Protocol

"Combined Behavioral and Drug Treatment of Overactive Bladder in Men"

(COBALT)

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Specific Aims

Overactive Bladder (OAB) is a very common, distressing condition that manifests in bothersome lower urinary tract symptoms (LUTS) of urgency, frequent urination, nocturia or urgency incontinence, and impacts the lives of millions of men. These symptoms are most often treated with pharmacologic therapies (primarily alpha-blocking agents and/or antimuscarinic agents) or behavioral treatment (pelvic floor muscle training, urge suppression, delayed voiding). Behavioral treatment has substantial evidence in women, as well as data from a recent trial indicating that behavioral training is as effective as antimuscarinic therapy for reducing OAB symptoms in men. Although behavioral and drug therapies (even combined drug therapies) are effective, a major limitation has been that they is not usually curative, and most patients, though improved, continue to have symptoms and bother. Thus, there is a need to improve interventions for OAB symptoms.

The proposed multi-site trial will extend our previous research by examining a possible way to enhance the effectiveness of OAB/LUTS treatment in men by combining behavioral and drug therapy. Previous research provides evidence that combined drug + behavioral treatment can improve these symptoms in women. However, results of studies in women cannot be generalized to men, because the etiologies and mechanisms of these symptoms may be different in men. Therefore, the goal of this study is to determine whether combining behavioral and drug therapy improves outcomes in the treatment of OAB symptoms in men, and to examine two models for implementing combined therapy. To this end, we propose the following three aims:

Specific Aim #1: to evaluate the effectiveness of combined behavioral + drug therapy compared to behavioral treatment alone and drug therapy alone for improving urgency, frequency, nocturia, incontinence, and quality of life in men.

Specific Aim #2: to compare two methods of implementing combined therapy: simultaneously as initial combined therapy vs. stepped therapy, in which initial treatment with behavioral or drug therapy alone is followed by combined behavioral and drug therapy.

Specific Aim #3: to examine the costs and cost-effectiveness of combined behavioral + drug therapy compared to behavioral therapy alone and drug therapy alone. This project will use the methods of cost-effectiveness analysis to help us understand the added costs and value of combining interventions.

With two years of NIDDK ARRA funding, we have completed a pilot and feasibility study and laid the groundwork for this multi-site, 3-arm, randomized trial of combined drug + behavioral therapy for men with OAB symptoms. Community-dwelling men, 40 years of age or older, with urgency and 9 or more voids per 24-hours on 7-day diary have been randomized to 6 weeks of behavioral treatment alone (pelvic floor muscle training + urge suppression + delayed voiding), drug therapy alone (selective alpha-1a-receptor antagonist + antimuscarinic), or combined behavioral + drug therapy. In the step-up phase of the trial, patients who first received behavior or drug treatment alone were stepped up into an additional 6 weeks of combined treatment, to improve outcome as much as possible. Outcomes of this stepped approach at 12 weeks are assessed by comparison with the group initially randomized to combined therapy and continued for 12 weeks. Bladder diaries completed by participants before and after treatment are used to calculate reduction in the frequency of urination (primary outcome) and other targeted LUTS (urgency, urgency incontinence, and nocturia). Other secondary outcome measures include validated patient global ratings of improvement and satisfaction, the Overactive Bladder Questionnaire (OAB-q) to assess symptom bother and condition-specific health-related quality of life, and the International Prostate Symptom Score questionnaire (IPSS) to assess symptoms. We hypothesize that combined therapy will result in better outcomes than either behavioral or drug therapy alone.

To date, we have demonstrated feasibility and productivity by achieving the following benchmarks: established a 3-site network, finalized the study protocol, developed all data collection tools and forms, obtained IRB approvals at all sites, created the UAB Coordinating Center led by the biostatistician, established and piloted the database on a dedicated SharePoint site, completed centralized training for coordinators and interventionists, recruited, enrolled and randomized 86 participants, and completed treatment for 73 participants with an 8.2% drop-out rate. The data have provided an estimate of the outcome variability of combined therapy in this sample, enabling sample size calculation for the definitive trial. With this foundation, we propose to include the participants already enrolled in the pilot and feasibility study as a formal internal pilot and request funding to continue this trial as designed and initiated to completion of the needed sample (N=201). Including participants already treated in the internal pilot represents an efficient approach to completing the trial successfully in a timely and cost-effective manner. Completion of the trial will allow definitive results for the three specific aims and conclusions about the effectiveness and relative value of combined behavioral + drug therapy for OAB symptoms in men.

RESEARCH STRATEGY

SIGNIFICANCE

Overactive bladder (OAB) is a very common, distressing condition that manifests in bothersome lower urinary tract symptoms (LUTS) of urgency, frequent urination, urge incontinence, and nocturia, and impacts the lives of millions of men.[1-3] OAB is usually defined as urgency, with or without urge incontinence, and is commonly associated with increased daytime frequency of urination (voiding more than 8 times per day) and/or nocturia (waking from sleep more than once at night to void).[4]

Epidemiological studies indicate that OAB symptoms affect between 17% and 45% of community-dwelling adults,[1,2,5,6] and that they increase with age in both men and women.[1,2,7-9] Data on men living in the community indicate that 12% of men experience urinary incontinence with 5-16% experiencing moderate to severe symptoms.[10] Research on incontinence specifically and OAB symptoms in general has demonstrated that they can have a major impact on quality of life,[11] and that frequency and/or urgency might be equally as bothersome as urine leakage.[1] Urinary incontinence, in particular, is a significant source of dependency among older adults and a widely cited factor in nursing home admissions. The costs of OAB and urinary incontinence are enormous, accounting for an estimated $12.6 billion and $19.5 billion each year respectively.[12]

The two main treatments for OAB symptoms are pharmacologic therapies (with alpha-blocking agents, antimuscarinic agents, and/or 5-alpha reductase inhibitors) and behavioral treatments (including bladder training and behavioral training with pelvic floor muscle training and urge suppression strategies).

Drug Therapy

The goal of pharmacotherapy is to decrease detrusor overactivity and increase bladder capacity, thus reducing LUTS. For men, most urologists believe this is accomplished best by relieving obstruction caused by benign prostatic hypertrophy.[13] Alpha-adrenergic receptor antagonists (alpha-blockers) are common first-line pharmacotherapy for LUTS in men. 5-Alpha reductase inhibitors (5-ARIs) and antimuscarinics may be added if the alpha-blockers do not satisfactorily control the symptoms or substituted if the alpha-blockers are not tolerated. Recent data also support the use of daily phosphodiesterase-inhibitors for the treatment of LUTS in men.[14-16] Having four different classes of pharmaceuticals with unique mechanisms of action for improving male LUTS supports the concept that LUTS in men have multiple causes.

