Published in final edited form as:

Contemp Clin Trials. 2012 January ; 33(1): 184–196. doi:10.1016/j.cct.2011.09.019.

Anticholinergic Versus Botulinum Toxin A Comparison Trial for the Treatment of Bothersome Urge Urinary Incontinence: ABC Trial

Anthony G. Visco, M.D.^a, Linda Brubaker, M.D., M.S.^b, Holly E. Richter, Ph.D., M.D.^c, Ingrid Nygaard, M.D.^d, Marie Fidela Paraiso, M.D.^e, Shawn A. Menefee, M.D.^f, Joseph Schaffer, M.D.^g, John Wei, M.D.^h, Toby Chai, M.D.ⁱ, Nancy Janz, Ph.D.^j, Cathie Spino, D.Sc.^j, Susan Meikle, M.D. M.S.P.H.^k, and for the Pelvic Floor Disorders Network

^aDepartment of Obstetrics and Gynecology, Duke University Medical Center, Durham, North Carolina, USA

^bDepartments of Obstetrics & Gynecology and Urology, Stritch School of Medicine, Loyola University, Chicago, Illinois, USA

^cDepartment of Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham, Alabama, USA

^dDepartment of Obstetrics and Gynecology, University of Utah, Salt Lake City, Utah, USA

^eDepartment of Obstetrics and Gynecology, Cleveland Clinic, Cleveland, Ohio, USA

^fDepartment of Obstetrics and Gynecology, Kaiser Permanente San Diego, San Diego, California, USA

^gDepartment of Obstetrics and Gynecology, University of Texas Southwest, Dallas, Texas, USA

^hDepartment of Urology, University of Michigan, Ann Arbor, Michigan, USA

ⁱDepartment of Urology, University of Maryland, Maryland, USA

^jDepartment of Biostatistics, University of Michigan, Ann Arbor, Michigan, USA

^kContraception and Reproductive Health Branch, Center for Population Research, The Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health

Abstract

This trial compares the change in urgency urinary incontinence episodes over 6 months, tolerability and cost effectiveness between women receiving daily anticholinergic therapy plus a single intra-detrusor injection of saline versus a single intra-detrusor injection of 100 unit of botulinum toxin A plus daily oral placebo tablets. We present the rationale and design of a randomized controlled trial, Anticholinergic versus Botulinum Toxin, Comparison Trial for the Treatment of Bothersome Urge Urinary Incontinence: ABC Trial, conducted by the NICHD-

© 2011 Elsevier Inc. All rights reserved.

Corresponding Author: Anthony G. Visco, M.D., Division of Urogynecology and Reconstructive Pelvic Surgery, Department of Obstetrics and Gynecology, Duke University Medical Center, DUMC 3192, Durham, NC 27710, 919-401-1006, Fax: 919-401-1033, anthony.visco@duke.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

funded Pelvic Floor Disorders Network. We discuss the innovative nature of this trial and the challenges related to choice of patient population, maintaining masking, cost-effectiveness, ethical considerations, measuring adherence, and placebo development and testing. Enrollment began in April, 2010. 242 participants will be randomized and primary outcome data analysis is anticipated to begin in mid 2012. Several challenges in the trial design are discussed. Randomization to placebo intradetrusor injections may limit recruitment, potentially impacting generalizability. Other challenges included the heavy marketing of drugs for overactive bladder which could impact recruitment of drug naïve women. In addition, anticholinergic medications often cause dry mouth, making masking difficult. Finally, adverse reporting of transient urinary retention is challenging as there is no standardized definition; yet this is the most common adverse event following intradetrusor botulinum toxin injection. The ABC trial will help women with urgency urinary incontinence balance efficacy, side effects and cost of anticholinergic medication versus botulinum toxin intradetrusor injection. The results have the potential to fundamentally change the therapeutic approach to this condition.

Keywords

Urge incontinence; Urgency urinary incontinence; Overactive bladder; Botulinum toxin; Anticholinergic therapy; Solifenacin; Trosipium; Randomized Clinical Trial

Introduction

Urge urinary incontinence is a prevalent, chronic and potentially debilitating condition characterized by unpredictable, large volume urine loss associated with urgency.¹ Anticholinergic medications are a common first-line treatment for urgency urinary incontinence (UUI). A recent Agency for Healthcare Research and Quality (AHRQ)-sponsored systematic review on treatment of overactive bladder suggests that anticholinergic medications have minimal to modest efficacy.² Many patients do not have adequate symptom relief or do not tolerate common side effects of drugs, such as dry mouth or constipation. While these medications are useful in certain patients, both efficacy and long-term medication compliance are suboptimal. A population-based study of 757 women found that only 56% of the women felt their OAB medication was effective and 50% stopped taking their medication at some point.³ The most common reasons for discontinuation were inadequate efficacy (42%), followed by adverse events or intolerability (30%), physician switched medication (17%), and cost (14%).³

Since Schurch's 2000 report that intravesical botulinum A toxin could improve urinary continence in patients with refractory detrusor overactivity, multiple investigators have reported evidence of efficacy for patients with refractory urgency urinary incontinence.^{4,5} Prior work by the Pelvic Floor Disorders Network (RUBI trial)⁶ demonstrated that 200 units of botulinum A therapy was an effective and durable treatment for refractory overactive bladder (median duration of response, 373 days), but a higher rate of incomplete bladder emptying was found exclusively in the active treatment arm, requiring clean intermittent self-catheterization (CISC) at times and prompting early study termination.⁶ More recent studies, including a large dose-finding study, have since been presented, suggesting that a reduced dose of 100 units has a preferred safety profile.⁷⁻⁹

The majority of studies of botulinum A toxin have been conducted in patients with refractory symptoms. Botulinum A toxin has not been evaluated as first-line therapy, primarily because it is a costly, procedural-based treatment. However, given the suboptimal efficacy and long-term compliance of anticholinergic medications, researchers must assess whether botulinum A toxin has a role as first or second line therapy for women with

moderate to severe UUI. A cost effectiveness decision analysis found that botulinum toxin was cost effective compared to anticholinergic therapy over a two-year timeframe.¹⁰

The AHRQ systematic evidence review found that current evidence is insufficient to guide choice of other therapies including sacral neuromodulation, instillation of oxybutynin and injections of botulinum toxin supporting the need for a randomized trial comparing these treatment modalities to standard pharmacologic therapy. To reduce this evidence gap, the Anticholinergic vs. Botulinum Comparison (ABC) trial was designed to compare the effectiveness of intradetrusor botulinum A toxin (100 units) to a six-month anticholinergic regimen for the treatment of moderate to severe UUI in a double-blind, randomized trial.

Material and Methods

The Pelvic Floor Disorders Network

The NIH-sponsored Pelvic Floor Disorders Network (pfdn.org) seeks to conduct high-impact research to advance knowledge and improve care for women with female pelvic floor disorders including urinary and fecal incontinence as well as pelvic organ prolapse. Seven clinical sites (see appendix) supported by a data coordinating center at the University of Michigan, NIH Project Scientist, and an external Steering Committee Chair form the PFDN. An independent data safety and monitoring board (DSMB) reviews protocols for ethical and safety standards, monitors the safety of ongoing clinical trials, and provides advice on study conduct. Following IRB approval at the data coordinating center and each clinical site, written informed consent for research is obtained from each participant prior to enrollment.

Enrollment for the ABC trial began in April, 2010 and is estimated to be completed by June, 2011 after randomization of 242 subjects. This trial is registered at <http://www.clinicaltrials.gov> (NCT01166438).

