Effects of combined behavioral intervention and tolterodine on patient-reported outcomes

Jean F. Wyman, PhD,[1] Carl Klutke, MD,[2] Kathryn Burgio, MD,[3] Zhonghong Guan, MD,[4] Franklin Sun, MS,[4] Sandra Berriman, PhD,[4] Tamara Bavendam, MD[4]

[1]School of Nursing, University of Minnesota, Minneapolis, Minnesota, USA
[2]Department of Surgery, Washington University School of Medicine, St. Louis, Missouri, USA
[3]Birmingham/Atlanta Geriatric Research, Education and Clinical Center, Department of Veterans Affairs, and University of Alabama at Birmingham, Birmingham, Alabama, USA
[4]Pfizer Inc, New York, New York, USA

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Objective: *To assess the effects of tolterodine extended release (ER) plus behavioral intervention on urgency and other patient-reported outcomes in subjects with overactive bladder (OAB) who were previously dissatisfied with antimuscarinic treatment.*

Methods: *In this 16-week, multicenter, open-label study, eligible adults (aged ≥ 18 y) reported dissatisfaction with their most recent antimuscarinic OAB medication; ≥ 8 micturitions and ≥ 2 urgency episodes per 24 hours and ≥ 1 UUI episode in 5 day bladder diaries; and OAB symptoms for ≥ 3 months. Subjects received tolterodine ER plus a behavioral educational handout with verbal reinforcement of behavioral intervention content for 8 weeks. Those satisfied with treatment at week 8 continued with this therapy; those dissatisfied received tolterodine ER plus individualized behavioral intervention (pelvic floor muscle training, tailored behavioral techniques) for 8 weeks. Endpoints were changes from baseline in daytime and nocturnal micturition-related urgency episodes and frequency-urgency sum (a measure of urgency severity and frequency) reported in 5 day bladder diaries at weeks 4, 8, 12, and 16; Patient Perception of Bladder Condition (PPBC), Overactive Bladder Questionnaire (OAB-q), and Urgency Perception Scale (UPS) scores at weeks 8 and 16.*

Results: *Daytime and nocturnal urgency episodes and frequency-urgency sum were significantly reduced at all time points (all $p < 0.0001$). Significant improvements were also observed in PPBC, OAB-q Symptom Bother and Health-Related Quality of Life, and UPS scores at weeks 8 and 16 (all $p < 0.0001$).*

Conclusions: *Patients with OAB who are dissatisfied with antimuscarinic therapy may experience improved treatment outcomes by adding a self-administered behavioral intervention to their drug regimen.*

Key Words: Overactive bladder, behavioral intervention, patient-reported outcomes, urgency urinary incontinence, combination therapy, antimuscarinic

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Address correspondence to Dr. Jean F. Wyman, School of Nursing, University of Minnesota, 5-140 Weaver-Densford Hall, 308 Harvard Street, S.E., Minneapolis, MN 55455 USA

Introduction

Overactive bladder (OAB) is defined by the International Continence Society as urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia.[1,2] It is a prevalent condition, reported by approximately 11% of men and 13% of women in Europe and North America.[3] OAB with or without urgency urinary incontinence (UUI) is associated with

an increased risk for several comorbidities, including falls and fractures, urinary tract and skin infections, sleep disturbances, and depression.[4] OAB symptoms are also bothersome and profoundly affect aspects of health-related quality of life (HRQL).[5]

Although antimuscarinics are first-line treatments for OAB,[6] conservative behavioral approaches to the treatment of OAB and UUI have emerged that aim to change patient behavior and teach continence skills.[7-10] When used alone, behavioral interventions significantly reduce the frequency of incontinence episodes.[8,9] Behavioral interventions have demonstrated efficacy in improving the outcomes of pharmacotherapy for OAB and UUI.[7,8,11] For example, combined treatment with behavioral intervention and an antimuscarinic has been shown to reduce incontinence episodes in older women with UUI,[12] to significantly reduce voiding frequency, and to increase voided volume per micturition,[13] compared with drug therapy alone. Another study showed that a significantly greater proportion of subjects receiving tolterodine plus a brief educational intervention either started or continued with drug treatment and reported improvement in bladder symptoms compared with subjects receiving tolterodine alone.[14]