Alpha-1-adrenergic receptor antagonists, which reduce smooth muscle tone in the prostate and bladder neck and decrease bladder outlet resistance, often improve OAB symptoms. Even in men with urodynamic studies that rule out clinically overt obstruction, the contribution of low levels of obstruction to the etiology of OAB symptoms is unknown and alpha blocker therapy may relieve their symptoms.[17] Although most alpha-1a-adrenergic receptor antagonists are equally effective, selective alpha-1a-adrenergic receptor antagonists such as tamsulosin are generally preferred to non-selective alpha-1-adrenergic receptor antagonists due to improved side effect profiles. The decreased affinity for the receptors in vascular smooth muscle minimizes the likelihood of causing orthostatic hypotension, which is common in older men and can lead to falls. Selective alpha-1a-blockers are the standard of care in the urologic community.[17]

For men with larger prostates (>30 grams) 5-alpha reductase inhibitors (5-ARIs) have been shown to be effective for the treatment of LUTS.[18] Of the two FDA approved 5-ARIs (two isoforms exist), both decrease the circulating amount of dihydrotestosterone (DHT) in the prostate, which decrease androgenic growth and prostate size. The reduction in DHT corresponds to a15-25% shrinkage of the prostate over a 6-month period. Thus, 5-ARIs in men with larger prostates produce LUTS improvement. Recent studies also indicates that PDE improve LUTS among men with BPH; however, the exact mechanism is not known.[14-16]

Antimuscarinic agents inhibit detrusor contractions by interfering with the major neurohumoral stimulus for bladder contraction, acetylcholine, acting on post-ganglionic parasympathetic muscarinic receptor sites on the bladder smooth muscle.[19] There are now 6 antimuscarinic drugs available in the United States, but few comparative trials among these drugs to guide selection.[20] Evidence supports equal efficacy for available antimuscarinic drugs, but fewer side effects with extended release formulations.[20] Extended release formulations also allow once-a-day dosing, which increases adherence compared with drugs that require multiple doses per day. We chose to use extended-release tolterodine for the proposed trial because it has the most efficacy and safety data in men with LUTS.[18,21,22]

Evidence suggests that treatment with combined alpha-1a-blockers and antimuscarinics is much more effective than either agent alone. A 12-week, multi-site, randomized trial in 654 men with OAB compared a selective alpha-1a-blocker (tamsulosin), an antimuscarinic (tolterodine), and the two combined. This trial demonstrated improvement in urge urinary incontinence in all three arms, but improvement in urgency, frequent urination, and nocturia only occurred with the two drugs combined. The International Prostate Symptom Score QOL item was improved at all time points for combined therapy and for weeks 1 and 12 for the alpha-blocker alone, but at no time points for the antimuscarinic drug alone.[23] Several more trials have shown the efficacy and safety of combined drug therapy in men with LUTS.[18,22,24] Based on this evidence, we elected to use combined selective alpha-1a-blocker and antimuscarinic therapy in this proposal, specifically tamsulosin and tolterodine.

Behavioral Treatments

Many studies have demonstrated that behavioral interventions are effective for reducing LUTS, in women and men, particularly urge incontinence and voiding frequency.[25-32] The purpose of behavioral treatment is to improve bladder control through systematic changes in patient behavior and environmental conditions. Behavioral treatments were recognized for their efficacy by the 1988 Consensus Conference on Urinary Incontinence in Adults.[33] Later, they were recommended as a first-line therapy by the Guideline for Urinary Incontinence developed by the AHCPR (now AHRQ).[34] The primary behavioral interventions for OAB symptoms are bladder training and behavioral training with pelvic floor muscle exercise.

Bladder training is a behavioral intervention developed originally for the treatment of urge urinary incontinence. The goal of bladder training is to break the cycle of urgency and frequency using consistent, incremental voiding schedules. The most definitive study of bladder training is a randomized clinical trial that demonstrated a mean 57% reduction in frequency of incontinence in older women.[25] Our own previous work has utilized behavioral training to teach patients specific skills and behaviors to improve bladder control.[26-32] Behavioral training is an intervention that combines exercise science, motor learning, motor control, and behavior therapy principles into an increasingly accepted, conservative treatment for urge incontinence and other LUTS. The goal of behavioral training is to improve bladder control by teaching the patient to voluntarily suppress detrusor contractions. This involves a new response to urgency through learned use of pelvic floor muscle contractions to control urgency and inhibit detrusor contractions. [35]

Historically, pelvic floor muscle exercises have been regarded primarily as a treatment for stress incontinence, but it is increasingly recognized that pelvic floor muscles play a role in treating urge UI and other OAB symptoms. Ordinarily, patients with OAB feel compelled to rush to the nearest bathroom when they feel the urge to void. In behavioral training, they are told how this natural response is actually counterproductive and can increase the probability of incontinence. Not only does rushing add physical pressure on the bladder, it enhances the sensation of fullness, exacerbates urgency, and triggers detrusor contraction. Further, when the patient reaches the vicinity of the toilet, he/she is exposed to visual cues that can trigger incontinence. Although the new response is counterintuitive at first, patients can learn instead to stop what they are doing, sit down if possible, and contract the pelvic floor muscles repeatedly to suppress detrusor contraction, diminish urgency, and prevent urine loss. They concentrate on voluntarily inhibiting the urge sensation and wait for the urge to subside before they walk at a normal pace to the toilet.

The effectiveness of behavioral training has been established in several studies.[26-32] In the first randomized controlled trial, conducted with older women, behavioral training reduced incontinence episodes significantly more than drug treatment and patient perceptions of improvement and satisfaction with their progress were higher with behavioral training.[26] Mean reductions of incontinence using a comprehensive program of behavioral training range from 63% to 86%.Our clinical trial data indicate that older women with urge or mixed (urge and stress) incontinence achieved a mean 81% reduction of incontinent episodes and decreased frequency of urination from 10 voids per 24 hours to 8 voids per 24 hours with behavioral training administered by a certified nurse practitioner.[36] Subsequent studies in women and in men with post-prostatectomy incontinence demonstrated that the results of behavioral training using biofeedback versus verbal feedback based on vaginal or anal palpation did not differ significantly,[30,32] indicating that careful training with either method can achieve good results.

Although most studies of behavioral interventions for OAB have been conducted in women, there is a growing body of evidence for their effectiveness in men as well. For example, in studies of behavioral training in men with incontinence secondary to prostatectomy, frequency of incontinence episodes was reduced by a mean 51-81%.[28,32] Data from our recent trial demonstrated that behavioral training is also effective for reducing

frequency of urination in men with OAB symptoms (See Preliminary Studies).[31] The proposed study will further our understanding of the role of behavioral treatment for men with OAB symptoms, particularly in relation to standard drug therapy, and extend this research to examine the effectiveness of combined behavioral and drug therapy as a way to enhance clinical outcomes of intervention.

Combined Behavioral and Drug Therapy

Although behavioral and drug therapies are known to reduce OAB symptoms, especially urge incontinence, few patients are actually cured with either treatment alone, and little is known of their combined effects. One potential way to improve the efficacy of OAB treatment is to combine these treatment modalities. Some clinicians combine behavioral and drug treatments with the hypothesis that decreasing detrusor instability with a pharmacologic agent provides a measure of control that will allow the patient to be able to better learn volitional control of detrusor contractions.

There are two reasons to believe that combining drug and behavioral treatment might enhance patient outcomes. First, although the mechanisms by which these therapies work have not been established completely, there is evidence that they operate by different means, suggesting that they may have additive effects.[36] Our previous research has shown that change on urodynamic parameters, such as bladder capacity or detrusor overactivity, may be mediators of change with drug therapy, but is clearly not necessary for improvement with behavioral intervention.[36] Second, there is now evidence in the literature of significant added benefit of combination therapy. In one study, older women who were not dry or completely satisfied after behavioral or drug treatment were offered combined therapy.[37] The data suggested an added benefit of combination therapy in these patients. The results were encouraging but are not considered definitive due to the small sample size and issues with selection bias. In another study, a simple bladder training program provided a modest increase in the effectiveness of tolterodine for reducing frequency of urination in patients with OAB.[38] Patients in that trial were not necessarily incontinent and received the behavioral treatment in written format only. More recently, a randomized controlled trial conducted by the Urinary Incontinence Treatment Network (NIDDK) compared combined behavioral and drug therapy to drug therapy alone for treatment of urge incontinence in women.[39] At the end of active therapy, treatment groups did not differ significantly on the proportion who achieved $\geq$70% reduction of incontinence. However, combined treatment did add benefit during active therapy in terms of patient satisfaction, perceived improvement, and reducing irritative bladder symptoms in women.

