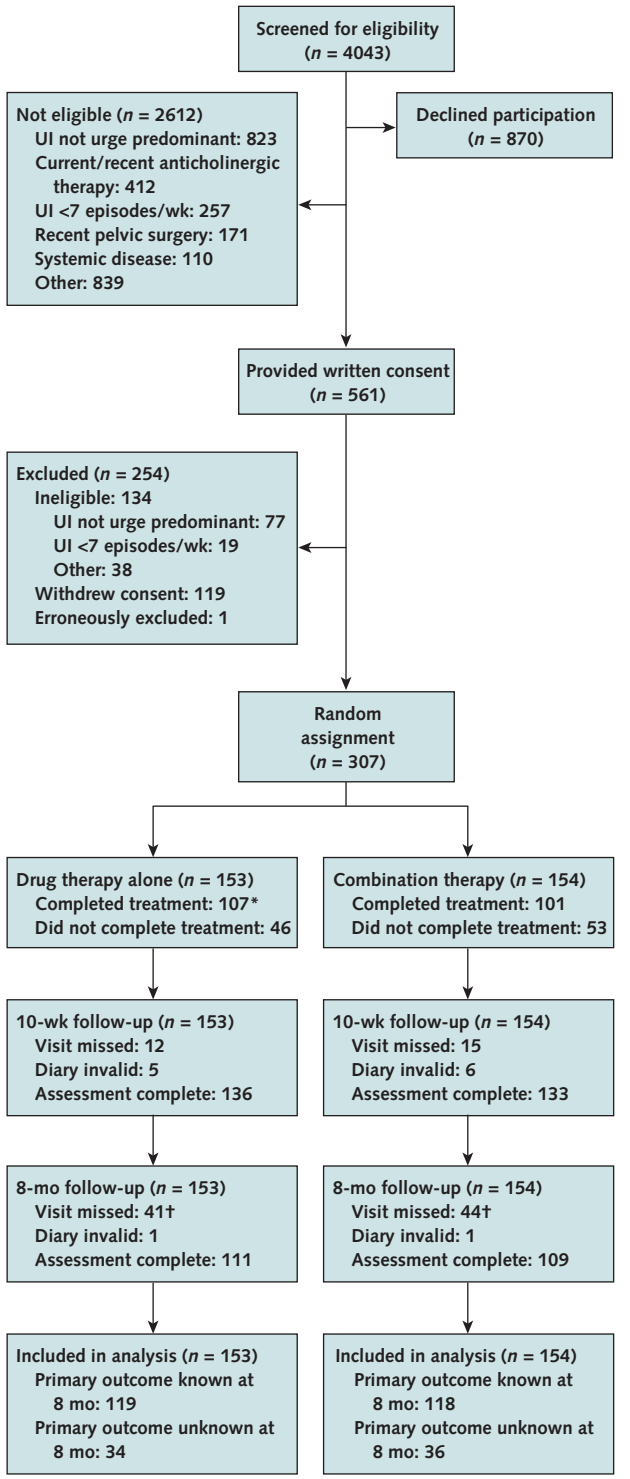
Role of the Funding Source

Our study was supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases, whose program staff were involved in the design and conduct of the study, analysis and interpretation of data, and preparation and review of the manuscript. Additional support, including provision of study drugs and funding, was contributed by Pfizer, whose staff reviewed and commented on the manuscript but were not involved in other aspects of the research.

RESULTS

We screened 4043 women; of the 561 who consented, we randomly assigned 307 (**Figure 1**). A total of 290 (94%) women attended at least 3 therapy visits, and 208

Figure 1. **Study flow diagram.**



UI = urinary incontinence.
* Defined as attending 3 or 4 intervention visits and taking 80% of prescribed drug.
† 17 women (8 in the drug therapy alone group and 9 in the combination therapy group) returned to drug or other therapy before 8 months.

Table 1. **Participant Characteristics, by Treatment Group**

Characteristic	Combination Therapy (*n* = 154)	Drug Therapy Alone (*n* = 153)
Mean age (SD), *y*	55.8 (14.2)	58.0 (13.5)
Ethnicity, *n (%)**		
Hispanic	13 (9)	17 (11)
Non-Hispanic white	105 (69)	85 (56)
Non-Hispanic black	22 (14)	35 (23)
Other non-Hispanic	13 (9)	15 (10)
Marital status, *n (%)*		
Married or living with partner	70 (46)	68 (44)
Not married	84 (54)	85 (56)
Level of education, *n (%)*		
High school or less	40 (26)	31 (20)
Some college or associate's degree	58 (38)	60 (39)
College	32 (21)	40 (26)
Graduate or professional degree	24 (16)	22 (14)
Mean Nam–Powers occupational status score (SD)	57.5 (23.3)	64.0 (24.3)
Mean duration of urge incontinence (SD), *y*	9.8 (9.5)	9.1 (10.3)
Previous nonsurgical treatment for incontinence, *n (%)*	59 (38)	46 (30)
Previous incontinence surgery, *n (%)*	19 (12)	22 (14)
Diuretic use, *n (%)*	15 (10)	14 (9)
Mean body mass index (SD), kg/m^2	33.2 (9.5)	32.3 (7.6)
Menopausal status, *n (%)*		
Premenopausal	35 (23)	31 (20)
Postmenopausal	96 (62)	102 (67)
Perimenopausal	20 (13)	18 (12)
Unsure	3 (2)	2 (1)
Type and frequency of incontinence, *n (%)*		
Urge, 7–13 episodes/wk	2 (1.3)	2 (1.3)
Urge, ≥14 episodes/wk	2 (1.3)	4 (2.6)
Mixed, 7–13 episodes/wk	46 (29.9)	46 (30.1)
Mixed, ≥14 episodes/wk	104 (67.5)	101 (66.0)

* We obtained information on the ethnicity of participants to characterize the study sample. The investigators defined the response options, and the participants classified themselves.