In a recent, 16-week, multicenter, multiphase, single-arm, open-label study, behavioral therapy combined with tolterodine extended release (ER) resulted in high rates of treatment satisfaction and significantly improved OAB symptoms in subjects who were dissatisfied with their most recent antimuscarinic therapy.[15] The results indicated that patients with OAB who are dissatisfied with antimuscarinic treatment can achieve treatment satisfaction by using a simple self-administered behavioral intervention consisting of an educational pamphlet and verbal reinforcement of the information. In addition, the findings did not differ for subjects who had previously been dissatisfied with tolterodine compared with those who had previously been dissatisfied with another antimuscarinic.

In this study, we present a protocol-specified analysis of secondary outcomes from this 16-week open-label study. These outcomes included the treatment effects of tolterodine ER plus behavioral intervention on urgency, the defining symptom of OAB, as measured by bladder diaries as well as subjects' general assessment.[15] Also assessed were the effects of this intervention on other OAB-specific, validated, patient-reported outcome (PRO) instruments that measure symptom bother, HRQL, and perception of bladder-related problems. These measures complement diary measures because they reflect the patient's perspective on treatment impact, which may not always parallel changes in symptoms.[16,17]

Methods

Study design

This is a protocol-specified analysis of data from a 16-week, multicenter, multiphase, single-arm, open-label study (ClinicalTrials.gov Unique ID: NCT00230789), the details of which have been published elsewhere.[15] Briefly, subjects who reported being dissatisfied with their most recent antimuscarinic OAB therapy at screening received a combination of tolterodine ER (4 mg; morning or nighttime dosing) with self-administered behavioral intervention for the first 8 weeks of the study. Subjects who reported treatment satisfaction after the first 8 weeks of the study continued with tolterodine ER and self-administered behavioral intervention; those who reported being dissatisfied with treatment received a combination of tolterodine ER and individualized behavioral intervention for an additional 8 weeks.

Behavioral interventions

The behavioral interventions were implemented according to a standardized protocol and were described previously.[15] Briefly, the self-administered behavioral intervention consisted of a focused, patient-friendly, 2-page educational pamphlet[15] giving general information about OAB and behavioral interventions, including scheduled voiding, pelvic floor muscle training, urgency control strategies, and lifestyle interventions (fluid modifications, bladder irritant avoidance, constipation prevention, smoking cessation, and weight loss). Male and female versions of the OAB patient education sheet are available at http://www.pfizerpro.com/toviaz in the patient education section. Study physicians and/or nurses reviewed the pamphlet with subjects for up to 10 minutes at each visit and encouraged them to use it at home. Subjects reporting dry mouth or constipation during the study were provided with additional handouts on management strategies.

In the individualized behavioral intervention, study physicians and/or nurses assessed the behavioral interventions that were attempted or currently used by the subject and provided education, encouragement, and assistance to refine the strategies included in the educational pamphlet to fit the subject's preferences and needs. This intervention took approximately 30 minutes and was performed at weeks 8 and 12. Subjects also received a pelvic floor muscle examination conducted by the study physicians and/or nurses to ensure proper exercise technique, but no biofeedback equipment was used.

Subjects

Subjects were male and female outpatients (aged ≥ 18 y) recruited in 66 centers within the United States, reporting ≥ 8 micturitions per 24 hours, ≥ 2 micturition-related urgency episodes per 24 hours, and ≥ 1 UUI episode in a 5-day bladder diary completed at baseline; OAB symptoms for ≥ 3 months; and at least "some moderate problems" on the Patient Perception of Bladder Condition (PPBC) questionnaire.[18] Subjects were recruited at each center through newspaper advertisements, flyers, physician referrals, and through patient registries. The study protocol was approved by the Institutional Review Boards of each participating investigational center. Subjects were compensated for travel expenses at the discretion of the study center. Eligible subjects reported being "a little dissatisfied" or "very dissatisfied" with their previous treatment with 1 to 2 antimuscarinic OAB medications (darifenacin, oxybutynin, tolterodine, trospium, solifenacin) on the validated Perception of Treatment Satisfaction question.[19]