INNOVATION

Despite the growing body of evidence for combined behavioral and drug therapy to enhance outcomes in women with OAB symptoms, little is known of the effectiveness, the potential, or the acceptability of combining these therapies in men. There are no controlled trials of the effects of combined behavioral and drug therapy in men with LUTS. The proposed study will address this gap in knowledge, by evaluating the effects of combined therapy versus either behavioral or drug therapy alone. Further, the proposed study will compare three combined therapy protocols: 1) stepped therapy with behavioral therapy started first, 2) stepped therapy with drug therapy started first, and 3) beginning both behavioral and drug therapy at the same time. This is important to clinicians who need evidence on the best way to combine these therapies.

This study will yield important information related to optimizing treatment of LUTS in men. Although some clinicians advocate combined treatment for OAB in men, most do not integrate behavioral components such as bladder training and pelvic floor muscle rehabilitation into standard therapy. Behavioral interventions can be implemented by nurses, nurse practitioners, and physical therapists and should have potential for widespread application in a variety of outpatient settings. If combined treatment proves more effective than behavioral or drug therapy alone in this trial, it would provide justification for widespread dissemination of behavioral treatment for LUTS in men. Thus, this study has potential to alter standards of care for LUTS.

APPROACH

Research Team Experience with Behavioral Studies

This research team has conducted several projects that form a foundation for the proposed work. We have demonstrated the effectiveness of behavioral treatment compared to drug treatment for urge incontinence in women;[26] examined the effectiveness of combining behavioral and drug therapy for women using a conditional stepped therapy design;[37] studied the role of biofeedback in behavioral training and whether it is a necessary component of training;[30,32] investigated the efficacy of behavioral training for urge incontinence in men post-

prostatectomy;[28] validated global patient ratings to capture patient satisfaction and perceptions of improvement with treatment;[40] and evaluated the effectiveness of behavioral treatment for OAB symptoms in men, including exploring the effects of combining behavioral and drug therapy in men using a stepped therapy design.[31]

Preliminary Study: Behavioral vs. Drug Treatment for Overactive Bladder in Men
(Burgio KL, Goode PS, Johnson TM 2nd, Hammontree L, Ouslander JG, Markland AM, Colli J, Vaughan CP, Redden DT. Behavioral versus drug treatment for overactive bladder in men: the male overactive bladder treatment in veterans (MOTIVE) trial. J Am Geriatr Soc, in press, Funded by VA Rehabilitation R & D)[31]

The Male Overactive Bladder Treatment in Veterans (MOTIVE) Trial, a 2-site (Birmingham and Atlanta) randomized controlled equivalence trial, provides the foundation for the proposed trial. The primary purpose of this study was to evaluate the effectiveness of behavioral treatment compared to a standard (antimuscarinic) therapy for symptoms of OAB. Subjects were 143 men 42-88 years of age, with urgency and frequent urination (>8 voids per day), with or without incontinence and without significant obstruction. Following a 4-week run-in period, in which all patients were treated with an alpha blocker to empirically treat any undetected obstruction, patients who continued to experience OAB symptoms were stratified on severity and presence of urge incontinence and randomized to 8 weeks of behavioral treatment or drug therapy (individually-titrated, extended-release oxybutynin, 5-30mg daily). The behavioral treatment was a comprehensive, behavioral training program, including pelvic floor muscle rehabilitation, self-monitoring with bladder diaries, and teaching urge suppression and other skills to inhibit detrusor contraction, thus reducing urgency, frequency, incontinence, and nocturia. Seven-day bladder diaries with a validated urgency scale were used to calculate changes in 24-hour voiding frequency, nocturia, urgency, and incontinence. Secondary outcomes included global patient ratings and American Urological Association Symptom Index.

Mean voids/day decreased from 11.3 to 9.1 (-18.8%) with behavioral treatment and 11.5 to 9.5 (-16.9%) with drug therapy. Equivalence analysis indicated post-treatment means were equivalent ($p < .01$). After treatment, 85% of participants rated themselves as much better or better; over 90% were completely or somewhat satisfied, with no between-group differences. The behavioral group showed greater reductions in nocturia (mean= -.70 vs. -.32 episodes/night; p=.05). The drug group showed greater reductions in maximum urgency scores (mean= -.44 vs. -.12; p=.02). Other group differences were nonsignificant. Thus, both behavioral and antimuscarinic therapy were effective when added to alpha-blocker therapy in men. We conclude that behavioral treatment is at least as effective as antimuscarinic therapy for reducing OAB symptoms in men.

The second purpose of the study was to explore combining behavioral and drug therapy in a stepped fashion. Patients who did not achieve satisfactory outcomes after 8 weeks of either behavioral or drug therapy alone were offered step-up to combined behavioral + drug therapy to improve outcome as much as possible. After improving from 12.1 voids per day to 10.5 with behavioral treatment alone, the 13 subjects who added drug therapy achieved 9.1 voids per day following another 8 weeks of therapy. After improving from 11.6 voids per day to 9.9 with drug therapy alone, 27 subjects who added behavioral therapy achieved 9.0 voids per day (including 12 who discontinued drug). This study provides preliminary evidence for the benefit of offering behavioral or drug therapy for OAB symptoms in men who are not satisfied with initial single therapy.

Progress Report: Feasibility and Pilot Study - Combined Behavioral and Drug Treatment of Overactive Bladder in Men (*R01DK82548 funded by NIDDK, Comparative Effectiveness Research ARRA, 10/1/2009-7/31/2011*)

The primary purpose of this planning grant was to lay the groundwork for a future randomized controlled trial that would test the effectiveness of combining behavioral treatment and drug therapy as a way to improve outcomes in the treatment of OAB symptoms in men. To complete the work expeditiously within the ARRA timeframe and to prepare for the future randomized, controlled trial (RCT), we planned a multi-center trial. In addition to the University of Alabama at Birmingham (UAB), which has served as the coordinating center as well as a clinical site, we developed a network with two other sites with expertise in male LUTS:

- Emory University/Atlanta VA Medical Center, Atlanta, GA (Ted Johnson, MD, geriatrician)
- University of Texas Health Science Center, San Antonio, TX (Stephen Kraus, MD, urologist)

Over the past 2 years, this 3-site network has planned and conducted a pilot and feasibility study 1) to test the feasibility of conducting a 3-site, 2-stage, 3-arm randomized clinical trial of behavioral treatment, drug therapy, and combined drug + behavioral therapy for men with OAB, and 2) to provide an estimate of the efficacy and variability of combined therapy in this population. Data were needed on combined therapy as an initial approach in men to allow sample size calculation for the future RCT.

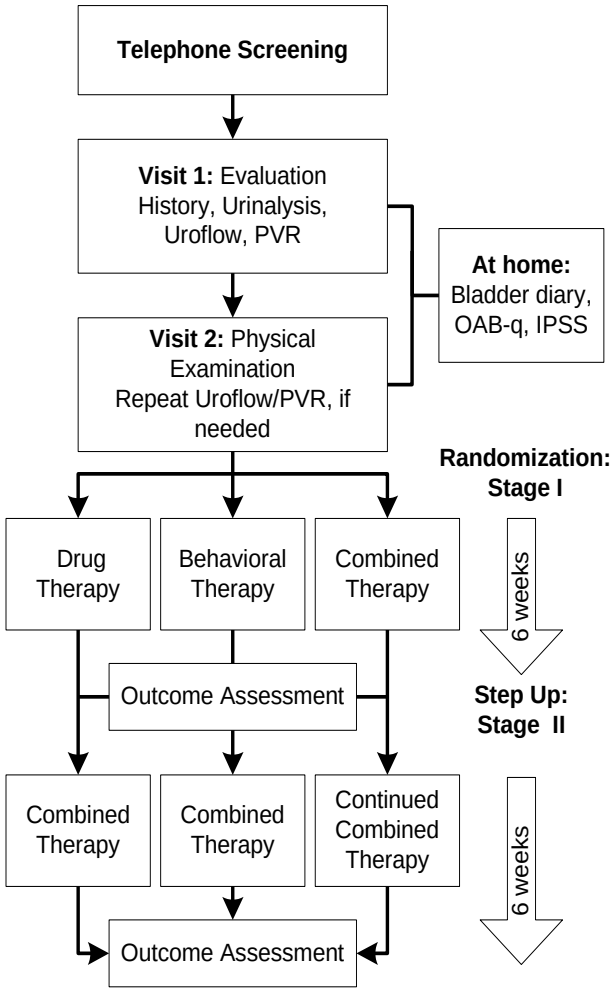
After 2 years, the following benchmarks have been achieved:

- Finalized the RCT protocol through regular investigator meetings held in-person and by telephone
- Developed all data collection tools and forms
- Obtained IRB approvals at all three sites
- Created the Coordinating Center at UAB, led by the biostatistician (David T. Redden, PhD), and demonstrated successful data monitoring and management during the pilot study
- Established and piloted the database on a dedicated SharePoint site, which allowed for timely data monitoring
- Developed training materials and completed centralized training for coordinators and interventionists
- Recruited, enrolled, and randomized 86 participants (exceeding the target)
- Completed treatment for 73 participants with only 6 drop-outs (8.2%; 7 participants are still in treatment)
- Completed primary data entry for 65 participants who have completed to date
- Completed sample size calculations based on our previous trial of single therapies[31] and this pilot study, in which we estimate the effect of initial combined therapy. The 95% confidence intervals have been examined and all calculations indicate that the assumptions used in the original sample size calculation of 201 are reasonable and highly justified.

With this foundation, we propose to include the participants already enrolled in the pilot and feasibility study as an **internal pilot** and to continue the planned multi-site clinical trial as designed and initiated to completion of the needed sample (N=201). Including participants already treated in the internal pilot represents an efficient approach to completing the trial successfully in a timely and cost-effective manner.

Overview of Experimental Design and Methods

This project will be a 3-site, 2-stage, 3-arm randomized clinical trial. The study will be conducted at UAB, Emory University, and University of Texas Health Sciences Center, San Antonio. Men with OAB symptoms who meet the inclusion criteria will be stratified on voiding frequency and presence/absence of incontinence and randomized to 6 weeks of behavioral training alone, drug therapy alone, or combined behavioral + drug therapy. Six weeks was chosen for each stage of the study based on the flattening of OAB symptom improvement curves after 4-6 weeks with drug[23] and behavioral therapy.[26] Bladder diaries completed by subjects before and after the treatment will be used to calculate reduction in the frequency of urination (primary outcome) and other OAB symptoms (urgency, urge incontinence, and nocturia). Other secondary outcome measures will include patient global ratings of improvement and satisfaction;[40] the Overactive Bladder Questionnaire (OAB-q)[41-43] to measure bother associated with OAB symptoms and impact on health-related quality of life; and the International Prostate Symptom Score questionnaire (IPSS) to assess LUTS. After 6 weeks of treatment, participants on monotherapy will be stepped up to combined behavioral and drug therapy for an additional 6 weeks of treatment.



Power Calculations and Sample Size Estimates

The primary aim of this research proposal is to examine whether treatment of OAB symptoms with combined behavioral and drug therapy provides greater response than treatment by either modality (behavioral training or drug therapy) alone. To test this aim, two separate hypotheses will be tested. Specifically, the change in average number of voids per day after 6 weeks of treatment will be compared between the group of men randomized to combination therapy and those randomized to drug therapy alone, and then between the group

of men randomized to combination therapy and those randomized to behavioral therapy alone. In order to maintain an appropriate experiment wise Type I error rate, each hypothesis will be conducted at an alpha level of .025.

Over the past two years, this trial has been initiated in order to demonstrate feasibility of the intervention and ability to recruit patients, and to validate the assumptions of the initial power calculations. Based upon the preliminary results of our previous study,[31] we assumed normally distributed outcomes, an average of 9 voids per day after 6 weeks of drug therapy only, and a standard deviation of 2.5 for average number of voids per day. Under these conditions, sample sizes of 60 per group would provide 90% power to detect a difference of 1.5 voids (drug therapy alone average daily voids of 9.0, combination therapy average daily voids of 7.5) with estimated group standard deviations of 2.5 and 2.5 and with a significance level (alpha) of 0.025 using a one-sided two-sample t-test. This calculation is applicable also for the comparison of combination therapy to behavior therapy alone. Although we have had little loss to follow-up or discontinuation in our previous trial, we increased our overall sample size to 201 (67 per group) in anticipation of 10% loss to follow-up.

Under our current ARRA pilot/feasibility funding, we have completed data entry for 65 individuals who have completed the initial 6 weeks of treatment. The most crucial assumption within the previous power calculation is the assumed standard deviation of 2.5. In our pilot investigation, the 95% confidence interval for this parameter is (2.00, 2.80). Therefore, we believe the assumed standard deviation of 2.5 remains reasonable and maintain that 201 randomized individuals will be sufficient to provide adequate power to detect our pre-specified effect sizes. Furthermore, the pre-specified effect sizes are contained within their respective 95% confidence intervals indicating these assumptions remain valid. Based upon these facts, we request funding to recruit 122 additional individuals to achieve the sample size of 201.

Participants and Screening

Participants for this study will be community-dwelling men, age 40 years or older, with symptoms of OAB as manifested by urgency and frequent urination (≥ 9.0 voids per day), with or without urge incontinence. They will be recruited through the investigators' clinics, public announcements, mailings, and advertisements. Potential participants will be screened initially by telephone. To be eligible for in-clinic evaluation, they must:

1. Be able to come to the clinic for treatment.
2. Report symptoms of OAB, including urgency and frequent urination with or without urge incontinence.
3. Have no history of radical prostatectomy, botulinum toxin bladder injections, or implanted sacral neuromodulation device.
4. Have had no transurethral resection of the prostate (TURP), simple prostatectomy, or other BPH surgery within the past 5 years.
5. If not ambulatory, must be able to toilet independently.
6. Not have narrow angle glaucoma, Parkinson's disease, multiple sclerosis, myasthenia gravis.
7. Not be on active cancer treatment
8. If on antimuscarinic or alpha-blocker medication, must be willing to temporarily discontinue (wash out).

Our goal is to recruit approximately 500 men into the evaluation phase in order that 201 will ultimately be randomized and complete the protocol. 73 men have already completed treatment in the internal pilot, and it is estimated that another 6 will complete (of 7 currently in treatment) for a total of 79 completers. Therefore, in the proposed completion of this trial, we will randomize an additional 122 men, achieving the total sample of 201.

Pre-Treatment Clinical Evaluation

The purpose of the clinical evaluation is to characterize the participants and to exclude men with clinically significant urinary obstruction or who are otherwise not appropriate for behavioral or drug therapy or for participation in a clinical trial. The evaluation will be conducted in two visits separated by a period of one week.

In the first evaluation visit, an interview will be conducted by the nurse specialist, consisting of the continence history, medical history, and mental status screening. The medical history will include inquiry regarding medical conditions and habits and events that may have implications for intervention. The Mini-Cog, a validated 3-item recall and clock drawing dementia screening test will be administered to screen for dementia.[44] A urinalysis will be performed, and for participants with diabetes, a glycosylated hemoglobin, unless the participant has documentation of a test with results ≤ 9.0 within the past 3 months. A prostate specific antigen (PSA) will be drawn to be used as a predictor of treatment response. Simple uroflowmetry will be performed, followed by a post-void residual (PVR) determination using the BladderScan®, which non-invasively measures bladder

volume using ultrasound. To insure adequate urine volume at start of uroflowmetry, the bladder volume will be determined using the BladderScan®. If initial bladder volume scans less than 125 mL, participants will be offered water to drink until they reach 125 mL. If they cannot wait, a urinalysis will be obtained and the uroflow delayed until the next visit. Also, if the PVR is > 150 mL or flow rate is < 8.0 mL/sec and the participant did not have the urge to urinate when asked to void, he can be instructed to come to the next visit with a full bladder so the tests can be repeated. At the second visit, a physical examination will be performed, including measurement of height, weight, abdominal girth, and blood pressure.