(68%) took at least 80% of the prescribed drug. All women who adhered to the drug regimen attended at least 3 visits, so the overall treatment adherence rate was 68% (66% in the combination therapy group and 70% in the drug therapy alone group).

Table 1 lists patient characteristics by treatment group. Although all participants had urge-predominant incontinence, most (97.4% in each group) also had symptoms of stress incontinence. Because so few women had urge incontinence only, we combined the data across type and controlled only for the frequency of incontinence stratum in further analyses.

Outcomes after Drug Therapy Discontinuation

We included all 307 women in the life-table analysis of the primary outcome. For 237 women, we knew whether treatment had failed at the end of stage 2 either because they had a complete assessment at 8 months (220 patients) or had requested to resume drug or other therapy before that time (17 patients). We included the remaining 70 women in the conditional interval-specific estimate for any visit at which we knew they had not resumed drug therapy. Of these, 68 were lost to follow-up (that is, they did not complete the 8-month visit) and 2 provided an invalid diary. The 2 treatment groups remained balanced on baseline characteristics after we excluded the 70 women with incomplete follow-up assessment (data not shown). The life-table analysis estimates of 8-month success rates were 41% for both groups (difference, 0 percentage points [95% CI, −12 to 12 percentage points]) (**Table 2**). **Table 3** lists specific reasons for therapy failure.

Secondary Urinary Symptom Outcomes

Of the 307 randomly assigned women, 27 did not attend the 10-week visit and 11 did not have a valid bladder diary at the end of active treatment, leaving 269 (88%) women for analysis. The 2 treatment groups remained balanced on baseline characteristics when we excluded the 38 women with missing 10-week diary data (data not shown). The mean number of incontinence episodes decreased substantially in both groups; however, the difference between treatment groups was minimal (**Table 4**). The percentage of women who achieved at least 70% reduction in incontinence episodes was higher in the combination therapy group than in the drug therapy alone group (69% vs. 58%; difference, 11 percentage points [CI, −0.3 to 22.1 percentage points]). Similarly, 21% of the women in the combination therapy group and 17% of those in the drug therapy alone group reported in their bladder diaries that they were totally dry.

At the end of stage 1, we found small changes in the average number of voids per day in both groups: a slight decrease in the combination therapy group (−0.5 void per day) and a slight increase in the drug therapy alone group (0.4 void per day), resulting in a difference of 0.9 fewer void per day (CI, 0.3 to 1.5 fewer voids per day) in the

Table 2. **Outcome Status at 8-Month Follow-up**

Outcome Status	Combination Therapy (*n* = 154)	Drug Therapy Alone (*n* = 153)	Difference, *percentage points*
Failure, *n (%)*	75 (49)	78 (51)	–
Success, *n (%)**	43 (28)	41 (27)	–
Missing, *n (%)*†	36 (23)	34 (22)	–
8-month success rate (95% CI), %			
Life-table analysis estimate	41 (32 to 50)	41 (33 to 50)	0 (−12 to 12)
Complete cases estimate	36 (27 to 45)	34 (25 to 43)	2 (−10 to 14)
Assuming those missing were failures	28 (21 to 35)	27 (20 to 34)	1 (−9 to 11)

* Defined as not receiving drugs or any other therapy for urge incontinence and a 70% or greater reduction in frequency of incontinence episodes from baseline to the end of 8 months, as recorded in the bladder diary.
† Missing 8-month visit or invalid diary.

combination therapy group than in the drug therapy alone group.

Mean symptom distress scores decreased during stage 1 and increased slightly from the end of stage 1 to the end of stage 2 for both groups (**Figure 2**). Nevertheless, the combination therapy group still showed greater improvement in symptom distress than the drug therapy alone group ($P < 0.001$ for time-by-treatment interaction).

Similar to the trend observed for the UDI, mean symptom bother scores on the OAB-q had decreased at the end of stage 1 and at the end of stage 2 (36.7 and 30.9 points for the combination therapy group, respectively, and 30.4 and 20.4 points for the drug therapy alone group), indicating that symptoms were less severe than at baseline. The improvement in symptom bother was greater in the combination therapy group than in the drug therapy alone group ($P < 0.001$ for time-by-treatment).

Patient Ratings

More women in the combination therapy group than in the drug therapy alone group reported that they were completely satisfied with their progress at the end of stage 1 (53% vs. 40%; difference, 13 percentage points [CI, 1 to 25 percentage points]) and at 8 months (33% vs. 20%; difference, 13 percentage points [CI, 2 to 24 percentage points]). Similarly, more women in the combination therapy group than in the drug therapy alone group rated their improvement with treatment as "better" or "much better" at the end of stage 1 (90% vs. 77%; difference, 13 percentage points [CI, 4 to 22 percentage points]) and at 8 months (69% vs. 43%; difference, 26 percentage points [CI, 14 to 38 percentage points]). Among women who perceived improvement after active treatment, persistence in perceived improvement at 8 months was greater for women in the combination therapy group (72%) than for women in the drug therapy alone group (54%) (difference, 17 percentage points [CI, 4 to 30 percentage points]).