Outcome measures

Bladder diary measurement of urgency

Subjects completed a 5-day bladder diary at baseline and at weeks 4, 8, 12, and 16, in which they recorded the time of every micturition and rated the sensation associated with every micturition using the 5-point Urinary Sensation Scale (USS; 1 = no urgency, 2 = mild urgency, 3 = moderate urgency, 4 = severe urgency, 5 = UUI).[20] Daytime micturition-related urgency episodes were defined as micturitions receiving a USS rating of ≥ 3 that were recorded between the time the subject arose and the time they went to bed for the night. Nocturnal micturition-related urgency episodes were defined as micturitions receiving a USS rating of ≥ 3 that were recorded during the remainder of the 24-hour period. Changes from baseline to weeks 4, 8, 12, and 16 were assessed in the number of daytime and nocturnal micturition-related urgency episodes and daytime and nocturnal frequency-urgency sum (a measure of urgency severity and frequency that equals the sum of all USS ratings reported in the 5-day bladder diary).

Urgency Perception Scale

The validated Urgency Perception Scale (UPS)[21] was used to assess subjects' perception of urgency to urinate and was administered at baseline and at weeks 8 and 16. The UPS is a single-item instrument with a 3-point, ordered, categorical response scale as follows: (1) "I was usually not able to hold urine at all"; (2) "I was usually able to hold urine until I reached a toilet"; (3) "I was usually able to finish what I was doing before going to the toilet."

Patient Perception of Bladder Condition

The Patient Perception of Bladder Condition was administered at baseline and at weeks 8 and 16. The PPBC is a validated single-item questionnaire that asks subjects to indicate their overall bladder condition ranging from: 1, "My bladder condition does not cause me any problems at all"; to 6, "My bladder condition causes me many severe problems".[18] Lower response scores are indicative of a more positive perception of overall bladder condition.

Overactive Bladder Questionnaire

The 33-item validated Overactive Bladder Questionnaire (OAB-q) was administered at baseline, week 8, and week 16. The OAB-q includes an 8-item Symptom Bother scale and a 25-item HRQL scale.[22] Subjects rated the level of bother associated with their bladder condition during the past 4 weeks on the Symptom Bother scale from 1 ("not at all") to 6 ("a very great deal"), on which lower scores indicate less symptom bother. The HRQL scale comprises four domains (Coping, Concern, Sleep, and Social Interaction). For each domain, subjects indicate how often their OAB symptoms affected various activities during the past 4 weeks on a scale of 1 ("all of the time") to 6 ("none of the time"), on which higher scores indicate better HRQL. Each OAB-q scale or domain score is transformed so that scores range from 0 to 100.[22]

Statistical methods

The full analysis set included all subjects who took ≥ 1 dose of study drug and had ≥ 1 outcome assessment (either baseline or postbaseline), and the safety analysis set included all subjects who took ≥ 1 dose of study drug.

Summary statistics (mean and SD) were calculated for numeric changes in bladder diary variables from baseline to weeks 4, 8, 12, and 16 and for changes in PPBC, UPS, and OAB-q scale and domain scores from baseline to weeks 8 and 16. Mean differences between baseline and each post-baseline time point were assessed using paired *t* tests with a significance level of $p < 0.05$.

The overall changes in PPBC and UPS scores from baseline to week 8 and 16 were categorized as either a ≥ 0 numeric change (improvement) or ≤ 0 numeric change (no improvement) compared with baseline. A 4-category analysis was also performed for PPBC scores (2-point improvement, 1-point improvement, no change, and deterioration), and a 3-category analysis

was performed for UPS scores (≥ 1-point improvement, no change, and deterioration).

A subanalysis comparing the outcomes of subjects who had been previously dissatisfied with tolterodine treatment with those who had been previously dissatisfied with other antimuscarinic agents was prespecified in the study protocol in addition to the analysis for all subjects without this stratification. Because similar results were observed in subjects previously dissatisfied with tolterodine and those dissatisfied with other antimuscarinic agents, unless indicated, only the results obtained from analyses of the entire cohort are reported here.