Bladder Diary

The primary outcome measure will assess changes in the frequency of urination, as well as other symptoms of overactive bladder as secondary outcomes, including urgency, incontinence, and nocturia. Bladder diaries completed by subjects prior to randomization and following each Stage of treatment will be used to calculate reduction in these 4 symptoms.

Each eligible participant will be provided with a booklet containing 7 days of bladder diary forms. Six complete days will be required. He will be asked to carry the booklet with him and to complete the forms with entries documenting: the time of every void, the time of every episode of urine loss, the presence of urgency with each void and incontinent episode, and severity of urgency (measured with the Indevus Urgency Severity Scale (IUSS),[45] which will be incorporated into the bladder diary). Bedtime and time of arising will be noted each day to assist in calculating nocturia. In addition, participants will record voiding times and voided volumes for a period of 24 hours.

Inclusion Criteria

1. Community-dwelling men
2. Age 40 years or older
3. Participant-reported urgency and ≥9.0 voids per 24 hours (on average) on the 7-day baseline bladder diary.

Exclusion Criteria

To avoid enrolling subjects who are inappropriate for the treatment protocol, exclusion from the protocol or delayed entry will be based on the following criteria:

1. Urinary flow rate < 8.0 mL/sec on a void greater than 125 ml.
2. Post-void residual volume greater than 150 mL (based on bladder ultrasound after voiding in the presence of a normal urge to urinate).
3. Urinary tract infection (defined as growth of greater than 10,000 colonies per mL of a urinary pathogen on urine culture). Participants will be referred for treatment with antibiotics and may be enrolled if OAB symptoms persist after the infection is resolved.
4. Transurethral resection of the prostate (TURP), simple prostatectomy, or other BPH related surgery within the past 5 years.
5. Current active treatment for prostate cancer.
6. History of radical prostatectomy.
7. Previous artificial urinary sphincter, sling procedure, bladder-injection of botulinum toxin, or implanted sacral neuromodulation device.
8. Poorly controlled diabetes (glycosylated hemoglobin ≥9.0 within last 3 months). Subjects with poorly controlled diabetes will be offered enrollment if the OAB symptoms persist after the diabetes is controlled.
9. Hematuria on microscopic examination in the absence of infection. A urologic consultation will be recommended and enrollment will depend on clearance by a urologist and agreement by the Site PI.
10. Any unstable medical condition (particularly: cancers under active treatment, decompensated congestive heart failure, history of malignant arrhythmias, unstable angina, diagnosed by history or physical exam).
11. Neurologic conditions such as Parkinson's, spinal cord injury, multiple sclerosis, or myasthenia gravis.
12. Impaired mental status. Participants who screen as probable dementia on the Mini-Cog.
13. Contraindications to the study drugs (tolterodine and tamsulosin) including history of postural hypotension with syncope, history of acute urinary retention requiring catheterization, narrow angle glaucoma, or history of gastric retention.
14. Hypersensitivity to tolterodine or tamsulosin.
15. Current use of alpha-blocker. Evaluation will be delayed until the drug has been discontinued for 2 weeks.
16. Current use of an anti-muscarinic for OAB. Evaluation will be delayed until the drug has been discontinued for 2 weeks.

17. If on a diuretic, dose has not been stable for at least 4 weeks.
18. If taking dutasteride or finasteride, dose has not been stable for at least 6 months.
19. If on an antibiotic for prostatitis. Participants will be offered re-evaluation if OAB symptoms persist when antibiotics are completed.
20. Full course of behavioral training.

Stage 1: Stratification and Randomization

In order to assure between-group comparability, subjects will be stratified on two dimensions: presence/absence of urge incontinence and symptom severity (frequency of urination). Baseline bladder diaries documenting the frequency of urination will be used to assign subjects to one of two strata: mild frequency (9 -12.0 voids per 24-hour day) vs. moderate/severe frequency (>12.0 per 24-hour day). Within each stratum, blocked randomization will be performed using a variable block size and a table of random numbers to avoid inequity in the total number of subjects assigned to each group. Stratification will be used *only* to ensure that the treatment groups are similar on severity, not to *compare* levels of severity. Also, blocking is used not to create comparison groups but only to ensure that the groups are similar in *size*. Subjects will then be assigned to behavioral treatment alone, drug therapy alone, or combined behavioral + drug therapy. In Stage 1, the interventions will be implemented in 3 clinic visits over a period of 6 weeks.

Behavioral Treatment Alone

The behavioral treatment protocol is adapted from that used in our previous studies. It consists of behavioral training and includes skills and strategies for postponing urination, controlling urgency and preventing urge incontinence. This includes pelvic floor muscle training and daily bladder diaries to track increasing voiding intervals and enhance awareness of bladder habits. Training will be supplemented with instructions for daily home practice between clinic visits.

In treatment visit 1, a rectal examination will be performed to assess perineal skin, peri-anal sensation, anal wink, resting tone, prostate enlargement, and strength of the external anal sphincter. Then, pelvic floor muscle training will be conducted using verbal feedback based on anal palpation. Verbal feedback and instruction will be used to teach participants how to contract and relax the pelvic floor muscles while keeping abdominal muscles relaxed. The goal is to increase intraurethral pressure (by means of contracting peri-urethral muscles) while intra-abdominal pressure, which contributes to bladder pressure, is minimized. Our previous work with urethral electromyography and anal sphincter manometry has clearly demonstrated that contraction of external anal sphincter muscles is associated with increases in urethral sphincter muscle activity.[46] Participants will be taught to contract the pelvic floor muscles during 2- to 10-second periods separated by 2 to 10 seconds of relaxation, depending upon their initial ability.

Recommendations for home practice will include 45 pelvic floor muscle exercises (paired contraction/ relaxation) every day, divided into manageable sessions, usually 3 sessions of 15 exercises each. The initial duration of each individual sphincter contraction will be determined based on the ability demonstrated by each participant in the training session. Across sessions, the duration will be increased gradually to a maximum of 10 seconds. Participants will be advised to practice in various positions including lying, sitting, and standing and whenever possible, to integrate the exercises into other daily activities such as standing in line or sitting in a car at a stop light.

In treatment visit 2 (2 weeks later), a treatment adherence questionnaire will be completed in the waiting room prior to seeing the interventionist. The interventionist will review the questionnaire with the participant to identify barriers to adherence and make recommendations for improving adherence. Participants will be taught urge suppression strategies, how to cope with and respond adaptively to the sensation of urgency using techniques to manage urgency, postpone urination, and to avoid urine loss.[35] Patients with OAB, and especially those with incontinence, typically report that they rush to the toilet when they experience a sensation of urgency to void. They will be instructed not to rush to the toilet, because this movement increases pressure on the bladder, stimulates detrusor contractions, increases urgency, and increases the likelihood of incontinence. Instead, they will be encouraged to pause, to sit down if possible, to practice relaxing, and to contract the pelvic floor muscles several times in an effort to diminish urgency, inhibit detrusor contraction, and prevent urine loss. When urgency subsides, they should walk at a normal pace to the bathroom.

Over the next several weeks, they will be encouraged to delay voiding instead of going to the bathroom immediately after suppressing the urge to void. At first, they will be instructed to practice delaying for 10 minutes. Over time, the interval will be increased gradually with the goal of reaching a normal voiding interval.