Design overview

The ABC trial assesses whether there is a significant difference in the reduction in the average number of urgency urinary incontinent episodes over six months between intradetrusor botulinum toxin A injection and oral anticholinergic therapy in women with moderate to severe UUI. In order to optimize generalizability of this trial, we include women with moderate to severe UUI who are naïve to drug or had persistent symptoms refractory to up to two, commonly-used anticholinergic medications.

The ABC trial is a randomized, double-blind, active-controlled clinical trial design. To achieve masking in this setting, a dual placebo approach was used in which subjects randomized to botulinum toxin A 100 units will receive placebo pills. Subjects randomized to anticholinergic regimen will undergo placebo (saline) injection and receive active oral anticholinergic medication. Given the chronic nature of UUI, we will follow subjects up to an additional six months off study drug to determine duration of treatment effect. To comprehensively assess effectiveness, we would ideally continue masked therapy for at least 2 years, however, this would have necessitated some participants undergo multiple placebo injections, making this option untenable. Figure 1 summarizes the ABC Trial Design.

In planning this trial, the investigators considered adding behavioral therapy to both treatment arms. Data are mixed about whether this improves outcomes.¹¹ Further, this combination therapy is rarely offered in the primary treatment of women with UUI. Therefore, the investigators made the decision to compare the most common first-line therapy (medication) without the addition of behavioral therapy.

Study population

Women who are drug naïve or refractory to up to two specified anticholinergic medications will be recruited from clinics and the community, by various marketing methods including advertising. We defined our study population as women with moderate to severe UUI defined as ≥ 5 urgency urinary incontinence episodes on a 3-day prospective bladder diary (with cut-point chosen to have an adequate number of leakage episodes at baseline to increase the likelihood of showing a difference between groups and avoiding floor effects). We excluded subjects who had previous pharmacologic therapy with solifenacin, darifenacin or trospium choride as these were either actual study drugs or similar compounds.

While inclusion of both drug naïve and drug refractory subjects in the ABC trial may increase heterogeneity, it is important to recognize that the severity of UUI needed to meet the inclusion criteria for the ABC trial includes moderate to severe incontinence as subjects will need to demonstrate 5 urgency urinary incontinence episodes on a prospective 3-day voiding diary (minimum of 1.67 episodes per day). This is actually more severe than the degree of UUI in the Allergan-sponsored Botox dose finding study that included doses as high as 300 units.⁹ In that dose finding study, subjects needed to document ≥ 8 incontinence episodes over a 7-day voiding diary (minimum of 1.14 episodes per day).

Inclusion/Exclusion Criteria—Table 1 summarizes the detailed inclusion and exclusion criteria. In addition to those listed in Table 1, we also considered limiting inclusion to women with urodynamically proven detrusor overactivity incontinence but concluded that including women with the symptom of UUI was more clinically relevant and would improve generalizability since this is generally the trigger for initiating treatment with anticholinergic medication.

Rationale for anticholinergic medication and regimen chosen for this protocol

Anticholinergic medications are a general class of medications that inhibit parasympathetic nerve impulses by selectively blocking the binding of the neurotransmitter acetylcholine to its receptor in nerve cells. Study investigators debated the merits of a standard regimen of anticholinergic medication that allowed for both dose escalation and medication change versus employing a “usual care” approach which would allow the investigators to choose the anticholinergic medication. Ultimately, the study team chose to proceed with a standard regimen of anticholinergic medication since it became clear that it would be nearly impossible to maintain blinding with the “usual care” option.^{12,13,14}

Since the primary outcome is assessed monthly over 6 months, the study was designed to target a reasonable anticholinergic regimen that would allow for dose escalation and would be the most likely to encourage compliance, ease of dosing, and would have the highest efficacy with the lowest side effects. We also chose anticholinergics with different mechanisms of action to allow the anticholinergic arm to have the best chance of success.

The two drugs that were selected were solifenacin and trospium XR. The choice of these two medications was made because solifenacin is a M3 selective anticholinergic and is the only such selective anticholinergic that has been shown to have improved efficacy to tolterodine in a randomized trial.¹⁵ Trospium was chosen because it has non-selective anti-muscarinic activity, had recently become available in once daily dosing and may have local urothelium effects since it is not metabolized and is excreted in the urine almost entirely as trospium.¹⁶ Trospium XR also has the lowest rate of dry mouth (8.7%) of any oral anticholinergic medication. The inclusion criteria were set to include subjects that may have been treated with either tolterodine or oxybutynin since tolterodine was the most commonly prescribed anticholinergic in the US at the time of study design and prior to the use of

tolterodine, the most prescribed medication for this indication was oxybutynin. Since our study population included subjects found to be refractory to single drug therapy with oxybutynin, tolterodine and/or fesoterodine the choice of anticholinergics in the drug treatment arm needed to be medications other than these anticholinergic agents. We included a second drug to mimic the usual clinical practice of using more than one anticholinergic and also because data suggest that failure after one drug does not predict failure of another drug.¹⁷ Both drugs have been shown in non-comparative studies to have similar efficacy and side effect profiles¹⁸⁻²¹ and both study medications are available in daily dosing.

Baseline assessments

Tables 2 and 3 summarize the schedule of study visits. At the baseline visit, the study is explained and an IRB-approved written consent is obtained. Baseline data collected in the clinic will include: demographics, a directed history and physical examination including height and weight, urinalysis, a serum creatinine level, and a measure of the post-void residual volume (PVR). Women complete a 3-day voiding diary, which is then reviewed to confirm study eligibility. Participants must have a filling cystometrogram within the last 12 months; this is not used to determine eligibility but rather, to characterize the study population. Before randomization, women or a care-taker are instructed regarding the proper technique for CISC. The study staff confirm that the subject or designated care-taker is able to perform this procedure. As a patient safety measure, subjects unable to perform CISC or who do not have a care-taker that can perform CISC are not eligible for randomization and are withdrawn from the study.

All ongoing therapies for UUI are recorded at the baseline visit and updated at each visit. Subjects are asked to discontinue any use of oxybutynin, fesoterodine, or tolterodine for urinary symptoms three weeks prior to baseline assessment and agree not to begin any off-protocol treatment for UUI including medication management, supervised or unsupervised behavioral therapy, or neuromodulation.

The PVR volume is measured with either a catheter or by ultrasound. If a PVR is 150mL or greater on two occasions with a void over 150mL, the patient is not eligible for participation. If the PVR value is obtained by ultrasound and is ≥ 150 mL, the PVR is confirmed by catheterization which will be the gold standard. A negative urinalysis (defined as $<1+$ nitrite and $<1+$ leukocyte) by an appropriately obtained dipstick urinalysis is obtained prior to injection.

Requirement of 3 day diary at entry

On the voiding diary, women record the time of all voids and all incontinence episodes and mark the type of leakage (stress, urge, or other) for each episode. Time of awakening and bedtime are recorded, as well as number of pads used per day. The subject must show 5 or more urge incontinence episodes during the 3-day period to be eligible. A minimum of 2 consecutive days of recording are required for the diary to be considered adequate.

Urodynamic Assessment

Women who have not undergone a urodynamic evaluation within the past 12 months will undergo a multi-channel cystometrogram performed according to the International Continence Society (ICS) standards to assess for detrusor overactivity and detrusor overactivity incontinence with provocative maneuvers such as cough, water sound, standing and heel bounce. The volumes at which women note first sensation a strong desire and maximum cystometric capacity are recorded.