Results

Demographics and baseline clinical characteristics

The disposition and demographics of enrolled subjects have been described previously.[15] Briefly, of 417 subjects enrolled, 416 received tolterodine ER treatment combined with self-administered behavioral intervention. Among these 416 subjects, 48 (12%) discontinued, including 11 (3%) for reasons related to the study drug (10 [2%] due to an adverse event and 1 [0.2%] due to a lack of efficacy), and 37 (9%) for reasons not related to the study drug (23 [6%] due to default on study protocol, 5 [1%] due to an adverse event, and 9 [2%] due to other reasons). Antimuscarinics received before enrollment in the study for the treatment of OAB included, tolterodine (n = 221; 53%), oxybutynin (n = 86; 21%), solifenacin (n = 85; 21%), darifenacin (n = 28; 7%), and trospium chloride (n = 4; 3%). Among subjects in the full analysis set, the mean percentage compliance with study medication was 98% (n = 374). All subjects received self-administered behavioral intervention during the first 8 weeks of the study; 87% (n = 328) of subjects at week 8 and 89% (n = 330) of subjects at week 12 continued to receive self-administered behavioral intervention; 13% (n = 50) and 11% (n = 42) of subjects were receiving individualized behavioral intervention at these time points. Most (98%, n = 405) subjects were assessed as able to isolate the pelvic floor muscles at baseline.

Among the safety analysis set, the mean age of subjects was approximately 60 years, 87% were women, and 79% were white, Table 1. The mean duration since first diagnosis of OAB symptoms was 6.7 years (range, 0.0-56.3 y), and 92% (n = 382) of subjects reported having ≥ 1 disease or syndrome at screening. At baseline, 99% (n = 391) of subjects reported some moderate, severe, and many severe bladder-related problems on the PPBC (four subjects reported "some minor problems" on the PPBC and were in default of the enrollment criteria for the study).

Urgency diary measurements

After 4 weeks of combined tolterodine ER and behavioral intervention, mean (SD) daytime and nocturnal micturition-related urgency episodes were significantly reduced from baseline (-2.8 [3.6] and -0.7 [1.1], respectively; both $p < 0.0001$), Figure 1a. These significant improvements in daytime and nocturnal micturition-related urgency episodes (all $p < 0.0001$) continued through 8 weeks (-3.4 [3.7] and -0.8 [1.1]), 12 weeks (-3.8 [3.8] and -1.0 [1.2]), and 16 weeks (-4.1 [3.9] and -1.0 [1.3]), Figure 1a.

Compared with baseline, the mean (SD) daytime and nocturnal frequency-urgency sums were significantly reduced after 4 weeks of combined intervention (-9.4 [11.1] and -2.7 [4.3], respectively; both $p < 0.0001$), Figure 1b. These values were again significantly reduced (all $p < 0.0001$) through week 8 (-11.3 [11.4] and -3.1 [4.2]), week 12 (-12.5 [11.7] and -3.6 [4.6]), and week 16 (-13.5 [11.8] and -3.7 [4.8]), Figure 1b.

Reductions in daytime and nocturnal urgency episodes and frequency-urgency sums were similar for subjects previously dissatisfied with tolterodine and those dissatisfied with other antimuscarinic agents (results not shown).