In addition to daytime training, nocturia will be managed with fluid restriction (3 hours before bedtime and during the night) and with urge strategies. Specifically, when participants awaken at night with the urge to void, they are to remain still in bed and attempt to diminish the urgency. If successful, they may go back to sleep. If not, they can void and return to bed.[47]

Treatment visit 3 (at 4 weeks) will be used to review progress as documented in bladder diaries; address new problems; reinforce and "fine-tune" participants' home practice; and encourage persistence. Strategies to control urgency, frequency, and urge incontinence will be reviewed based on symptoms documented in the bladder diary. Verbal feedback with anal palpation or observation of perineal excursion will be repeated as needed if participants are not sure of their muscle control or if they are not progressing. During the 6 weeks of treatment, participants will continue to keep a bladder diary so that project staff can monitor progress and to guide interventions.

Drug Therapy Alone

Participants in the drug group will receive an anti-muscarinic (sustained release tolterodine 4 mg) + an alpha blocker (tamsulosin 0.4mg daily). In treatment visit 1, a baseline side effects profile will be completed and the participants educated about the drug and its possible side-effects. They will be provided with handouts with suggestions for managing the most common side-effects, dry mouth and constipation. They will be given a 6-week supply of medication and an appointment for the post-treatment assessment visit. The clinic phone number and pager number will be provided to the participant for 24-hour availability of a physician if they develop study-related problems.

Telephone visit (at 3 weeks): The interventionist will conduct a telephone visit to assess side-effects and adherence. The side-effects checklist will be repeated and minor side-effects treated symptomatically. If needed, the tolterodine dose will be adjusted to 2 mg to improve tolerability, and a supply of medication will be sent by overnight mail with specific written instructions to discontinue the 4 mg dose and begin the 2 mg dose, as well as to continue the tamsulosin.

Combined Behavioral + Drug Therapy

Participants in combined therapy will receive behavioral and drug therapy as described above following the same time line and visit schedule as behavioral treatment.

Stage 1 Post-Treatment Assessment

Immediately prior to the 6-week visit, participants will complete the 7-day post-treatment diary, 24-hour record of voided volumes, and questions about treatment adherence (for participants in a behavioral arm), and these will be collected and used by the interventionist at the visit. The patient global ratings, the OAB-q, and the IPSS will be completed prior to the visit and collected in a sealed envelope. The subjects will be told *a priori* that their responses to the questionnaires will not be revealed to the staff who were responsible for their treatment. In this way, we hope to improve the honesty of their answers. The bladder diaries, voiding log, and questionnaires will be reviewed and scored by a research assistant who is blind to the treatment conditions to which participants are assigned. The side-effects checklist, simple uroflow, and PVR will be repeated. For participants receiving drug therapy, a pill count will be conducted to assess adherence.

Stage 2: Stepped Therapy

After the post-treatment assessment for Stage 1, subjects in the *behavioral treatment alone* group will have their behavioral treatments reinforced and then be stepped up to combined therapy. They will be instructed to continue their pelvic floor muscle exercise and strategies to maintain treatment effects. In addition, they will be started on drug therapy and followed as described in Drug Therapy Alone above (1 additional telephone visit at 3 weeks). Participants in the *drug therapy alone group* will also be stepped up to combined therapy. They will be instructed in pelvic floor muscle exercises, followed by delayed voiding and skills and strategies for postponing urination, controlling urgency and preventing urge incontinence in the same visit sequence as described in Behavioral Treatment Alone above (2 additional visits across 6 weeks). They will continue to take their medications at the dose established. Following the second Stage of treatment, the post-treatment assessment will be repeated.

Outcome Measures

The primary outcome will be change in the frequency of urination as documented in the bladder diary. Changes in other LUTS, including urgency, incontinence, and nocturia, will be secondary outcomes. Bladder diaries completed by subjects prior to randomization and following each Stage of treatment will be used to calculate changes in these 4 symptoms. Other outcome measures will include 1) change from baseline in voided volumes (based on 24-hour record), 2) change from baseline on the OAB-q (measuring symptom bother and condition-specific health-related quality of life),[41-43] 3) change from baseline on the IPSS (measuring symptoms), and 4) patient global ratings of satisfaction (using the Patient Satisfaction Question)[40] and improvement (using Estimated Percent Improvement and Global Perception of Improvement).[40]

Bladder Diary. The bladder diary has been found to be a reliable method of evaluating the frequency of incontinent episodes and voluntary urination.[48] It is used routinely in this field of research. We have used it with patients for 29 years and found that even patients who are functionally illiterate can complete meaningful bladder diaries with appropriate instructions. The bladder diary has been used successfully as the primary outcome measure in previous trials funded by NIA and NIDDK[25,26,30,39] and is currently used in both behavioral and surgical trials being conducted by the NIDDK Urinary Incontinence Treatment Network and the NICHD Pelvic Floor Disorders Network.

Indevus Urgency Severity Scale.[45] The IUSS is an event-specific measure of the intensity of urgency events associated with OAB. It is embedded in the bladder diary and asks patients to rate the degree of urgency with each void and incontinent episode. It is unique in that it measures the sensation of urgency and is anchored to the impact of urgency on activity. Response options are:

0: None – no urgency
1: Mild – awareness of urgency, but is easily tolerated and you can continue with your usual activity or tasks.
2: Moderate – enough urgency discomfort that it interferes with or shortens your usual activity or tasks.
3: Severe – extreme urgency discomfort that abruptly stops all activity or tasks.

The IUSS has good test-retest reliability of 0.80 between day 2 and day 5 of a bladder diary. It is highly responsive to improvements on other clinical parameters (decreases in voiding frequency and incontinence episodes). Construct and criterion validity have been established by comparison to the OAB-q (and its subscales) and the Incontinence Impact Questionnaire (and its subscales). Further, it is reported to have minimal respondent burden.[45]

Patient Global Ratings. Three validated single-question global ratings of improvement, the Patient Satisfaction Question (PSQ), Estimated Percent Improvement (EPI), and Global Perception of Improvement (GPI) will be used to assess patients' perceptions of their treatment outcomes.[40] The 3 global ratings have been validated and were shown to have acceptable convergent and discriminant validity for measuring outcomes in studies of treatment for urinary incontinence.[40]

Overactive Bladder Questionnaire (OAB-q).[41-43] The OAB-q is a self-administered questionnaire designed to measure both continent and incontinent symptoms of OAB and impact on health-related quality of life in men and women. The instrument consists of a symptom bother scale (8 items) and a health-related quality of life scale (25 items) with 4 subscales (reflecting Coping behaviors, Concern/worry, Social interaction, Sleep) Reliability and validity of the instrument have been established in a community sample and a clinical sample, including both men and women.[41] Responsiveness to change with treatment has also been described in drug trials[42,43] and in a study of combined drug and behavior therapy in women with urge-predominant incontinence.[37] In the study of combined therapy, the OAB-q showed improvement with treatment in both the drug only arm and the drug + behavioral treatment arm. Further, the OAB-q symptom bother scale discriminated between changes in the two treatment groups.

International Prostate Symptom Score (IPSS). The IPSS is an 8-item questionnaire that asks patients to rate how often over the past month they had each of 7 symptoms related to BPH: incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia. Response options range from "not at all" to "almost always." The scale yields a symptom severity score and levels of severity are categorized as: mild (1-8), moderate (9-19), or severe (20-35). The eighth item measures quality of life due to urinary symptoms and asks patients, "If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?" Response options range from "delighted" to "terrible."