Randomization and masking

At the injection visit, women are randomized in a 1:1 fashion to botulinum toxin A or anticholinergic management using permuted blocks, with a fixed block size known only to the DCC. Randomization is stratified by previous exposure to anticholinergics or drug naïve, by baseline urgency urinary incontinent episodes (5 to 8 vs. 9 or more), and by site. The DCC generated the random allocation sequence and loaded them into its e-Randomization system, a secure web-based application that allowed research coordinators to enter the subject ID and stratification information. The system then provided the randomization number to the coordinator who provided the subject ID and randomization number to the site pharmacist who accesses the e-randomization system to receive the study treatment associated with the randomization number. The computer-based method to determine the random allocation avoids the potential violations of the randomization scheme associated with the envelope method, such as biased opening, loss, or misplacement in the randomization queue of the appropriate envelope.

Both subjects and study personnel are masked to the study treatment group by employing a dual placebo, double-blind design. Subjects randomized to anticholinergic management receive their anticholinergic regimen as well as a saline intradetrusor injection, while subjects randomized to botulinum toxin A receive active intradetrusor injection as well as matched placebo pills for solifenacin 5mg, solifenacin 10mg or trospium XR 60mg. To maintain the masking, subjects randomized to anticholinergic are dose escalated or change anticholinergics at the same intervals and based on the same criteria as those randomized to placebo anticholinergics.

Study Intervention

Injection

Cystoscopic injection is standardized using a Wolf injection cystoscope (Richard Wolf Medical Instruments Corp, Vernon Hills, IL) and 100-200mL of total intravesical fluid is instilled to allow for adequate visualization of the bladder urothelium. The physician injects a total of 10.1 mL of the masked substance, containing 10mL of either botulinum toxin A (100U/10 ml) or placebo with 0.1 mL indigo carmine (to better visualize injection sites) into approximately 15 to 20 different detrusor muscle sites under direct visualization using disposable needles. Injections will be spread out to equally cover the posterior bladder wall and dome, but sparing the bladder trigone and ureteral orifices. An additional 1mL of saline flush is injected into the bladder at the end to ensure that all study drug is delivered and does not remain within the injection needle. The anterior bladder dome will not be injected because this area is more difficult to inject cystoscopically. Each subject receives a single bladder injection in this trial.

Dose Escalation/Medication Change

Drug dosing was structured to allow flexibility. There will be a total of three steps for potential changes in pharmacotherapy. Dosing begins with solifenacin 5mg po qd for the first 8 weeks (Step 1) and allows for potential dose escalation to solifenacin 10mg po qd for the second 8 weeks (Step 2); if subjects do not have sufficient efficacy on solifenacin 10mg po qd, they may be switched to trospium XR 60mg po qd for the final 8 weeks of the study (Step 3).

The decision to dose escalate at Step 2 or Step 3 is based on both the Patient Global Symptom Control rating scale (PGSC) and presence and severity of side effects. (Table 4). If a subject's symptoms are adequately controlled based on a PGSC score of 4 or 5, on solifenacin 5mg daily, she may continue that study medication for the entirety of the double-

blind portion of the study (6 months). Additionally, if a subject is dose-escalated to solifenacin 10mg daily at study months 2 or 4, and her symptoms are adequately controlled, she may continue the solifenacin 10mg dose for the remainder of the double-blind portion of the study. The possible scenarios for a subject's possible study medication regimen are depicted in Table 5.

The PGSC question is as follows:

My current treatment is giving me adequate control of my urinary leakage.

Disagree 1 2 3 4 5 Agree
Strongly Strongly

During the follow-up phase of the trial, the PGSC is administered monthly, beginning at 6 months for up to a year, to determine the duration of effect of treatment received during the first 6 months of the trial defined as a PGSC score of 4 or 5. If the subject has no or a poor response (PGSC response: 1 to 3) or if she requests or reports taking off-protocol treatments including supervised behavioral therapy, off-protocol anticholinergic therapy, botulinum toxin injection(s) or neuromodulation at 6 months, she will be withdrawn after completing an end of study evaluation.

Primary Outcome Measure

The primary outcome measure for this trial is the change from baseline in mean number of urgency urinary incontinence episodes (UIE) on 3-day bladder diaries, measured monthly, over the 6-month double-blind active treatment period (i.e., at months 1, 2, 3, 4, 5 and 6). The investigators discussed whether an objective, subjective or composite outcome measure was most clinically relevant for this trial. As change in incontinent episodes as measured by bladder diary is the most commonly reported outcome in anticholinergic medication and Botox trials, and the bladder diary²² has been shown to be a reliable measurement method for evaluating the frequency of incontinence episodes, it was chosen as the primary outcome for this trial. The planned monthly assessment allows us to assess an “area under the curve” effect rather than a single point change in time. This was felt to be important given the different pharmacokinetics and dosing regimens of the two treatment arms. Further, with several trials previously utilizing this outcome measure, it allowed for estimates of effect and sample size calculation for this trial.

Secondary Outcome Measures

Secondary outcomes were chosen that assess other symptoms and events relative to these two treatment approaches for this lower urinary tract condition both from a patient (patient reported outcomes) and societal perspective, with the inclusion of economic analyses.

Symptom Specific, General Quality of Life and Economic Assessments

Subjective symptoms of UII are measured at baseline and follow-up using the Overactive Bladder Questionnaire short form (OABq-SF);^{23,24} urgency urinary incontinence symptoms as well as other pelvic floor symptoms and impact is measured using the Pelvic Floor Distress Inventory and Pelvic Floor Impact Short Form Questionnaires, respectively (PFDI-SF, PFIQ-SF);²⁵ general health related quality of life (QOL) is measured with the Medical Outcomes Study Short Form (SF-12).²⁶ The Pelvic Organ Prolapse/Urinary Incontinence/Sexual Function Questionnaire Short Form (PISQ-SF)²⁷ is used to assess sexual function. A Productivity Loss Assessment²⁸ and utilization of medical resources assessment is used to report work/life productivity loss and cost-effectiveness associated with incontinence symptoms and treatments.

Post Intervention Treatment Specific Assessments

The proportion of subjects reporting improvement of symptoms is measured using the Patient Global Impression of Improvement (PGI-I) and satisfaction with medication efficacy and side effects of treatment using the Treatment Satisfaction Questionnaire for Medication (TSQM II).²⁹ Subject compliance with pill administration is assessed using computerized vials (MemCaps^{TM}). Standardized follow-up is performed to determine the proportion of subjects that experience partial urinary retention requiring CISC, and other potential side effects of the 2 treatments such as dry mouth, dry eyes, or constipation during the study. Subjects are also assessed for specific outcomes related to CISC such as urinary tract infections and pain.

Economic Evaluation

An important facet of this trial design is its comparison of a surgical procedure to oral therapy. Many policy makers assume that a procedure would be a more costly approach. However, lower efficacy for longer periods as may occur with oral medication, particularly if not generically available, could reasonably lead to higher costs than an office procedure. Thus, we planned to explicitly measure direct and indirect costs as well as quality adjusted life-years (QALYs) using standard approaches to determine if either approach would be preferred.

Data Collection

Data on intervention costs and subjects' use of medical and non-medical resources, as well as indirect costs, for urologic or gynecologic related care during the first 6 month double-blind part of the study will be collected. Abstraction of administrative data at each study site on medical care utilization will be performed, supplemented by subject self-reported data collected at regularly scheduled in-person interviews and telephone calls. In addition, subjects are asked to report use of non-medical resources (e.g., transportation to care and routine care costs for incontinence such as pad use and laundry) and productivity loss associated with their incontinence symptoms and treatments, such as work loss days, reduced efficiency while at work, and lost household productivity. Unit price of medical care will be assigned based on the corresponding Medicare reimbursement rate, while medication costs will be calculated using the average wholesale price.