Health-Related Quality-of-Life Outcomes

All 4 health-related quality-of-life impact measures improved in both treatment groups over time; however, the differences between groups were small.

Table 3. **Reasons for Therapy Failure***

Reason	Combination Therapy ($n = 75$), *n*	Drug Therapy Alone ($n = 78$), *n*
Before 8-month visit	29	36
Resumed drug use	29	34
Received other treatment	26	34
At 8-month visit	46	42
Resumed drug use	10	8
Received other treatment	10	9
<70% reduction in incontinence episodes	40	40

*Therapy could fail in a participant for more than 1 reason.

Adverse Events

A total of 12 events occurred in 6 participants (3 in each group). No deaths occurred. In the combination therapy group, 1 participant had a serious reaction to the study drug comprising 5 adverse events: blurred vision, syncope, night sweats, stomach cramping, and weakness. She discontinued use of the study drug after this experience. Another woman in that group had 3 adverse events: 2 episodes of small-bowel obstruction and an allergic reaction evidenced by pruritus and a rash. Her first bowel obstruction occurred during stage 1, and she was given extended-release oxybutynin instead of tolterodine. The other 2 events occurred during stage 2. A third woman had an adverse event (tachycardia) in the combination therapy group during stage 2.

In the drug therapy alone group, 1 woman had small-bowel obstruction during stage 1 but did not discontinue the drug. Another woman in that group experienced peripheral edema during stage 1 and discontinued use of the drug. In a third woman, renal cell carcinoma was diagnosed during stage 2.

DISCUSSION

Our results show that initial treatment with behavioral training in conjunction with an antimuscarinic drug did not increase the number of women with urge-predominant incontinence who were able to successfully discontinue drug therapy and maintain their improved continence compared with those receiving drug treatment alone. During active treatment, combination therapy resulted in greater reductions in the frequency of incontinence episodes than that achieved with drug therapy alone, although the CI on the difference included 0. In addition, evidence on secondary outcome measures indicated that combination therapy produced added benefit in terms of patient satisfaction, perceived improvement, and reduced bladder symptoms.

To our knowledge, this is the first clinical trial of urinary incontinence treatment to evaluate a combined end point of reduction in frequency of incontinence episodes and discontinuation of drug therapy. The impetus for this trial was the recognition that many patients who are prescribed an antimuscarinic medication do not adhere to the drug regimen on a long-term basis. Previous research (21) has shown that approximately two thirds of patients used antimuscarinic medication for less than 90 days and about three fourths for less than 150 days. In addition, antimuscarinics may work synergistically with behavioral intervention because of the differing mechanisms (22).

The purpose of behavioral training was to teach skills to prevent incontinence episodes, with the expectation that the benefits of training would persist after patients discontinued drug therapy. One possible explanation for the lack of effect is the context in which training was conducted. When a new motor skill is being learned, it should be

Table 4. **Adjusted Mean Incontinence Episodes per Week***

Variable	Incontinence Episodes, *n*	
	Combination Therapy (*n* = 154)	Drug Therapy Alone (*n* = 153)
Pretreatment	23.1	23.2
End of stage 1	2.7	4.7
Mean reduction	20.4	18.5
Difference between groups (95% CI), *percentage points*	1.9 (−2.0 to 5.9)	

* Computed from mixed-model analysis of variance, controlling for randomization stratum and site.

practiced in a context similar to that in which it will later be performed (23). We trained women to respond to urgency while receiving anticholinergic medications, which may have diminished or delayed sensation. When drug therapy was discontinued, we anticipated that participants could successfully implement urge-suppression skills in the new context. It is possible that the combined intervention did not allow the transfer of learned continence skills to the new sensory context after drug therapy was discontinued. A similar lack of training generalization to unpracticed sensory tasks has been reported in the perceptual learning literature (24, 25).

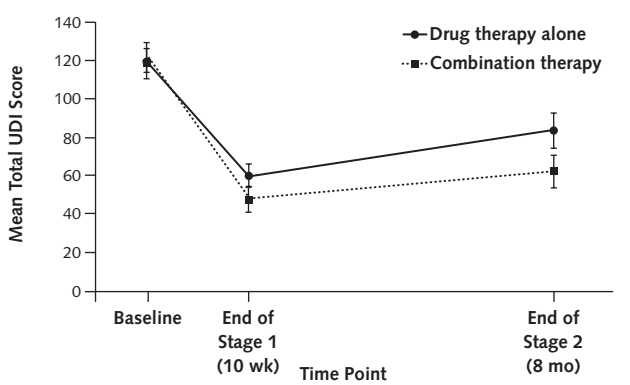
A MEDLINE search for English-language articles through December 2007 found no studies in which behavioral intervention enabled drug discontinuation; however, there are a few articles on combining active drug therapy with various behavioral interventions to enhance outcomes. Our findings are consistent with a previous trial (10) that did not show a difference in reduction of incontinence episodes between women who received tolterodine alone and those who received tolterodine combined with written instructions for a pelvic floor muscle exercise program. In another trial (9), written instructions for bladder training significantly increased the effects of tolterodine for reducing voiding frequency and increasing volume voided, but not for reducing incontinence episodes.