Measuring Costs and Health Effects for Cost-Effectiveness Analysis

As recommended by the U.S. Public Health Service's Panel on Cost-Effectiveness in Health and Medicine, this analysis will be performed from the societal perspective.[50] Following this approach, the costs of all health care resource utilization are included in the analysis, regardless of who bears those costs. To estimate the costs associated with the treatments under investigation, resource utilization will be measured for each subject in the trial. Major categories of resource utilization to be measured include: tests and procedures performed; time spent in office visits for physicians, nurses, and patients; indirect patient and facility costs; amount of study medication used; amount of other medications used (e.g., for treatment of side effects); and number of protective products and pads used. As resource utilization is recorded, distinctions will be made between resources that were consumed only due to protocol requirements and resource consumption that would have taken place even if it were not required by protocol (based on the judgment of the health care professionals providing the care). This will enable us to perform separate analyses that respectively include and exclude protocol-induced costs**.** It has been suggested that the exclusion of protocol-induced costs may increase external validity and provide information more useful (although still imperfect) for predicting what might be observed in a health care setting outside the controlled environment of a randomized controlled trial.[51]

Resource utilization will be translated into costs by applying unit cost estimates to each item of resource utilization. Nationally representative ("average") unit cost estimates will be used, because estimates based on the cost structure for any individual setting would lead to results with much more limited usefulness to decision makers in other settings. Prescription medications will be valued using average wholesale prices (AWP); although prices may vary greatly across different payors, the U.S. Public Health Service's Panel on Cost-Effectiveness in Health and Medicine has recommended using AWP as an approximation of the average unit price.[49]

For purposes of economic evaluation, three different measures of health effects will be used for estimating the denominators in cost-effectiveness ratios: (1) the number of urinations avoided per week, (2) the number of accidents avoided per week, and (3) the number of accident-free days gained per week, with each of these measured as an incremental change from baseline measurement. The latter measure previously has been applied in a CEA of treatments for incontinence.[52] These measures were selected because effectiveness measures in CEA are required to have interval-scale measurement properties and because the resulting units of measurement for incremental cost-effectiveness ratios (dollars per urination avoided, dollars per accident avoided, dollars per accident-free day gained) would be easily understood.

Data Management and Analysis

Data management and quality control will be conducted at the UAB Coordinating Center under the supervision of the biostatistician, Dr. Redden, PhD. Data forms from all 3 sites will be posted to the existing SharePoint site and data entered by the UAB data manager. Bladder diaries will be reviewed and scored by a research assistant who is blind to treatment conditions. On a bi-monthly basis, the PI and statistician will meet with the data manager to review accrual, data entry, eligibility criteria, logic and range checks, and query sites regarding outliers or unusual data. Data management and analyses for this project will include the use of both SPSS and SAS.

Preliminary Analyses. Although subjects will be randomized, the equivalency of the 3 treatment groups will be evaluated on selected variables that might influence treatment outcome: age, baseline severity (frequency of OAB symptoms), presence/absence of urge incontinence, duration of symptoms, body mass index, and functional bladder capacity (from 24-hour voided volumes). The chi square statistic will be used for the categorical variables. Analysis of Variance will be used to compare groups on normally distributed continuous variables. The nonparametric equivalent of Analysis of Variance, the Kruskal Wallis procedure, will be used to compare groups on non-normally distributed continuous variables.

Aim #1: Comparison of Treatment Effects. The effectiveness of each intervention will be calculated by comparing the frequency of urination (primary) and other (secondary) OAB symptoms during the final 7 days of the 6-week intervention period with the 7-day baseline period. The primary analysis will be an "effectiveness" analysis based on the standard "intention to treat" approach, which includes participants who do not complete therapy. For participants who do not complete the protocol, post-treatment frequency of symptoms will be derived from their most recent 7 days of bladder diary.

Initially, descriptive analyses will be conducted to examine distributions of the frequency of OAB symptoms and possible covariates. Transformations may be employed to correct for skewness or heterogeneity as needed.

To examine the effects of combined therapy, two planned comparisons will be conducted: one comparing combined therapy to behavioral treatment alone, and one comparing combined therapy to drug therapy alone. Unadjusted examination of these two hypotheses will be conducted using two-sample t-tests. Two multiple regression models, also known as Analysis of Covariance models, will be used to test the hypotheses after adjusting for baseline voiding frequency, age, and other baseline and demographic factors. The primary outcome variable is reduction in 24-hour voiding frequency. Secondary outcome measures will be analyzed in a similar fashion, including change in mean urgency scores, frequency of nocturia, and frequency of urge incontinence episodes, change in voided volumes, change in the OAB-q and IPSS scores, and the patient global ratings (PSQ, GPI, EPI).

Aim #2: Initial Combined vs. Stepped Combined Therapy. To examine the effects of combining behavioral and drug therapy from the beginning vs. in a stepped fashion, outcomes at 12 weeks in the original combined therapy group (as initial therapy) will be compared to those of the behavioral alone and drug alone groups (stepped therapy)

Aim #3: Analyzing Costs and Cost-Effectiveness. Multivariate analysis methods will be used to test for effects of treatment on health care costs, while controlling for observed baseline characteristics. Ordinary least squares regression will be used, and the need for transformation of the dependent variable (such as the common econometric practice of using the natural logarithm of costs rather than costs as the dependent variable, in order to produce more nearly normal errors and to reduce heteroskedasticity) will be explored.[53] This analysis will determine whether the treatment conditions differ significantly in terms of overall costs and cost per unit of the various health effects.

The costs and effects of the therapies will also be compared based on the theory and methods of CEA.[54-57] Point estimates of cost-effectiveness will be produced by applying the decision rules of CEA: the incremental cost-effectiveness ratios will be calculated to compare combined therapy to behavior therapy alone and to drug therapy alone. The incremental cost-effectiveness ratio is calculated as the ratio of the incremental difference in mean cost to the incremental difference in mean health effects. The ratio represents the additional cost incurred for each additional unit of health gain obtained by choosing a more costly, more effective therapy rather than a less costly, less effective therapy, and can be interpreted as a measure of “value for money.” We will rely primarily on graphical presentations and traditional sensitivity analysis to convey information about the uncertainty regarding the cost-effectiveness estimates in this project.

Design Limitations

In a traditional drug therapy trial, participants are blinded to treatment group to control for the possible beneficial effects of knowing one is receiving therapy. In our proposed trial, participants and interventionists cannot be blinded. However, all participants will know they are receiving an active therapy with proven efficacy. In this context, we believe that all participants will have a reasonable expectation of benefit. Further, there are salient features of the protocol that are common across the three treatment arms and support the internal validity of the study. The bladder diary, ordinarily a component of behavioral intervention, will be completed by all participants on a daily basis. This will control for the effects of self-monitoring, which can increase awareness and change behavior. In the treatment visits, the interventionist will provide individualized advice specific to each participant’s program. This will involve management of side-effects for those on drug therapy and behavioral advice for those in behavioral intervention. Thus, all participants will interact with the same interventionist, complete the same diary, and receive advice and individualized adjustment of their treatment program. Although not a strict practical clinical trial as described by Tunis et al in JAMA (2003),[58] the proposed study asks practical questions about the effects and costs of different approaches to the treatment of OAB symptoms. In allowing participants to know what treatment they are receiving, the design of the proposed study enhances generalizability by preserving features of treatment that resemble the conditions of clinical care settings.

Protection of Human Subjects

1. RISKS TO THE SUBJECTS

a. *Human Subjects Involvement and Characteristics*

The proposed study is a randomized controlled trial of combined behavioral + drug therapy to reduce lower urinary tract symptoms (LUTS) of overactive bladder (OAB) in men.

Subjects will be community-dwelling men with symptoms of OAB/LUTS as manifested by urgency and frequent urination (≥ 9 voids per day), with or without urge incontinence. Subjects will be recruited through the investigators' clinics, and other related services and clinics, including Urology, Geriatric Medicine, and Primary Care. In addition, we will recruit through public announcements, mailings, and advertisements (e.g., newspapers, radio advertisements, and newsletters).

Potential subjects will be screened initially by telephone to determine eligibility for participation. To be eligible, they must:

1. Be able to come to the clinic for treatment.
2. Report symptoms of OAB/LUTS, including urgency and frequent urination with or without urge incontinence.
3. Have no history of radical prostatectomy, botulinum toxin bladder instillation, or implanted sacral neuromodulation device.
4. Have had no transurethral resection of the prostate (TURP), simple prostatectomy, or other BPH surgery within the past 5 years.
5. If not ambulatory, must be able to toilet independently.
6. Not have narrow angle glaucoma, Parkinson's disease, multiple sclerosis, myasthenia gravis.
7. Not be on active cancer treatment
8. If on antimuscarinic or alpha-blocker medication, must be willing to temporarily discontinue.