Algorithms developed by Yang et al will be used to derive a preference-based measure of health (i.e., utility value) from the OABq-SF data.³⁰ This utility value will subsequently be used for calculation of quality adjusted life years (QALYs) by assuming linear changes in each patient's utility values over time between every two assessments and calculating the area under the curve over the 6-month period.³¹ In addition, sensitivity analysis will be conducted by using QALYs calculated from the SF-12 questionnaire,³² a multidimensional generic measure of health-related quality of life administered at baseline, as well as 3 and 6 months after randomization.

Cost Effectiveness Analysis

The cost-effectiveness analysis will be conducted from a societal perspective. Because each subject has a follow-up period of 6 months for the economic evaluation component of the study, no discounting will be performed. Differential mean costs and differential mean QALYs between the botulinum toxin A and the anticholinergic group will be estimated using multiple regression analysis accounting for treatment group, study site, prior anticholinergic therapy, and baseline number of urge incontinent episodes on the 3-day voiding diary, as well as other characteristics of the subjects that are found to differ significantly between the two groups. We will calculate the incremental cost-effectiveness

ratio (ICER), which is the differential mean costs divided by the differential mean QALYs between the two groups, to assess the additional costs associated with each additional QALY gained. Base case analysis will be conducted based on QALYs calculated from OAB-q, which we believe more closely reflects the impact of UUI symptoms on subjects' quality of life. Sensitivity analysis will be conducted using QALY values calculated from the more generic, but widely used SF-12 instrument. In addition, sensitivity analysis will be performed to include data on subjects with incomplete cost or utility values using the multiple imputation method.³³

Statistical analysis

The primary analysis will use a modified intent-to-treat approach, which includes subjects who are randomized, treated, and have a baseline and at least one follow-up observation of UUI episodes. Given that the trajectories of the primary end point, change from baseline in mean number of UUI episodes over the 6-month double-blind period (i.e., change from baseline to months 1, 2, 3, 4, 5 and 6), are expected to differ because of the mechanisms of action of the two treatment modalities, a longitudinal approach incorporating all time points will be employed. Specifically, a mixed effect model for repeated measures with treatment group and the three stratification factors as fixed covariates will be fit, with time of assessment treated as a continuous variable and the end point modeled as a function of time. If the assumptions of the model are not met, other methods will be investigated including non-linear parametric, semi-parametric or non-parametric tests, as well as utilizing a measure of the accumulated effectiveness over time, quantified by the measure Area Under the Curve (AUC), using a mixed effect model.

Sensitivity analyses will be performed to assess how subjects who withdrew may affect conclusions of the analysis. An intent-to-treat analysis set (including subjects who are randomized, treated and have a baseline assessment of urge incontinent episodes) will be used to assess treatment effects with multiple imputation methods³⁴ employed to impute outcomes for subjects with no post-baseline diary data. Depending on the extent and pattern of missingness, other simpler sensitivity analyses may be used: for example, change from baseline to the end of treatment for subjects completing the study (completers) may be analyzed using an analysis of variance model. The model will include the same covariates that are included in the primary mixed effects analysis.

Sample size

The sample size was based on achieving at least 80% power to compare botulinum toxin A and anticholinergic therapy using the primary end point of change from baseline in mean number of urgency urinary incontinent episodes over the 6-month double-blind period. A sample size of 242 subjects (121 per treatment group) provides at least 80% power to detect a relative difference of 53% between botulinum toxin A and standardized anticholinergic therapy, assuming a treatment difference of -0.80 and a common SD of 2.1 (effect size = 0.381), and a two-sided type I error rate of 5%. The sample size was adjusted to allow for a 10% loss to follow-up over the 6-months of treatment as well as one interim analysis to stop early for benefit when approximately half of the randomized subjects are followed for 6 months. The purpose of the interim analysis is to stop for benefit. Stopping boundaries will be generated using Lan-DeMets alpha spending functions with the O'Brien-Fleming type approach.³⁵ The alpha level for the interim analysis is 0.003, the final test will be conducted at the 0.047 level of significance. The first interim analysis allows for 77% power to detect an effect size of 0.71 (100% relative difference in treatments) and 84% power to detect an effect size of 0.76 (106% relative difference in treatment). Interim data analyses will be presented to the Data Safety and Monitoring Board for their review and recommendation.

We used a simpler method for the sample size calculation of this study that provides a conservative estimate of study power (i.e. the actual study power will be somewhat larger than estimated by our calculations). This method avoided making additional assumptions for which data are limited or unavailable that would have been required to base the sample size on longitudinal methods (e.g., estimation of the within-subject correlation over multiple observations).

Placebo development and manufacturing

We originally explored donation of active drugs and placebos from pharmaceutical companies, however, such public-private partnerships were not established. We moved forward with the task of developing and manufacturing placebos for solifenacin 5mg, solifenacin 10mg and trospium XR 60mg.

Solifenacin 5 and 10mg are available as tablets with an outer coating that contributes to its half-life allowing for daily dosing. This precluded crushing of the tablet. We ultimately chose to over-encapsulate the tablets with DB caps®, opaque gelatin capsules specifically designed for this purpose. We were reassured that this was a reasonable approach as solifenacin is a Class I compound that is highly soluble, rapidly dissolving and highly permeable with absolute bioavailability of $\geq 90\%$. Despite this reassurance, we felt obligated and completed extensive *in vitro* bioavailability and dissolution testing that confirmed that the only difference was an expected 3-4 minute delay due to the time necessary for the DB capsule disintegration. Expert reviewers determined that the 3-4 minute delay was unlikely to have any impact on bioavailability since clinical pharmacokinetic data presented by the manufacturer describe an absolute bioavailability of approximately 90% with a Tmax ranging from 3 to 8 hours.

It was originally thought that Trospium would be more challenging as it was less well-absorbed and contained various beads within the manufactured capsule. We felt uncomfortable for this reason to proceed with over-encapsulation as our means for masking Trospium. Through various brainstorming sessions, it was ultimately decided to “repackage” the Trospium XR by individually re-encapsulating the contents of the Trospium XR capsule into a new opaque gelatin capsule. *In vitro* bioavailability and dissolution testing was performed and determined that the reencapsulated Trospium was similar to the manufactured Trospium. We further tested the emptied Trospium capsules and found no residual Trospium.

All testing was performed at Campbell University Pharmaceutical Sciences Institute (CUPSI). Members of the team and other external consultants reviewed our methods, results and interpretation.

Placebo/Drug Distribution

The anticholinergic regimen included three distinct doses or drugs which were different in color and/or size. Because of dose escalation/drug change nature of the anticholinergic regimen, the calculation of the number of active medications to purchase and the number of placebo pills to manufacture was more complicated than in a simple two treatment study or a study with a fixed dose escalation scheme. In addition, drug expiration date needed to be considered because the known expiration of the study medications (approximately 28 months for solifenacin 5mg and 10mg and 18 months for trospium XR 60mg) were shorter than the projected recruitment period, after allowing 7 months for purchase, manufacturing and distribution. Thus, simulations were used to estimate the amount of each study medication needed for each lot, as well as the number of lots, for various recruitment rates per site and various dose escalation/dose change scenarios at each step. The goal was to

provide a sufficient amount of study medications to each site at the start of the study, with some remaining at the depot (CUPSI), to minimize the cost of additional manufacturing runs. Simulations indicated that while it might be possible to have one manufacturing run for Solifenacin 5mg and 10mg, there was a high probability of needing 1-2 additional manufacturing runs for tiroprium XR 60mg. Real-time reconciliation of study drug supplies at each site, relative to enrollment and dose escalation/dose changes, are employed by the DCC, using web-based dynamic reporting and e-mail notification to key personnel to ensure that sufficient drug is available at each site. Pre-defined triggers were developed to start additional manufacturing runs.