Although we did not find an additive effect of combination therapy on drug discontinuation, it is encouraging that levels of patient satisfaction and perceived improvement were greater in those who received combination therapy, both during active treatment and after discontinuation of drug therapy. It is possible that therapeutic interactions with the behavioral interventionist made women feel better about their treatment or that mastery of new continence skills gave them a better sense of control over urgency episodes. However, these women also reported greater reductions in symptom distress and bother on the UDI and OAB-q, which measure response to several symptom dimensions. This suggests that the patient's experience and satisfaction with treatment are not determined by change in frequency of incontinence episodes alone but may be influenced by changes in other features of their condition, such as volume of urine loss, frequency of voiding, or intensity of the urge sensation.

A limitation of this study is that the drug therapy alone group was also exposed to components of behavioral training. We gave these patients written recommendations for fluid management, and they completed the same daily bladder diaries as did participants in the combination therapy group. Neither of these behavioral components is usually provided when a drug is prescribed for urinary incontinence, and either may have improved outcomes in the drug therapy alone group, reducing differences between treatment groups. In particular, the self-monitoring effect of completing bladder diaries could have increased patients' awareness of their behavior and facilitated improvement. We provided instructions for fluid management to both groups because many providers, when prescribing antimuscarinics, advise their patients to avoid excess fluids to enhance efficacy. We asked patients in both groups to keep bladder diaries because they were needed as an outcome measure. Although completing daily bladder diaries could have facilitated improvement, our use of diaries in both groups controlled for this potential self-monitoring effect, so that any effects of behavioral training would not be attributable to this element.

In addition, only 68% of the women completed the assigned treatment, primarily because they did not complete the drug regimen. Treatment adherence was similar in the 2 treatment groups, and women who did not complete the assigned treatment were eligible for follow-up, consistent with the intention-to-treat principle. Thus, the internal validity of the study was preserved. Nevertheless, this completion rate indicates the difficulty many women

Figure 2. **Adjusted mean total Urogenital Distress Inventory (*UDI*) scores over time.**



Higher scores indicate greater symptom distress. Scores ranged from 0 to 255 at baseline, 0 to 230 at the end of stage 1, and 0 to 211 at stage 2, of a possible 300. We calculated adjusted mean UDI score and corresponding 95% CIs by using mixed-effect modeling, controlling for study site and randomization stratum.

have in using this drug and the need to develop improved therapies for urinary incontinence.

We were able to assess 8-month outcome status on 77% of randomly assigned participants, which is approximately the follow-up rate we expected when planning the study. Our primary outcome analysis (based on life-table methods) assumed that the success rate in the missing cases was the same as that in the observed cases. We also computed success rates with the assumption that all missing cases were treatment failures. Although the success rates differ according to those assumptions, the difference between the treatment groups is consistent across all analyses.

In conclusion, although the effectiveness of drug therapy and behavioral interventions for reducing urinary incontinence is well established, combining these treatments as initial therapy does not seem to be a useful approach to help women with urge incontinence discontinue drug therapy and subsequently sustain clinically important reductions of incontinence episodes. We found evidence that combination therapy produced added benefit in terms of patient satisfaction, perceived improvement, and reduction of bladder symptoms, perhaps reflecting a treatment effect on symptoms other than incontinence. Although combination therapy may be beneficial for reducing incontinence frequency during active treatment, a stepped approach, in which a single intervention is initiated first and then a second therapy is added for patients who do not achieve a satisfactory outcome (8), may be more practical and cost-effective for optimal management of women with urge incontinence.

From the University of Alabama at Birmingham and Department of Veterans Affairs, Birmingham, Alabama; University of Texas Health Sciences Center, San Antonio, Texas; University of California, San Diego, San Diego, California; Duquesne University and Magee Women's Hospital, University of Pittsburgh, Pittsburgh, Pennsylvania; University of Texas Southwestern, Dallas, Texas; University of Maryland, Baltimore, Maryland; Oakwood Hospital, Dearborn, Michigan; University of Utah Health Sciences Center, Salt Lake City, Utah; Loyola University Medical Center, Maywood, Illinois; New England Research Institutes, Watertown, Massachusetts; National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland; and University of Virginia Health Systems, Charlottesville, Virginia.

Presented as a poster presentation at the annual meeting of the International Continence Society, 20–24 August 2007, Rotterdam, the Netherlands, and as an oral presentation at the American Urogynecologic Society Annual Scientific Meeting, 27–29 September 2007, Hollywood, Florida.

Acknowledgment: The authors thank Susan McDermott, MPH, RN, CS, New England Research Institutes, for her role in project coordination and interventionist training; Heather Litman, PhD, New England Research Institutes, for statistical analysis; and the study interventionists, listed in **Appendix 1** (available at www.annals.org), for implementing the interventions.

Grant Support: By the National Institute of Diabetes and Digestive and Kidney Diseases (grants U01 DK58225, U01 DK58234, U01 DK58229, U01 DK58231, U01 DK60397, U01 DK60401, U01 DK60395, U01 DK60393, U01 DK60380, and U01 DK60379). Additional support, including provision of study drugs and funding, was contributed by Pfizer.