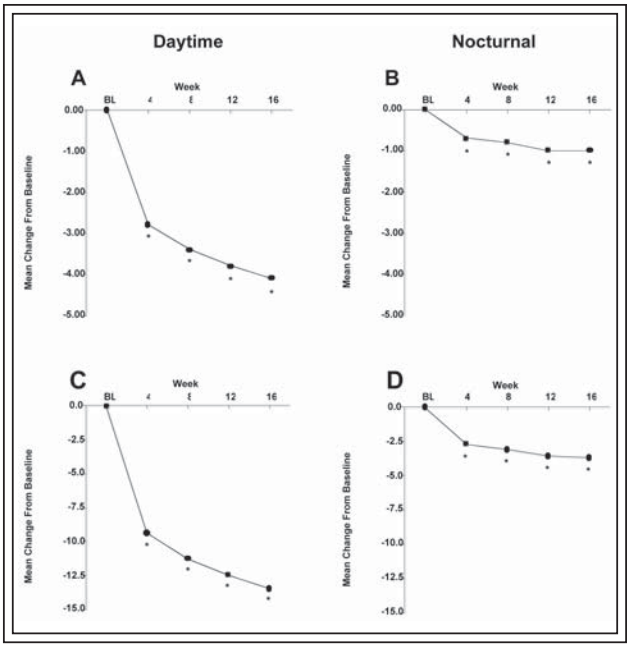

Figure 1. Mean numeric change from baseline to weeks 4, 8, 12, and 16 in daytime and nocturnal micturition-related urgency episodes (A and B); daytime and nocturnal frequency-urgency sum (C and D). BL = baseline. *$p < 0.0001$ compared with baseline.

TABLE 1. **Demographic and baseline clinical characteristics***

Women, n (%)	360 (87)
Age, mean (SD) y	60.2 (13.8)
Range	20-91
Race, n (%)	
White	330 (79)
Black	43 (10)
Asian	22 (5)
Other	21 (5)
Subjects with ≥ 1 current disease or syndrome, n (%)	382 (92)
Duration since first diagnosis of OAB, y (range)	6.7 (0.0-56.3)
Urinary Sensation Scale (USS) variables, mean (SD)	
Micturition-related urgency episodes†	
Daytime	7.4 (3.6)
Nocturnal	1.7 (1.2)
Frequency-urgency sum‡	
Daytime	31.4 (12.0)
Nocturnal	7.0 (4.8)
Urgency Perception Scale, n (%)	
Not able to hold urine	123 (31)
Able to hold urine without leaking until I reach a toilet immediately	257 (66)
Able to finish the ongoing work before going to the toilet without leaking	11 (3)
Patient Perception of Bladder Condition, n (%)	
No problems at all	0 (0)
Some very minor problems	0 (0)
Some minor problems	4 (1)
Some moderate problems	162 (41)
Severe problems	173 (44)
Many severe problems	56 (14)
Overactive Bladder Questionnaire, mean (SD)	
Symptom bother	61.3 (18.5)
Total HRQL	51.1 (22.5)
Concern	46.1 (25.7)
Coping	45.2 (25.9)
Sleep	45.6 (26.7)
Social interaction	73.1 (24.7)

HRQL = Health-related Quality of Life;
OAB = overactive bladder
*Demographic and clinical data represent the safety and full analysis sets, respectively (n = 416).
†Defined the number of micturitions receiving a USS rating ≥ 3.
‡Defined as the sum of all reported urgency ratings.

Urgency Perception Scale

Compared with baseline, mean (SD) Urgency Perception Scale (UPS) scores were significantly improved at week 8 and 16 (0.5 [0.7] and 0.6 [0.7], respectively; both $p < 0.0001$). A two-category analysis showed that 48% (n = 187) of patients in the full analysis set with non-missing data (n = 391) reported an improvement in UPS scores from baseline to week 8, and 54% (n = 214) reported an improvement from baseline to week 16. The distribution of scores among three UPS categories also revealed that 48% and 54% of subjects reported improvement at week 8 and week 16 of treatment, with 3% of subjects reporting deterioration at each time point, Figure 2.

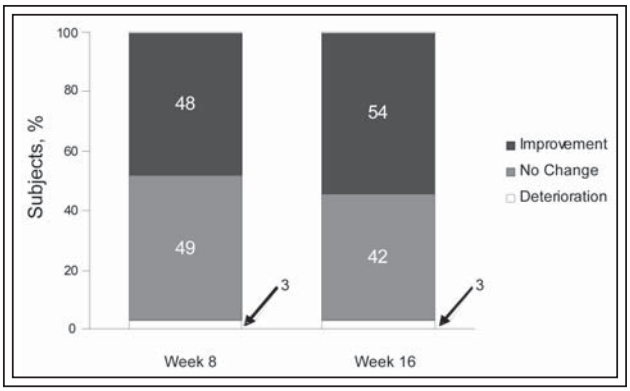

Figure 2. Categoric analysis of changes from baseline to week 8 and week 16 in Urgency Perception Scale scores. Numbers in bars correspond to percentages of subjects in each category.