Unique issues related to maintaining masking with this trial

Every effort is made to maintain masking of initial group assignment (botulinum toxin A or anticholinergic) until the end of the entire study including the 6-month extension period. Dry mouth, dry eyes and constipation are the most common side effects reported with anticholinergic therapy. However, randomized trials have reported complaints of dry mouth as high as 40% in subjects receiving placebo.³⁶ We share this information with both study subjects and study personnel will help reduce the likelihood that subjects suspect group assignment based on side effects. Further, all subjects receive recommendations regarding the use of sugar-free candy and receive dietary recommendations to prevent or treat constipation in an attempt to reduce the incidence or mitigate the impact of these complaints.

Urinary retention is expected to be more common in the group that receives botulinum toxin A injections. Since the current protocol injects only 100 units of botulinum toxin A, the rate of retention is expected to be considerably lower than in other studies utilizing higher doses. Given that no study has reported clinical harm from post-void residual urine volumes between 100-300 (the common range in which 'retention' is defined), and that urinary tract infections may be caused rather than prevented by initiating intermittent self-catheterization at volumes in the lower range, the protocol committee chose to initiate catheterization at residual volumes > 300 mL *or* > 150 mL in the presence of bothersome retention symptoms. Therefore, given the more liberal definition of retention, the rate of retention is expected to be lower which would further have a lower impact on unmasking and outcome assessment.

Discussion

Study design challenges

The ABC trial is innovative and challenges the current approach to the treatment of urgency urinary incontinence, a prevalent condition that significantly impacts quality of life. The results of this trial have the potential to radically shift the management of urge incontinence from a daily pharmacologic therapy to a periodic office-based procedural approach.

Within the Pelvic Floor Disorders Network, research protocols are developed by a consensus process with involvement of members of each of the network sites, the DCC and NIH representatives. The final protocol requires that at least 8 of the 10 steering committee members vote to proceed. During the evolution of ABC, numerous informal votes were taken to gauge interest in proceeding along different directions. At the start of the planning process, a majority of the investigators considered it unethical to offer intradetrusor injections of botulinum toxin to women who had not already attempted more conservative therapy for their UUI.

This trial took approximately 18 months to design in part due to the time needed to develop and test placebo and active drug capsules. During the planning process, the literature evolved in two important ways that redirected our study design. First, an evidence report team commissioned by the Agency for Health Research Quality² conducted an extensive

systematic review of anticholinergic medications for urge incontinence and concluded that the reductions in urgency urinary incontinence episodes found reflected only “modest margins of benefit from baseline above placebo” and reinforced the fact that overactive bladder is a chronic condition.² Second, several other larger trials studying Botox intradetrusor injections were completed, contributing to a consistent body of evidence that such injections are safe. In addition, the rate of urinary retention, the primary adverse event associated with botulinum bladder injections, was much lower when lower doses of drug were injected, and when retention was defined less strictly. Given these facts, the protocol committee reached consensus with a dual-placebo 6 month randomized trial and extended inclusion to women naïve to pharmacologic management.

The initial trial design included an ambitious 18-month follow-up phase that allowed for multiple injections and a cross-over design. The potential information that would have been provided from this extension helped to alleviate the concern some members had about allowing only half the group to receive Botox. However, when the logistics of an extension trial were examined further, it became apparent this would exponentially increase the sample size necessary for our primary outcome. Furthermore, since women in both randomization groups receive some form of active treatment at no charge, the protocol committee ultimately decided that neither withholding Botox nor administering placebo injections disrupted clinical equipoise.

Since this trial's inception, a number of other studies demonstrated efficacy and low drop-out rates in responders who received multiple cystoscopic injections of botulinum toxin A.^{37,38} In fact, repeated injections (if indicated) may translate into improved outcomes and long-term patient compliance when compared to oral medication for UUI. Moreover, cystoscopic botulinum toxin A injection is a procedure that is easily administered in an office setting compared to percutaneous intraspinal placement of an electrode as is needed with the InterStim procedure.³⁹ Interestingly, there is one randomized trial currently recruiting patients that compares InterStim therapy (sacral neuromodulation) to standard anticholinergic therapy. This investigation is currently recruiting adult participants who “have failed or could not tolerate at least one anticholinergic or antimuscarinic and have at least one anticholinergic or antimuscarinic medication not yet attempted” with targeted randomization of approximately 100 subjects at up to 30 sites in the US and up to 5 in Western Europe.(clinicaltrials.gov NCT:00547378)

The most appropriate dosage of Botox was not known at the start of the planning process but several publications later reported a dose of 100 units of botulinum toxin A as efficacious with lower partial urinary retention rates.^{7,8,41} Some studies even compared the 100 unit dose to higher doses including 150 and 200 units.^{7,41} It appears that the duration of effect of 100 units of botulinum toxin A is acceptable as the largest series (180 subjects) reported duration of effect of 8.5 months $\pm$ 2 months with a mean interval between injections of 11 months (range 3-21 months).⁴² Two of the studies also evaluated upper urinary tract (kidney) function with serum creatinine measurements and renal ultrasound and found no abnormalities even in the patients with partial urinary retention.^{7,8} We ultimately chose to assess a single injection of 100 units of botulinum toxin A.

We debated the values of a pragmatic trial, in which participants were randomized to an open menu of anticholinergic therapy over a six-month period, similar to routine clinical care, versus a clearly defined intervention. By choosing three different medications to study in a specific order, we felt that we mimicked a reasonable prescribing pattern of most clinicians in the group but maintained control over the intervention and ability to mask. However, the need for masking led to its own set of challenges.

Strengths

The ABC trial is novel and will have significant impact on the clinical care of women with urgency urinary incontinence, potentially revolutionizing the therapeutic approach. This trial is the first such study to compare daily pharmacologic oral therapy to an office-based procedure for the treatment of urge urinary incontinence. The rigorous randomized-controlled design of the ABC trial with effective double-blinding will improve our ability to interpret the results of our primary comparison. In addition, the multi-site performance and the broad eligibility criteria facilitate applicability of the findings of the study. The robust design of the ABC trial includes innovative features, such as the inclusion of drug-naïve subjects to facilitate the broad generalizability for the many women in the affected population, the use of MemCaps™ to monitor compliance and the use of dual-placebos to maintain masking. Given the aging of the population and the prevalence of UUI, evidence for optimal first and second line treatments is sorely needed. Although intradetrusor botulinum A toxin is relatively expensive within the first month of treatment, if greater efficacy is achieved over a longer treatment period, it is possible that the costs may become favorable compared to the cost of medication. The inclusion of detailed cost-effectiveness analyses in this trial comparing two different treatments, medication versus bladder injection, allows us to fully and accurately describe the differences and to inform policy makers of the costs relative to the incremental benefits expected for the use of this and any new technology or procedure.

Another strength is that we included subjects with moderate to severe urgency urinary incontinence to maximize the ability to assess for difference between treatment groups and to target a population in need for effective therapy. We further excluded subjects with refractory UUI as many of these patients with refractory symptoms would have already attempted (and failed) treatment with the ABC trial medication regimen, thus preventing bias against the anticholinergic arm of this trial. We sought to increase generalizability by choosing inclusion criteria that reflect a “mixture” of patient types, including those that have failed up to two previous medication treatments and those that have never attempted medication treatment. The recent information from an AHRQ-sponsored systematic evidence review on the treatment of overactive bladder showed minimal to modest efficacy with anticholinergic medications in a similarly heterogeneous population that included drug naïve patients underscoring the need for improved treatment options.² Finally, the ABC trial addresses recommendations from the AHRQ-sponsored systematic review by assessing a new and promising treatment for urge incontinence in a rigorous randomized manner.

