21

Burgio K[1], Urinary Incontinence Treatment Network [2]
1. University of Alabama at Birmingham and Birmingham VA Medical Center, 2. National Institute of Diabetes & Digestive & Kidney Diseases, NIH

COMBINING BEHAVIOR AND DRUG THERAPY TO IMPROVE DRUG WITHDRAWAL IN THE TREATMENT OF URGE INCONTINENCE: A RANDOMIZED TRIAL

Hypothesis / aims of study
The primary aim of this study was to determine whether combining behavioral training and drug therapy for the treatment of urge incontinence increases the number of women who can successfully discontinue drug therapy and sustain a significant reduction of incontinence episodes. Secondary aims were to investigate the impact of combined therapy on frequency of incontinence, urinary symptoms, patient satisfaction, and quality of life outcomes.

Study design, materials and methods
We conducted a multi-center randomized clinical trial of drug therapy combined with behavioral therapy compared to drug therapy alone in 307 community-dwelling women, (mean age = 56.8 years) with predominant urge incontinence. At randomization, women were stratified on type of incontinence (urge only vs. mixed) and severity (<14 vs. $\geq$ 14 incontinence episodes per week) based on bladder diary. While patients were aware of their randomization selection, investigators remained blinded to treatment modality. The first stage of the trial was 10 weeks of drug therapy with sustained-release tolterodine alone or combined with behavioral training (pelvic floor muscle training and exercise, bladder control techniques, delayed voiding, and fluid management). In the second stage, drug therapy was withdrawn and behavioral training stopped. The primary composite outcome measured at 8 months was (1) successful drug withdrawal (i.e. not requesting drug or any other treatment for incontinence) and (2) achieving and maintaining $\geq$ 70% reduction in the frequency of incontinence episodes on bladder diary. Other measures were a 7-day bladder diary, Patient Satisfaction Questionnaire [1], Urogenital Distress Inventory (UDI) [2], Overactive Bladder Questionnaire (OAB-q) [3], Incontinence Impact Questionnaire (IIQ) [2], and Short-Form Health Survey (SF-12). The sample size provided 85% power to detect a 20 percentage point difference between treatment groups for the primary outcome.

Results
After 10 weeks of active treatment, 70.7% of patients in combined therapy and 59.6% in the drug only group achieved a 70% or greater reduction of incontinence (P = 0.06). At the 8-month primary endpoint, an intention-to-treat analysis showed no significant difference between combined therapy and drug therapy alone in the number of women who were able to discontinue the drug and maintain a $\geq$ 70% reduction in incontinence episodes (27.9% vs. 26.8%, respectively, P = 0.83). Similarly, an analysis of completers (n = 242, 79%) showed that 35.8% of women in combined therapy and 33.6% of women in drug therapy alone had successfully discontinued drug therapy (P = 0.72). However, significantly more women in the combined therapy group reported that they were completely satisfied with their progress compared to women in the drug alone group, both at 10 weeks (53% vs. 40% P = 0.05) and at 8 months (33% vs. 20%, P = 0.007). Similarly, more women in the combined therapy group rated their improvement with treatment as “better” or “much better” compared to women in the drug only group at 10 weeks (47% vs. 33%, P = 0.016) and at 8 months (26% vs.12%; P < 0.001). On the UDI and OAB-q, there were also significant group differences across time (P = 0.027, P = 0.003 respectively), indicating lower symptom distress in the combined therapy group and a significant interaction between treatment and time point (P < 0.001 for each), with less worsening of symptoms following drug withdrawal in the combined therapy group. Both groups showed significant improvement on the IIQ and SF-12 with treatment, but differences between the groups for these quality of life measures were not significant.

Interpretation of results
Initial treatment with combined behavioral and drug therapy was no better than drug therapy alone in reducing the frequency of incontinence episodes. Moreover, combined therapy did not enhance the patient’s ability to withdraw from drug therapy successfully. Behavioral therapy was implemented while women were on drug therapy (i.e., in the context of diminished urge sensation and bladder overactivity) with the expectation that they would utilize their behavioral continence skills after the drug was withdrawn. Training patients while on drug therapy and then withdrawing drug may have undermined the successful use of continence skills in the context of increased urgency or bladder overactivity when the patient was no longer taking the drug. Further, initiating behavioral and drug therapy at the same time may undermine patient adherence to the behavioral program.

While combined therapy did not produce greater reductions in the frequency of incontinence episodes, it did result in greater patient satisfaction and perceived improvement. Greater improvements on the UDI and OAB-q indicate that these findings may be due to greater effects for combined therapy on a spectrum of bladder symptoms other than incontinence frequency.

Concluding message
Although drug therapies and behavioral interventions are well-established for their effectiveness in reducing urge incontinence, combining these modalities as initial therapy does not appear to be a useful approach to helping women with urge incontinence discontinue drug therapy and sustain improvements thereafter. A stepped approach, in which a single intervention is initiated first and then a second therapy added for patients who do not achieve a satisfactory outcome, may be a more practical and effective approach to management of women with urge urinary incontinence.

References
1. Neurourol Urodynam (2006) 25; 411-417.

2. Qual Life Res (1994) 3; 291-306.
3. Unpublished Report for Pharmacia Corp, Bethesda MD: MEDTAP International, Inc. (2002).

FUNDING: Supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases (U01 DK 58225, U01 DK58234, U01 DK58229, U01 DK58231, U01 DK60397, U01 DK60401, U01 DK60395, U01 DK60393, U01 DK60380, U01 DK60379). Additional support provided by the National Institute of Child Health and Human Development and Pfizer, Inc.
CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov NCT00090584
HUMAN SUBJECTS: This study was approved by the Institutional Review Board for Human Use at the University of Alabama at Birmingham and each clinical site in the UITN and followed the Declaration of Helsinki Informed consent was obtained from the patients.