Potential Financial Conflicts of Interest: *Consultancies:* K.L. Burgio (Pfizer, Astellas Pharma, GlaxoSmithKline, Lilly, Ortho-McNeil, Novartis, Merck), S.R. Kraus (Pfizer, Lilly), P. Norton (Lilly, Pfizer, Novartis, Procter & Gamble), M.P. FitzGerald (GlaxoSmithKline, Astellas Pharma), G.E. Lemack (Pfizer, Astellas Pharma, Allergan, Novartis), T.C. Chai (Pfizer, Procter & Gamble), S. Khandwala (Ethicon, Astellas Pharma, Novartis), P.S. Goode (Ortho-McNeil), B. Nielsen-Omeis (Lilly-ICOS), W. Steers (Dynogen, Astellas Pharma, Sanofi, GlaxoSmithKline). *Honoraria:* S.R. Kraus (Novartis, Ortho-McNeil, Pfizer), V. Mallett (Astellas Pharma), M.P. FitzGerald (Medtronic), H.E. Richter (Pfizer), T. Rozanski (Pfizer), G.E. Lemack (Pfizer, Astellas Pharma, Allergan, Novartis), S. Khandwala (Ethicon), W. Steers (Watson, Astellas Pharma). *Stock ownership or options (other than mutual funds):* S. Menefee (Pfizer), A.M. Stoddard (Johnson & Johnson, Bristol-Meyers Squibb, Elan, Procter & Gamble), J.W. Kusek (Lilly, Pfizer), W. Steers (Johnson & Johnson). *Grants received:* K.L. Burgio (Pfizer, Alza), S.R. Kraus (Astellas Pharma, GlaxoSmithKline), S. Menefee (Solace Therapeutics, Renessa), M.P. FitzGerald (Pfizer, Astellas Pharma), H.E. Richter (Pfizer, Lilly, Bionovo), T.C. Chai (Pfizer), L. Brubaker (Pfizer, Allergan), P.S. Goode (Pfizer), K. Kenton (Pfizer), S.L. Tennstedt (Pfizer, Lilly-ICOS), W. Steers (Pfizer). *Other:* K.L. Burgio (Pfizer), H.M. Zyczynski (Johnson & Johnson, Novartis, Ethicon), L. Brubaker (Allergan, Pfizer, Q-Med), W. Steers (Astellas Pharma, Allergan).

Reproducible Research Statement: *Study protocol:* Published elsewhere (11). *Statistical code and data set:* The protocol, analytic data set, and the computer code used to generate the results are available from the Urinary Incontinence Treatment Network Data Coordinating Center, New England Research Institutes, Watertown, MA 02472. The study data set will also be available through the National Institute of Diabetes and Digestive and Kidney Diseases Data Repository at www3.niddk.nih.gov/research/resources in early 2009.

Corresponding Author: Kathryn L. Burgio, PhD, University of Alabama at Birmingham, Birmingham Veterans Affairs Medical Center, 11G, 700 South 19th Street, Birmingham, AL, 35233; e-mail, kburgio@aging.uab.edu.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Fantl JA, Newman DK, Colling J, Delancy JO, Keeys C, Loughery R, et al.** Urinary Incontinence in Adults: Acute and Chronic Management. Clinical Practice Guideline No. 2. Rockville, MD: Agency for Health Care Policy and Research; 1996. AHCPR publication no. 96-0682. Accessed at www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat6.chapter.9995 on 2 June 2008.

2. **Wagner TH, Hu TW.** Economic costs of urinary incontinence in 1995. Urology. 1998;51:355-61. [PMID: 9510336]

3. **Coyne KS, Zhou Z, Thompson C, Versi E.** The impact on health-related quality of life of stress, urge and mixed urinary incontinence. BJU Int. 2003;92:731-5. [PMID: 14616456]

4. **Seim A, Eriksen BC, Hunskaar S.** A study of female urinary incontinence in general practice. Demography, medical history, and clinical findings. Scand J Urol Nephrol. 1996;30:465-71. [PMID: 9008027]

5. **Andersson KE.** Antimuscarinics for treatment of overactive bladder. Lancet Neurol. 2004;3:46-53. [PMID: 14693111]

6. **Borello-France D, Burgio KL.** Nonsurgical treatment of urinary incontinence.