Limitations

As with every randomized trial, there are several limitations to consider in our design. Despite some challenges, we chose a rigorous double-blind randomized approach to allow for a more robust interpretation of the data and to provide the highest level of evidence for clinical care and cost analyses. The research question does measure a relatively short-term primary outcome time-point (6 months). However, it is reasonable, in light of our primary hypothesis. We did consider both cross-over type interventions as well as looking at the effect of multiple botulinum toxin injections in the longer-term, but there was not a good solution for “retreatment” of those patients on medications that were not satisfied with symptom control without redesigning the trial.

This trial only “tests” solifenacin and trospium, but both of these medications are thought to work by mechanisms different from the older medications and may in fact, provide greater efficacy and decreased side-effects. The regimen chosen is reasonable given the current empiric approach to anticholinergic management. Although the use of intradetrusor

botulinum toxin A is not currently FDA-approved, two randomized trials have demonstrated efficacy^{5,6} and it is being increasingly used off-label for treatment of these lower urinary tract symptoms. Use in this trial is balanced by the ease, efficacy and safety noted in many previous studies. An Investigational New Drug (IND) number was obtained for use in this trial.

Conclusion

The design and implementation of the ABC trial challenged the investigators to reassess their beliefs and clinical opinions regarding the management of moderate to severe urgency urinary incontinence and to consider innovative therapies, study designs, and comparative groups while contemplating issues related to balancing efficacy with side effects, ethics issues, maintenance of blinding and specific issues related to comparing two very different treatment modalities. Findings from the ABC trial will provide valuable information that will help clinicians counsel women on the benefits and risks of botulinum toxin A intradetrusor injection versus oral anticholinergic therapy for the treatment of moderate to severe urgency urinary incontinence. This trial has the potential to fundamentally change the therapeutic approach to this very prevalent condition.

Acknowledgments

Supported by grants from The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, (2U01 HD41249, 2U10 HD41250, 2U10 HD41261, 2U10 HD41267, 1U10 HD54136, 1U10 HD54214, 1U10 HD54215, 1U10 HD54241) and the NIH Office of Research on Women's Health. This trial is registered at <http://www.clinicaltrials.gov> under Registration #: NCT01166438.

Appendix: Pelvic Floor Disorders Network Members

Clinical Sites

Cleveland Clinic

Mathew D. Barber, MD, MHS, Principal Investigator

Marie Fidela R. Paraiso, MD, Co-Investigator

Mark D. Walters, MD, Co-Investigator

J. Eric Jelovsek, MD, Co-Investigator

Linda McElrath, RN, Research Nurse Coordinator

Donel Murphy, RN, MSN, Research Nurse

Cheryl Williams, Research Assistant

Duke University

Anthony G. Visco, MD, Principal Investigator

Cindy L. Amundsen, MD, Co-Investigator

Alison C. Weidner, MD, Co-Investigator

Jennifer M. Wu, MD, MPH, Co-Investigator

Mary J. Raynor, RN, BSN, Research Coordinator

Mary McGuire, BS, Research Assistant

Grace Fulton, Research Assistant

Jean Maynor, RN, Research Coordinator

Loyola University, Chicago

Linda Brubaker, MD, MS, Principal Investigator

Kimberly Kenton, MD, MS, Investigator

MaryPat FitzGerald, MD, MS, Investigator

Elizabeth Mueller, MD, MSME, Investigator

Mary Tulke, RN, Study Coordinator

University of Alabama at Birmingham

Holly E. Richter, PhD, MD, Principal Investigator

Kathryn L. Burgio, PhD, Co-Investigator

R. Edward Varner, MD, Co-Investigator

Robert L. Holley, MD, Co-Investigator

Patricia S. Goode, MD, Co-Investigator

L. Keith Lloyd, MD, Co-Investigator

Tracey Wilson, MD, Co-Investigator

Alayne D. Markland, DO, Co-Investigator

Velria Willis, RN, BSN, Research Coordinator

Nancy Saxon, BSN, Research Nurse Clinician

LaChele Ward, LPN, Research Specialist

Lisa S. Pair, CRNP

University of California, San Diego and Kaiser, San Diego

Charles W. Nager, MD, Principal Investigator

Shawn A. Menefee, MD, Co-Investigator

Emily Lukacz, MD, Co-Investigator

Karl M. Lubber, MD, Co-Investigator

Michael E. Albo, MD, Co-Investigator

Keisha Dyer, MD, Co-Investigator

Gouri Diwadkar, Co-Investigator
Leah Merrin, Study Coordinator
Giselle Zazueta- Damian, Study Coordinator

University of Texas, Southwestern

Joseph Schaffer MD, Principal Investigator
Clifford Wai, MD, Co-Investigator
Marlene Corton, MD, Co-Investigator
David Rahn, MD, Co-Investigator
Gary Lemack, MD, Co-Investigator
Kelly Moore, Research Coordinator
Shanna Atnip, NP
Margaret Hull, NP
Pam Martinez, NP
Deborah Lawson, NP

University of Utah

Ingrid Nygaard, MD, Principal Investigator
Peggy Norton, MD, Co-Investigator
Yvonne Hsu, MD, Investigator
Linda Freeman, RN, Research Coordinator
Shirley Ranke, RN, Research nurse
Laura Burr, RN, Research nurse
Linda Griffen, RN, Research coordinator

University of Michigan (Data Coordinating Center – DCC)

Cathie Spino, DSc, Principal Investigator
John T. Wei, MD, MS, Co-Principal Investigator
Beverly Marchant, RN, Project Manager
Donna DiFranco, MPHMPHBS, Clinical Monitor
John O.L. DeLancey, MD, Co-Investigator
Dee Fenner, MD, Co-Investigator

Nancy K. Janz, PhD, Co-Investigator

Wen Ye, PhD, Statistician

Zhen Chen, MS, Statistician

Yang Wang Casher, MS, Database Programmer

NIH Project Scientist

Susan Meikle, MD, MSPH

External Chair for the Pelvic Floor Disorders Network, Vanderbilt

Kathie Hartmann, MD, PhD

References

1. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol.* 2003; 20:327–36. [PubMed: 12811491]
2. Hartmann, KE.; McPheeters, ML.; Biller, DH., et al. Prepared by the Vanderbilt Evidence-based Practice Center under Contract No 290-2007-10065-I. *Evid Rep Technol Assess (Summ).* Rockville, MD: Agency for Healthcare Research and Quality; 2009. Treatment of Overactive Bladder in Women; p. 1-8.AHRQ Publication No 09-E017
3. Diokno AC, Sand PK, Macdiarmid S, Shah R, Armstrong RB. Perceptions and behaviours of women with bladder control problems. *Fam Pract.* 2006; 23:568–77. [PubMed: 16731545]
4. Schurch B, Stohrer M, Kramer G, Schmid DM, Gaul G, Hauri D. Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. *J Urol.* 2000; 164:692–7. [PubMed: 10953127]
5. Sahai A, Khan MS, Dasgupta P. Efficacy of botulinum toxin-A for treating idiopathic detrusor overactivity: results from a single center, randomized, double-blind, placebo controlled trial. *J Urol.* 2007; 177:2231–6. [PubMed: 17509328]
6. Brubaker L, Richter HE, Visco A, et al. Refractory idiopathic urge urinary incontinence and botulinum A injection. *J Urol.* 2008; 180:217–22. [PubMed: 18499184]
7. Werner M, Schmid DM, Schussler B. Efficacy of botulinum-A toxin in the treatment of detrusor overactivity incontinence: a prospective nonrandomized study. *Am J Obstet Gynecol.* 2005; 192:1735–40. [PubMed: 15902187]
8. Schmid DM, Sauermann P, Werner M, et al. Experience with 100 cases treated with botulinum-A toxin injections in the detrusor muscle for idiopathic overactive bladder syndrome refractory to anticholinergics. *J Urol.* 2006; 176:177–85. [PubMed: 16753396]
9. Dmochowski, R.; Chapple, C.; Nitti, V.; al, e. Botulinum toxin A (BOTOX®) demonstrates dose-dependent efficacy and safety in idiopathic overactive bladder: a double-blind, placebo-controlled, randomized trial. American Urological Association Annual Meeting Chicago; IL. April 27. 2009
10. Wu JM, Siddiqui NY, Amundsen CL, Myers ER, Havrilesky LJ, Visco AG. Cost-effectiveness of botulinum toxin a versus anticholinergic medications for idiopathic urge incontinence. *J Urol.* 2009; 181:2181–6. [PubMed: 19296983]
11. Burgio KL, Kraus SR, Menefee S, et al. Behavioral therapy to enable women with urge incontinence to discontinue drug treatment: a randomized trial. *Ann Intern Med.* 2008; 149:161–9. [PubMed: 18678843]
12. Ciaschini PM, Straus SE, Dolovich LR, et al. Community based intervention to optimize osteoporosis management: randomized controlled trial. *BMC Geriatr.* 2010; 10:60. [PubMed: 20799973]
13. Thompson BT, Schoenfeld D. Usual care as the control group in clinical trials of nonpharmacologic interventions. *Proc Am Thorac Soc.* 2007; 4:577–82. [PubMed: 17878473]