Subjects will undergo a clinical evaluation consisting of a medical and continence history, and administration of the Mini-Cog, a validated 3-item recall and clock drawing screening test for cognitive impairment and dementia. A urinalysis will be performed, and for subjects with diabetes, a glycosylated hemoglobin, unless the subject has documentation of a test with results ≤ 9.0 within the past 3 months.

A prostate specific antigen (PSA) will be drawn to be used as a predictor of treatment response. Simple uroflowmetry will be performed, followed by a post-void residual (PVR) determination using the BladderScan®, which non-invasively measures bladder volume using ultrasound. Physical examination will be performed, including measurement of height, weight, abdominal girth, and blood pressure.

Assessment instruments will be completed at home: 1) 7-day bladder diary with an urgency scale for each void and incontinent episode, 2) 24-hour log of voiding times and voided volumes, 3) the Overactive Bladder Questionnaire (OAB-q), a self-administered questionnaire designed to measure both continent and incontinent symptoms of OAB and impact on health-related quality of life, and 4) the International Prostate Symptom Score questionnaire (IPSS), an 8-item questionnaire that asks patients to rate how often over the past month they had each of 7 LUTS.
To be eligible, potential subjects must have urgency and 9.0 or more voids per 24-hour day (on average) on the 7-day baseline bladder diary.

In order to avoid enrolling subjects who are inappropriate for the treatment protocol, exclusion from the protocol or delayed entry will be based on the following criteria:

1. Urinary flow rate < 8.0 mL/sec on a void greater than 125 ml.
2. Post-void residual volume greater than 150 mL (based on bladder ultrasound after voiding in the presence of a normal urge to urinate).
3. Urinary tract infection (defined as growth of greater than 10,000 colonies per ml of a urinary pathogen on urine culture). Subjects will be referred for treatment with antibiotics and may be enrolled if OAB/LUTS

symptoms persist after the infection is resolved.
4. Transurethral resection of the prostate (TURP), simple prostatectomy, or other BPH related surgery within the past 5 years.
5. Current active treatment for prostate cancer.
6. History of radical prostatectomy.
7. Previous artificial urinary sphincter, sling procedure, bladder-injection of botulinum toxin, or implanted sacral neuromodulation device.
8. Poorly controlled diabetes (glycosylated hemoglobin $\geq$9.0 within last 3 months). Subjects with poorly controlled diabetes will be offered enrollment if the OAB symptoms persist after the diabetes is controlled appropriately.
9. Hematuria on microscopic examination in the absence of infection. A urologic consultation will be recommended and enrollment will depend on clearance by a urologist and agreement by the Site PI that entry into the treatment protocol is not contraindicated.
10. Any unstable medical condition (particularly: cancers under active treatment, decompensated congestive heart failure, history of malignant arrhythmias, unstable angina, diagnosed by history or physical exam).
11. Neurologic conditions such as Parkinson's, spinal cord injury, multiple sclerosis, or myasthenia gravis.
12. Impaired mental status. Subjects who screen as probable dementia on the Mini-Cog.
13. Contraindications to the study drugs (tolterodine and tamsulosin) including history of postural hypotension with syncope, history of acute urinary retention requiring catheterization, narrow angle glaucoma, or history of gastric retention.
14. Hypersensitivity to tolterodine or tamsulosin.
15. Current use of an alpha blocker agent. Evaluation will be delayed until the drug has been discontinued for 2 weeks.
16. Current use of an anti-muscarinic agent for OAB. Evaluation will be delayed until the drug has been discontinued for 2 weeks.
17. If on a diuretic, dose has not been stable for at least 4 weeks.
18. If taking dutasteride or finasteride, dose has not been stable for at least 6 months.
19. If on an antibiotic for prostatitis. Subjects will be offered re-evaluation if OAB symptoms persist when antibiotics are completed.
20. Full course of behavioral training.

Subjects will be randomized to undergo 6 weeks of behavioral treatment alone, drug therapy alone, or combined behavioral + drug therapy. After the post-treatment assessment (at 6 weeks), subjects in the behavioral treatment alone and drug treatment alone groups will be stepped up into combined therapy for an additional 6 weeks of treatment. Subjects in combined therapy will continue it for another 6 weeks.

Post-treatment assessments will be completed after each treatment phase. Assessment will include the 7-day bladder diary, the 24-hour log of voiding times and voided volumes, the Overactive Bladder Questionnaire, International Prostate Symptom Score questionnaire, and patient global ratings (satisfaction, perceptions of improvement, etc). A side-effects checklist will also be completed.

b. Sources of Materials

Subject charts containing the data collection forms, completed bladder diaries, logs, and questionnaires, will be stored in locked cabinets in the project coordinator's office. Data will be derived from the bladder diary, the logs, the global ratings of satisfaction and improvement, and the questionnaires. Data will also be collected on resource utilization including: any tests and procedures performed; time spent in office visits for physicians, nurses, and subjects; indirect patient and facility costs; amount of study medication used; amount of other medications used (e.g., for treatment of side effects); and number of protective products and pads used. Forms will be uploaded to a secure, encrypted, password-protected SharePoint site designed and maintained by the UAB Coordinating Center and located on our designated university server.

Subject records will be de-identified using a numerical identifier in the database and linkages to the records will be secured on encrypted, password-protected servers by the data manager and biostatistician.

c. *Potential Risks*

Behavioral treatment: Behavioral treatment involves teaching pelvic floor muscle control using anal palpation. This is slightly uncomfortable for some men.

Drug therapy: Subjects in drug therapy will receive an anti-muscarinic (tolterodine 4 mg) + an alpha blocker (tamsulosin 0.4mg daily). Both drugs are FDA-approved. Common side effects of tolterodine include: dry mouth, dry eyes, constipation, and dyspepsia. Somnolence, headache, blurred vision, confusion, and dizziness can also occur. Tolterodine can increase susceptibility to urinary retention and heat stroke. Dose of tolterodine may be reduced to 0.2mg to minimize side effects while maximizing symptom reduction. Common side effects of tamsulosin include: headache, dizziness, rhinitis, and abnormal ejaculation. Orthostatic syncope has been reported, but is less common with this alpha-1a-adrenergic receptor specific sub-class of alpha blockers. The possible side effects of both medications will be explained to the subject as part of the informed consent process.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. *Recruitment and Informed Consent*

Subjects will be recruited through the investigators' clinics, and other related services and clinics. The study coordinator will screen potential subjects, explain the study, and inquire about willingness to participate. When a subject is interested in participating, the coordinator will explain the study's procedures, goals, and risks. Patients interested in participating will sign an Informed Consent Form approved by the University's Institutional Review Board for Human Use.

b. *Protection against Risk*

Data collected in this study will be treated as confidential and subjects will not be identified without their permission to anyone outside the project staff.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

Based on previous research, there is evidence that behavioral and drug therapy, either alone or in combination, will reduce the symptoms of OAB/LUTS. The minimal risk of participation is thus outweighed by the potential for each treatment group to benefit from both treatments.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

If the behavior + drug therapy is found to be more effective than either treatment alone, this information will highlight the need for combined therapy and will have potential to change standards of care. These potential improvements to care outweigh the minimal risk of participation.

5. DATA AND SAFETY MONITORING PLAN

Upon funding, we will recruit an external Data and Safety Monitoring Board (DSMB). We intend to recruit a behavioral scientist, a physician, and a biostatistician. If AEs do occur, they will be reported to the IRB and the DSMB. Every 6 months, reports will be issued to the DSMB regarding recruitment, completeness of data, observed number of AEs, and observed number of outcomes. These reports will be discussed by conference call.