Clin Obstet Gynecol. 2004;47:70-82. [PMID: 15024274]
7. **Burgio KL.** Behavioral treatment options for urinary incontinence. Gastroenterology. 2004;126:S82-9. [PMID: 14978643]
8. **Burgio KL, Locher JL, Goode PS.** Combined behavioral and drug therapy for urge incontinence in older women. J Am Geriatr Soc. 2000;48:370-4. [PMID: 10798461]
9. **Mattiasson A, Blaakaer J, Høye K, Wein AJ. The Tolterodine Scandinavian Study Group.** Simplified bladder training augments the effectiveness of tolterodine in patients with an overactive bladder. BJU Int. 2003;91:54-60. [PMID: 12614251]
10. **Millard RJ. Asia Pacific Tolterodine Study Group.** Clinical efficacy of tolterodine with or without a simplified pelvic floor exercise regimen. Neurourol Urodyn. 2004;23:48-53. [PMID: 14694457]
11. **Urinary Incontinence Treatment Network (UITN).** Design of the Behavior Enhances Drug Reduction of Incontinence (BE-DRI) study. Contemp Clin Trials. 2007;28:48-58. [PMID: 16919506]
12. **Herzog AR, Diokno AC, Brown MB, Normolle DP, Brock BM.** Two-year incidence, remission, and change patterns of urinary incontinence in noninstitutionalized older adults. J Gerontol. 1990;45:M67-74. [PMID: 2313045]
13. **Burgio KL, Locher JL, Goode PS, Hardin JM, McDowell BJ, Dombrowski M, et al.** Behavioral vs drug treatment for urge urinary incontinence in older women: a randomized controlled trial. JAMA. 1998;280:1995-2000. [PMID: 9863850]
14. **Burgio KL, Goode PS, Locher JL, Umlauf MG, Roth DL, Richter HE, et al.** Behavioral training with and without biofeedback in the treatment of urge incontinence in older women: a randomized controlled trial. JAMA. 2002;288:2293-9. [PMID: 12425706]
15. **Burgio KL, Goode PS, Richter HE, Locher JL, Roth DL.** Global ratings of patient satisfaction and perceptions of improvement with treatment for urinary incontinence: validation of three global patient ratings. Neurourol Urodyn. 2006;25:411-7. [PMID: 16652380]
16. **Shumaker SA, Wyman JF, Uebersax JS, McClish D, Fantl JA.** Health-related quality of life measures for women with urinary incontinence: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Continence Program in Women (CPW) Research Group. Qual Life Res. 1994;3:291-306. [PMID: 7841963]
17. **Coyne KA.** Summary of the Validation of the OAB-q: A Disease-Specific Overactive Bladder Questionnaire. Report for Pharmacia Corporation. Bethesda, MD: MEDTAP International; 2002.
18. **Ware J Jr, Kosinski M, Keller SD.** A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996;34:220-33. [PMID: 8628042]
19. **O'Brien PC, Fleming TR.** A multiple testing procedure for clinical trials. Biometrics. 1979;35:549-56. [PMID: 497341]
20. **Lan KK, DeMets DL.** Discrete sequential boundaries for clinical trials. Biometrika. 1983;70:659-63.
21. **Yu YF, Nichol MB, Yu AP, Ahn J.** Persistence and adherence of medications for chronic overactive bladder/urinary incontinence in the california medicaid program. Value Health. 2005;8:495-505. [PMID: 16091027]
22. **Goode PS, Burgio KL, Locher JL, Umlauf MG, Lloyd LK, Roth DL.** Urodynamic changes associated with behavioral and drug treatment of urge incontinence in older women. J Am Geriatr Soc. 2002;50:808-16. [PMID: 12028165]
23. **Schmidt RA, Lee TD.** Motor Control and Learning: A Behavioral Emphasis. Champaign, IL: Human Kinetics; 1999.
24. **Carey LM, Matyas TA.** Training of somatosensory discrimination after stroke: facilitation of stimulus generalization. Am J Phys Med Rehabil. 2005;84:428-42. [PMID: 15905657]
25. **Ahissar M, Hochstein S.** Task difficulty and the specificity of perceptual learning. Nature. 1997;387:401-6. [PMID: 9163425]

Current Author Addresses: Drs. Burgio and Goode: University of Alabama at Birmingham, Birmingham Veterans Affairs Medical Center, 700 South 19th Street, Birmingham, AL 35233.
Dr. Kraus: University of Texas Health Science Center, Department of Urology, 7703 Floyd Curl Drive, San Antonio, TX 78229.
Dr. Menefee: Kaiser Permanente, 4647 Zion Avenue, San Diego, California 92120.
Dr. Borello-France: Duquesne University, 111 Health Sciences Building, Pittsburgh, PA 15282.
Drs. Corton and Lemack: University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9032.
Drs. Johnson and Chai: University of Maryland, 22 South Greene Street, Baltimore, MD 21210.
Dr. Mallett: University of Tennessee, 853 Jefferson Avenue, Memphis, TN 38115.
Dr. Norton: University of Utah, 50 North Madison Drive, Salt Lake City, UT 84132.
Drs. FitzGerald, Brubaker, and Kenton: Loyola University Medical Center, 2160 South First Avenue, B103-Room 1004D, Maywood, IL 60153.
Ms. Dandreo and Drs. Stoddard and Tennstedt: New England Research Institutes, 9 Galen Street, Watertown, MA 02472.
Dr. Richter: University of Alabama at Birmingham, 618 20th Street, S NHB 219, Birmingham, AL 35233.
Dr. Rozanski: University of Texas Health Science Center, 7703 Floyd Curl Drive, MC7845, San Antonio, TX 78229.
Dr. Albo: University of California at San Diego Medical Center, 200 West Arbor Drive, San Diego, CA 92103.
Dr. Zyczynski: University of Pittsburgh, 300 Halket Street, Pittsburgh, PA 15213.
Dr. Khandwala: Oakwood Hospital and Medical Center, 18101 Oakwood Boulevard, Dearborn, MI 48124.
Ms. Baker: University of Utah, 30 North 1900 East, Salt Lake City, UT 84132.
Ms. Nielsen-Omeis: University of Texas Health Science Center, Department of Urology, 2833 Babcock Road #200, San Antonio, TX 78229.
Dr. Nager: University of California at San Diego, 9350 Campus Point Drive, La Jolla, CA 92037.
Drs. Kusek, Chang, and Nyberg: National Institutes of Health, 6707 Democracy Boulevard, Bethesda, MD 20892.
Dr. Steers: University of Virginia, Department of Urology, Box 800472, Charlottesville, VA 22908.