14. Smelt AF, van der Weele GM, Blom JW, Gussekloo J, Assendelft WJ. How usual is usual care in pragmatic intervention studies in primary care? An overview of recent trials. *Br J Gen Pract.* 2010; 60:e305–18. [PubMed: 20594432]
15. Chapple CR, Rechberger T, Al-Shukri S, et al. Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder. *BJU Int.* 2004; 93:303–10. [PubMed: 14764127]
16. Staskin D, Sand P, Zinner N, Dmochowski R. Once daily trospium chloride is effective and well tolerated for the treatment of overactive bladder: results from a multicenter phase III trial. *J Urol.* 2007; 178:978–83. discussion 83–4. [PubMed: 17632131]
17. Chancellor MB, Zinner N, Whitmore K, et al. Efficacy of solifenacin in patients previously treated with tolterodine extended release 4 mg: results of a 12-week, multicenter, open-label, flexible-dose study. *Clin Ther.* 2008; 30:1766–81. [PubMed: 19014833]
18. Cardozo L, Lisee M, Millard R, et al. Randomized, double-blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. *J Urol.* 2004; 172:1919–24. [PubMed: 15540755]
19. Zinner N, Gittelman M, Harris R, Susset J, Kanelos A, Auerbach S. Trospium chloride improves overactive bladder symptoms: a multicenter phase III trial. *J Urol.* 2004; 171:2311–5. quiz 435. [PubMed: 15126811]
20. Kelleher C, Cardozo L, Kobashi K, Lucente V. Solifenacin: as effective in mixed urinary incontinence as in urge urinary incontinence. *Int Urogynecol J Pelvic Floor Dysfunct.* 2006; 17:382–8. [PubMed: 16283422]
21. Rudy D, Cline K, Harris R, Goldberg K, Dmochowski R. Multicenter phase III trial studying trospium chloride in patients with overactive bladder. *Urology.* 2006; 67:275–80. [PubMed: 16461077]
22. Nygaard I, Holcomb R. Reproducibility of the seven-day voiding diary in women with stress urinary incontinence. *Int Urogynecol J Pelvic Floor Dysfunct.* 2000; 11:15–7. [PubMed: 10738929]
23. Matza LS, Thompson CL, Krasnow J, Brewster-Jordan J, Zyczynski T, Coyne KS. Test-retest reliability of four questionnaires for patients with overactive bladder: the overactive bladder questionnaire (OAB-q), patient perception of bladder condition (PPBC), urgency questionnaire (UQ), and the primary OAB symptom questionnaire (POSQ). *Neurourol Urodyn.* 2005; 24:215–25. [PubMed: 15747340]
24. Coyne KS, Matza LS, Thompson C, Jumadilova Z, Bavendam T. The responsiveness of the OAB-q among OAB patient subgroups. *Neurourol Urodyn.* 2007; 26:196–203. [PubMed: 17016794]
25. Barber MD, Walters MD, Bump RC. Short forms of two condition-specific quality-of-life questionnaires for women with pelvic floor disorders (PFDI-20 and PFIQ-7). *Am J Obstet Gynecol.* 2005; 193:103–13. [PubMed: 16021067]
26. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care.* 1996; 34:220–33. [PubMed: 8628042]
27. Rogers RG, Coates KW, Kammerer-Doak D, Khalsa S, Qualls C. A short form of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12). *Int Urogynecol J Pelvic Floor Dysfunct.* 2003; 14:164–8. discussion 8. [PubMed: 12955337]
28. Koopmanschap MA. PRODISQ: a modular questionnaire on productivity and disease for economic evaluation studies. *Expert Rev Pharmacoecon Outcomes Res.* 2005; 5:23–8. [PubMed: 19807557]
29. Atkinson MJ, Kumar R, Cappelleri JC, Hass SL. Hierarchical construct validity of the treatment satisfaction questionnaire for medication (TSQM version II) among outpatient pharmacy consumers. *Value Health.* 2005; 8 1:S9–S24. [PubMed: 16336491]
30. Yang Y, Brazier J, Tsuchiya A, Coyne K. Estimating a preference-based single index from the Overactive Bladder Questionnaire. *Value Health.* 2009; 12:159–66. [PubMed: 18647258]
31. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ.* 2005; 14:487–96. [PubMed: 15497198]
32. Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. *Med Care.* 2004; 42:851–9. [PubMed: 15319610]

33. Rubin, DB. Multiple imputation for nonresponse in surveys. New York: Wiley; 1987.
34. Little, RJA.; Rubin, DB. Statistical analysis with missing data. New York: Wiley; 1987.
35. Lan KK, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrics*. 1983; 70:659–63.
36. Appell RA. Clinical efficacy and safety of tolterodine in the treatment of overactive bladder: a pooled analysis. *Urology*. 1997; 50:90–6. discussion 7-9. [PubMed: 9426760]
37. Gordon MF, Barron R. Effectiveness of repeated treatment with botulinum toxin type A across different conditions. *South Med J*. 2006; 99:853–61. [PubMed: 16929880]
38. Karsenty G, Reitz A, Lindemann G, Boy S, Schurch B. Persistence of therapeutic effect after repeated injections of botulinum toxin type A to treat incontinence due to neurogenic detrusor overactivity. *Urology*. 2006; 68:1193–7. [PubMed: 17141831]
39. Borawski KM, Foster RT, Webster GD, Amundsen CL. Predicting implantation with a neuromodulator using two different test stimulation techniques: A prospective randomized study in urge incontinent women. *Neurourol Urodyn*. 2007; 26:14–8. [PubMed: 17123297]
40. Brubaker L, Kreder L, Richter HE, et al. Refractory Urge Urinary Incontinence and Botulinum A Injection: The Methods of the RUBI Trial. *J Applied Research*. 2006; 6:260–71.
41. Kuo HC. Will suburothelial injection of small dose of botulinum A toxin have similar therapeutic effects and less adverse events for refractory detrusor overactivity? *Urology*. 2006; 68:993–7. discussion 7-8. [PubMed: 17113890]
42. Schmid, DM.; Sauermann, P.; Werner, M.; Perucchini, D.; Sulser, T.; Schurch, B. Experience including 5 year results of 180 cases treated with low-dose (100 U) botulinum-A toxin injections in the detrusor muscle for overactive bladder refractory to anticholinergics. American Urological Association Annual Meeting; Anaheim, CA. 2007.