Patient Perception of Bladder Condition

Compared with baseline, mean (SD) Patient Perception of Bladder Condition (PPBC) scores were significantly improved at week 8 and 16 (-1.4 [1.1] and -1.8 [1.1], respectively; both $p < 0.0001$). Consistent with this, a 2-category analysis showed that 82% (n = 322) of subjects in the full analysis set with non-missing data (n = 392) reported an improvement in PPBC scores from baseline to week 8, and 88% (n = 349) reported an improvement from baseline to week 16. The 4-category distribution of PPBC scores also revealed notable percentage improvements (1-point improvement, 39%; ≥ 2-point improvement, 43%) after 8 weeks of treatment, Figure 3, which was maintained at week 16 (1-point improvement, 28%; ≥ 2-point improvement, 61%).

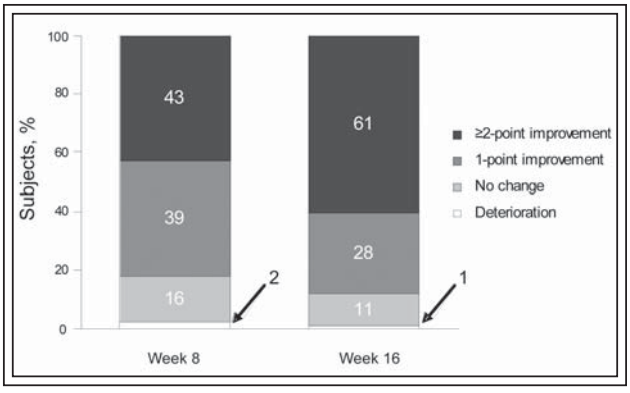

Figure 3. Categoric analysis of changes in Patient Perception of Bladder Condition scores from baseline to week 8 and week 16. Numbers in bars correspond to percentages of subjects in each category.

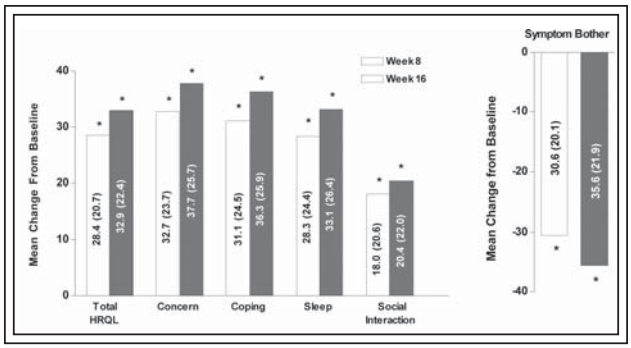

Figure 4. Baseline to week 8 and week 16 changes in Overactive Bladder Questionnaire scale and domain scores. Numbers in bars correspond to mean (SD) changes from baseline. *$p < 0.0001$ versus baseline.

Overactive bladder questionnaire

After 8 weeks of intervention, significant improvements from baseline to week 8 were reported for Symptom Bother, total HRQL, and Coping, Concern, Sleep, and Social Interaction scores (all $p < 0.0001$; Figure 4, and these improvements were maintained at week 16. Changes in scores from baseline to weeks 8 and 16 on the Symptom Bother and total HRQL scales and all four domains exceeded the Minimally Important Difference of 10 points, defined as the smallest difference in score that is clinically meaningful.[23]

Discussion

In a previous report based on data from this study, we investigated the effects of combined therapy with tolterodine ER and behavioral intervention on treatment satisfaction and bladder diary measures of incontinence and voiding frequency in subjects who were dissatisfied with previous antimuscarinic treatment.[15] We found that 91% of these subjects who were dissatisfied with previous antimuscarinic treatment became at least "a little satisfied" with tolterodine ER plus self-administered behavioral intervention at week 8, and most of these subjects reported being "very satisfied." Notably, among 33 subjects who were dissatisfied at week 8, 76% reported being at least "a little satisfied" at week 16 after individualized behavioral intervention. Significant improvements in bladder diary variables (total micturitions, urgency-related micturitions, UUI episodes, nocturnal micturitions) were observed by week 4 and continued through week 16. Treatment satisfaction ratings were significantly correlated with improvements in bladder diary variables, as has been observed in previous placebo-controlled studies.[19]