Author Contributions: Conception and design: K.L. Burgio, S.R. Kraus, D. Borello-France, H.W. Johnson, V. Mallett, P. Norton, M.P. FitzGerald, H.E. Richter, M. Albo, H.M. Zyczynski, G.E. Lemack, T.C. Chai, J. Baker, L. Brubaker, P.S. Goode, B. Nielsen-Omeis, C.W. Nager, K. Kenton, S.L. Tennstedt, J.W. Kusek, L.M. Nyberg, W. Steers.
Analysis and interpretation of the data: K.L. Burgio, S.R. Kraus, S. Menefee, D. Borello-France, V. Mallett, P. Norton, M.P. FitzGerald, T. Rozanski, H.M. Zyczynski, A.M. Stoddard, P.S. Goode, C.W. Nager, S.L. Tennstedt, J.W. Kusek, L.M. Nyberg.
Drafting of the article: K.L. Burgio, S.R. Kraus, S. Menefee, D. Borello-France, M. Corton, V. Mallett, P. Norton, M.P. FitzGerald, H.E. Richter, A.M. Stoddard, P.S. Goode, S.L. Tennstedt, W. Steers.
Critical revision of the article for important intellectual content: K.L. Burgio, S.R. Kraus, S. Menefee, D. Borello-France, M. Corton, H.W. Johnson, P. Norton, M.P. FitzGerald, K.J. Dandreo, H.E. Richter, T. Rozanski, M. Albo, H.M. Zyczynski, G.E. Lemack, T.C. Chai, J. Baker, L. Brubaker, A.M. Stoddard, P.S. Goode, B. Nielsen-Omeis, C.W. Nager, K. Kenton, S.L. Tennstedt, J.W. Kusek, W. Steers.
Final approval of the article: K.L. Burgio, S.R. Kraus, S. Menefee, D. Borello-France, M. Corton, H.W. Johnson, P. Norton, M.P. FitzGerald, K.J. Dandreo, H.E. Richter, T. Rozanski, M. Albo, H.M. Zyczynski, T.C. Chai, L. Brubaker, A.M. Stoddard, P.S. Goode, B. Nielsen-Omeis, C.W. Nager, K. Kenton, S.L. Tennstedt, J.W. Kusek, T.D. Chang, L.M. Nyberg, W. Steers.
Provision of study materials or patients: S.R. Kraus, S. Menefee, V. Mallett, P. Norton, M.P. FitzGerald, H.E. Richter, T. Rozanski, M. Albo, H.M. Zyczynski, T.C. Chai, J. Baker, L. Brubaker, P.S. Goode, B. Nielsen-Omeis, C.W. Nager, K. Kenton.
Statistical expertise: A.M. Stoddard.
Obtaining of funding: S.R. Kraus, P. Norton, H.E. Richter, M. Albo, T.C. Chai, L. Brubaker, S.L. Tennstedt, J.W. Kusek.
Collection and assembly of data: M. Albo, S. Khandwala.

Appendix 1: Urinary Incontinence Treatment Network

Steering Committee

Grant numbers in parentheses are unique identifiers assigned to each site by the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland.

University of Virginia, Charlottesville, Virginia: William Steers, MD (*Chair*).

William Beaumont Hospital, Royal Oak, and Oakwood Hospital, Dearborn, Michigan: Ananias Diokno, MD; Veronica Mallett, MD; and Salil Khandwala, MD (U01 DK58231).

Loyola University Medical Center, Maywood, Illinois: Linda Brubaker, MD, and Mary P. FitzGerald, MD (U01 DK60379).

University of Alabama at Birmingham, Birmingham, Alabama: Holly E. Richter, PhD, MD, and L. Keith Lloyd, MD (U01 DK60380).

University of California, San Diego, California: Michael Albo, MD, and Charles W. Nager, MD (U01 DK60401).

University of Maryland, Baltimore, Maryland: Toby C. Chai, MD, and Harry W. Johnson, MD (U01 DK60397).

University of Pittsburgh, Pittsburgh, Pennsylvania: Halina M. Zyczynski, MD, and Wendy Leng, MD (U01 DK58225).

University of Texas Southwestern, Dallas, Texas: Philippe Zimmern, MD, and Gary Lemack, MD (U01 DK60395).

University of Texas Health Sciences Center, San Antonio, Texas: Stephen R. Kraus, MD, and Thomas Rozanski, MD (U01 DK58234).

University of Utah, Salt Lake City, Utah: Peggy Norton, MD, and Lindsey Kerr, MD (U01 DK60393).

New England Research Institutes, Watertown, Massachusetts: Sharon L. Tennstedt, PhD, and Anne M. Stoddard, ScD (U01 DK58229).

National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland: T. Debuene Chang, MD; John W. Kusek, PhD; and Leroy M. Nyberg, MD, PhD.

National Institute of Child Health and Human Development, Rockville, Maryland: Anne M. Weber, MD.

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; Jerry Lowder, MD; Karl Luber, 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; and 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; and 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, MSN, WHNP; 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; and Karen VandeVegt, PT.

Biostatistical Coordinating Center

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

Data and Safety Monitoring Board

Elizabeth A. Gormley, MD (*Chair*), Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; Paul Abrams, MD, Bristol Urological Institute, Bristol, United Kingdom; Diedre Bland, MD, Blue Ridge Medical Associates, Winston–Salem, North Carolina; J. Quentin Clemens, MD, Northwestern University Medical School, Chicago, Illinois; John Connett, PhD, University of Minnesota, Minneapolis, Minnesota; William Henderson, PhD, University of Colorado, Aurora, Colorado; Dee Fenner, MD, University of Michigan, Ann Arbor, Michigan; Sheryl Kelsey, PhD, University of Pittsburgh, Pittsburgh, Pennsylvania; Deborah Myers, MD, Brown University School of Medicine, Providence, Rhode Island; Jacek Mostwin, MD, Johns Hopkins Hospital, Baltimore, Maryland; and Bassem Wadie, MBBCh, MSc, MD, Mansoura Urology and Nephrology Center, Mansoura, Egypt.