The present findings expand those of the previous study by demonstrating improvements in both daytime and nocturnal urgency-related micturitions within 4 weeks of treatment, with improvements being maintained at weeks 8, 12, and 16. This is important because of the prevalent and bothersome nature of nocturnal OAB symptoms.[5,24] These improvements in urgency episodes were paralleled by improvements in PPBC, OAB-q Symptom Bother and HRQL, and UPS scores by the first assessment at week 8, as well as at week 16. Taken together with the results of our previous study,[15] these findings suggest that in addition to high rates of treatment satisfaction and improvements in urgency and other diary variables, tolterodine ER plus behavioral intervention was associated with improvements in subjects' subjective assessment of their bladder-related problems, urgency, and emotional and physical aspects of HRQL.

These findings provide support for additive or synergistic treatment effects resulting from a combination of antimuscarinic and behavioral therapies.[8] The value of adding the self-administered educational pamphlet to tolterodine ER treatment during the first 8 weeks of the current study may be viewed as providing a simple means to reduce OAB symptoms and perceived impact of OAB in patients for whom previous antimuscarinic treatment had failed. Consistent with this, it was shown in a recent trial that the addition of behavioral training to drug therapy resulted in greater patient satisfaction and greater reductions in urinary symptom distress and bother.[25] However, this treatment regimen did not increase the number of subjects who could discontinue drug therapy while maintaining improved urinary incontinence.[25] Thus, although self-administered behavioral intervention alone might exhibit some treatment efficacy, this approach alone might not be sufficient to replace drug therapy.

In contrast to the present results, a recent study reported that improvements in bladder diary variables and HRQL elicited by darifenacin treatment were not enhanced by the addition of an educational program.[26] However, the study did not specify dissatisfaction with prior antimuscarinic treatment as an inclusion criterion. Moreover, the educational program used multiple pamphlets and multimedia materials, rather than the focused self-administered behavioral intervention used in the present study.

Collectively, the results presented here and in our previous study[15] indicate that clinicians may both increase treatment satisfaction and be able to avoid using more invasive therapies if pharmacotherapy alone fails by combining pharmacotherapy with simple behavioral intervention approaches. The results also suggest that it is not necessary to switch from one drug to another in order to improve the outcomes of patients who are dissatisfied with their treatment. Rather, it may be possible to improve symptom bother, HRQL, and perceived severity of bladder-related problems by introducing a self-administered behavioral intervention at the initiation of pharmacotherapy. This may be particularly relevant to patients who have been referred to an incontinence specialist after being started on drug treatment without behavioral education.

A limitation of this study is that it was not possible to determine the effects of behavioral intervention alone on urgency variables and other PROs, because all subjects received combined therapy. Nor is it possible to discern the effect of the therapeutic relationship on treatment outcomes since all subjects received brief or extended behavioral counseling in addition to their drug therapy. In addition, it should be noted that data obtained from subjects who had received the self-administered behavioral intervention and the individualized behavioral intervention during the last 8 weeks of the study were pooled for assessment of outcomes at week 16. Whereas the study design allowed for a comparison between the outcomes of subjects who had received each intervention at week 16, statistical analysis of observed differences was rendered impractical by the relatively small number of subjects who opted for the individualized intervention during the last 8 weeks of the study (n = 50). Another limitation is that the reasons for dissatisfaction cited by subjects for their most recent antimuscarinic therapy were not collected in this study, which might potentially affect responses reported on the PROs measures used. Other questions remaining to be addressed include the extent to which verbal reinforcement contributes to the efficacy of the behavioral interventions and whether the use of simple educational handouts can also improve subjects' tolerance of adverse effects.

Conclusions

The results of this study reveal the utility of adding a simple behavioral educational intervention in combination with pharmacotherapy to improve urinary urgency and other PROs among patients with OAB who have not responded to previous antimuscarinic treatment. Clinicians can help ensure optimal treatment outcomes for patients who receive drug therapy by providing brief instruction using standard educational materials on behavioral interventions for OAB. This approach imposes little cost or burden on the clinician and is well suited to and easily implemented in primary and specialty care settings. □

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