Appendix 2: Helpful Hints for Pelvic Floor Muscle Exercises

In women, important pelvic organs (the bladder, uterus, and bowel) are supported by muscles and other tissues. Stress incontinence occurs when the supportive structures weaken. Stress incontinence typically occurs with a sneeze, cough, lifting a heavy object, or during exercise. Urge incontinence, on the other hand, occurs when the bladder muscle contracts at the wrong time, causing urine to be pushed out. Exercising the pelvic floor muscles can help reduce both forms of incontinence. This handout will help you understand the muscles and how to exercise them better. The pelvic floor muscles, called the levator ani muscles, attach to your pelvis in a way that creates a "sling or hammock-like" support. These muscles support the pelvic organs and help prevent urine leakage.

The following tips may help you exercise these muscles effectively.

1. Recognizing the right muscles to contract is important. The muscles you need to work are the same muscles you would use to hold back gas or a bowel movement. When you squeeze these muscles, you should feel a tightening around your vagina and anus. As these muscles get stronger, think about drawing the pelvic floor (the area around your vagina and anus) "up and inward."

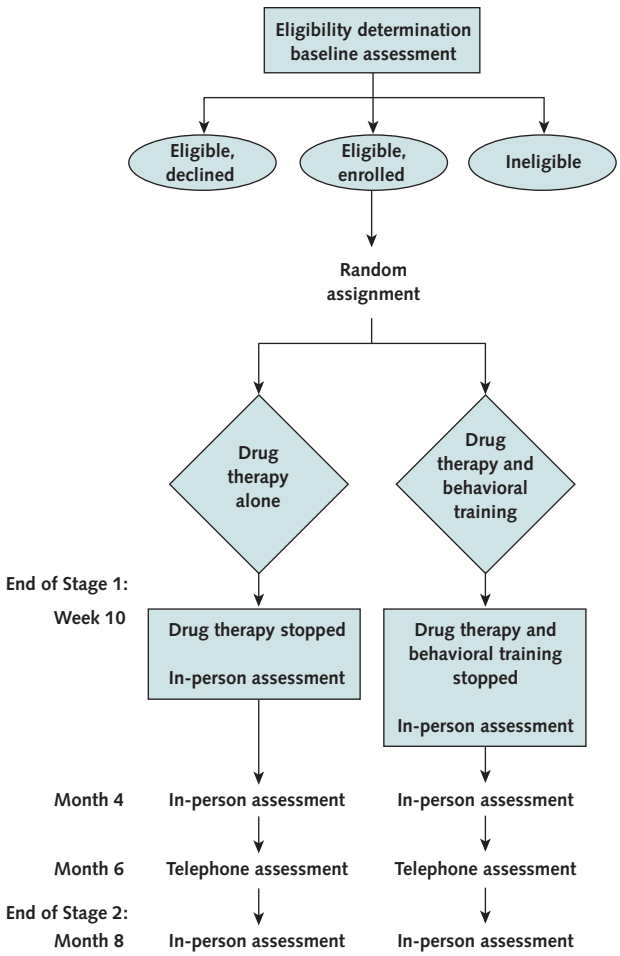
2. Breathe during the exercises. Holding your breath can raise your blood pressure. If you have difficulty breathing, count aloud while you contract your muscles. This will force you to breathe while you exercise.

3. Do not "bear down" or push when you exercise. This will cause strain on your pelvic floor. Instead, you need to think about drawing the pelvic floor upwards, like an elevator.

4. Tensing your stomach muscles can also place a strain on your pelvic floor. Place a hand on your abdomen as you exercise. This will help you tell if you are tensing these muscles instead of the pelvic floor muscles.

5. Relax your muscles completely between each contraction for the entire time recommended by your interventionist. Relaxing the muscle between each contraction allows blood and oxygen to flow to the muscle. Proper relaxation will prevent your muscles from getting too tired.

Appendix Figure. **Alternate study flow diagram.**



Appendix Table. **Exclusion Criteria**

Age <21 y
Pregnant, planned to become pregnant in the next 8 mo, or could bear children but declined to use medically acceptable birth control
<6 mo postpartum delivery or other termination after 20 wk of gestation
Unable to contract pelvic floor muscles during evaluation
Participated in a formal behavioral therapy program of >2 mo in the past 2 y
Reported continual leakage or always being damp
Hypersensitive to study drug (extended-release tolterodine)
Systemic disease known to affect bladder function (e.g., Parkinson disease, multiple sclerosis, spina bifida, or spinal cord injury or trauma)
Currently using catheter to empty bladder
Postvoid residual volume >150 mL
Treatment for pelvic organ prolapse with pessary <3 mo
Incontinence, vaginal, bladder, or prolapse surgery in the past 6 mo
Urethral diverticulum, current or repaired
Previous augmentation cystoplasty or artificial sphincter
Neuromodulation for pelvic indications
Currently using anticholinergic agents, cholinergic agonists, tricyclic antidepressants, or duloxetine—must have discontinued use for ≥4 wk
Currently using diuretics with dosage change in past 3 mo
Uncontrolled medical problem (e.g., poorly controlled diabetes or decompensated congestive heart failure)
History of bladder or pelvic cancer or pelvic radiation therapy
Glaucoma, without ophthalmologist clearance
Gastric retention (by medical history)
Nonambulatory (may use assistive device)
Participation in another intervention trial that might influence the results of the trial