Figure 1.
Study Design Flow Diagram

Table 1
Inclusion and Exclusion Criteria

Inclusion Criteria

- Females at least 21 years of age
- Five or more urge urinary incontinence episodes on a three-day voiding diary. Urge incontinence episodes will be determined based on voiding diary and subject indication of coincident urge symptoms, allowing self-characterization of incontinence type.
- Urge predominant (urge >50% of total incontinent episodes) urinary incontinence based on self-reported characterization of incontinent episodes on diary.
- Demonstrated ability (or have caregiver demonstrate ability) to perform clean intermittent self-catheterization in the event that this would be required.
- Request for treatment for urge urinary incontinence. The patient may have tried other non-pharmacologic treatments for urge incontinence, such as supervised behavioral therapy, supervised physical therapy, unsupervised physical therapy, supervised biofeedback, and transvaginal electrical stimulation.
- Subject has undergone 3-week washout period if subject were on anticholinergic therapy prior to enrollment.
- Subject is able to complete all study related items and interviews.

Exclusion Criteria

- Any previous therapy with trospium chloride, solifenacin, or darifenacin
- Failed three or more anticholinergic drugs.
- Contraindication to anticholinergic therapy, specifically with solifenacin or trospium.
- Current symptomatic urinary tract infection that has not resolved prior to randomization.
- Uncontrolled narrow-angle glaucoma
- Gastric retention
- Baseline need for intermittent self catheterization
- PVR >150ml on 2 occasions with void(s) of greater than 150ml
- Surgical treatment for stress incontinence (sling, Burch or urethral injection) or pelvic organ prolapse recommended or planned at enrollment by study investigator(s).
- Any prior intra-detrusor botulinum toxin A injections
- Previous or currently implanted neuromodulation (sacral or tibial).
- Surgically altered detrusor muscle, such as augmentation cystoplasty.
- Known allergy to botulinum toxin A.
- Women with known neurologic disease believed to potentially affect urinary function (Multiple sclerosis, spinal cord injuries, myasthenia gravis, Charcot-Marie-Tooth disease).
- Known allergy to lidocaine.

- Currently pregnant or lactating patients or patients planning pregnancy within the next year.
  - Sexually active premenopausal women with a uterus who have either not had a tubal ligation or are not on a medically approved form of contraception for at least 3 months prior to and throughout the duration of the study.
  - Cystoscopic findings that preclude injection, in the opinion of the investigator.
  - Current or prior bladder malignancy.
  - In the opinion of the investigator, inability to understand diary instructions and complete 3-day voiding diary.
  - Subjects who are on anticoagulant therapy, excluding aspirin
  - Subject has been previously diagnosed with interstitial cystitis or chronic pelvic pain syndrome.
  - Subjects with hematuria who have not undergone a clinically appropriate evaluation.
  - Subjects taking aminoglycosides at the time of injection.
  - Serum creatinine level greater than twice the upper limit of normal within the previous year.
  - Two or more hospitalizations for medical conditions in the previous year.
  - Plans to move out of area in the next 6 months.
-

Table 2

Schedule of Evaluations During the Double-Blind Treatment Phase of the Study

Double-Blind Treatment Period (Study Months 1-6)																		
	Pre-Injection (Baseline)						Injection Visit		Treatment Period (Post-Injection)									
	Scre en/ Enro ll	Verify Elig. Call	QOL Pre- Inj.	QOL 2 wk adapt I	Pre- Inj.	Inject. /Study Med	Step1			Step 2			Step 3					
							2 day post Inject Call	2 wk Visit ^{1/0}	1 mo Visit ^{1/0}	2 mo Visit ^{1/1}	3 mo Call ^{1/1}	3 mo QOL	4 mo Visit ^{1/1}	5 mo Call ^{1/1}	6 mo QOL	6 mo Visit ^{1/1}		
Window (day)	-90 to -10d	-90 to -14d	-90 to -1d ^{**}		n/a	n/a	± 1d	± 7d	± 7d	± 7d	± 7d	± 7d	± 7d	± 7d	2 wks before 6 mo visit	± 7d		
Consent	X																	
Medical History	X																	
Med & Therapy Review	X				X			X	X	X			X	X		X		
Pregnancy Test					X													
Physical Exam	X																	
Randomization & Study Medication						X												
Serum Creatinine ²	X ²																	
Urine dip ⁴	X				X			X	X	X			X			X		
Urine collection ³	X					X												
Blood collection ⁵	X																	
Cystometrogram(CMG)	X																	
Post void residual ⁶	X							X	X	X			X			X		
LOT ⁶			X															
PGSC ⁶									X [*]				X [*]			X		
QOL ⁶			X									X			X			
OABq –SF ⁸	X								X	X	X	X	X	X		X		
Adaption Index ¹²	X																	
Voiding Diary		R ⁹					Remind ¹⁰	R	R	R	R	R	R	R		R		
Adverse event screen						X	X	X	X	X	X	X	X	X		X		

Subjects must have a documented negative urine dipstick or urine culture at the time of the injection.

¹ UTI may prolong windows 7 days.

² Serum creatinine performed if not documented within previous year.

³ Urine collection at baseline for biomarkers and at injection for PCR.

⁴ Subjects that have a positive urine dipstick result will also receive a urine culture. Subjects must have a documented negative urine dipstick or urine culture at the time of the injection.

⁵ Optional blood specimens collected for pharmacogenomic and biomarker testing.

⁶ PVR= post void residual volume; LOT=Life Orientation Test; PGSC=Patient Global Symptom Control rating; AE= adverse event.

⁷ QOL: Quality of Life Assessments are: PFDI-SF, PFIQ-SF, SF-12, PGI-1 and TSQM II are only administered at 3 and 6 months.

⁸ OABq-SF: Overactive bladder questionnaire, short form

⁹ R= review diary

¹⁰ Remind= coordinator reminds subject to complete diary.

¹¹ Coordinator will phone subject one week ($\pm$ 1 day) prior to the visit/call to remind subject to complete the 3-day voiding diary.

¹² Adaptation Index is only collected in the first 40 subjects at baseline and 2 weeks later, prior to injection.

* The PGSC may be obtained via telephone up to 72 hours prior to the scheduled 2 and 4 month visits to facilitate pharmacy preparation and dispensing.

** The first 40 subjects, will have baseline obtained >2 weeks prior to injection to allow for repeat Adaptation Index

Table 3
Schedule of Evaluations During the Off-Treatment Follow-Up Phase of the Study

Off-Treatment Follow-Up (Study Months 7-12)						
	7 month Phone call	8 month Phone call	9 month Phone call	10 month Phone call	11 month Phone call	12 month Phone call
Window (days)	±7d	± 7d	± 7d	± 7d	± 7d	± 7d
PGSC ¹	X	X	X	X	X	X
Medication & Therapy Review	X	X	X	X	X	X
OABq –SP ²	X	X	X	X	X	X
Adverse Event Screen ³	X	X	X	X	X	X

¹ PGSC=Patient Global Symptom Control rating

² Note: Adverse events related primarily to voiding dysfunction will be collected.

³ Adverse Event Screen

Table 4

Dose Escalation/Change in Study Medication and Management of Side Effects between Medication Steps, based on Efficacy and Tolerability.

		Efficacy	
		Yes (PGSC* 4,5)	No (PGSC 1-3)
Tolerability	Yes	No change in medication No need to manage side effects	Dose escalate or change study medication
	No	No change in medication Aggressively manage side effects	Dose escalate/change study medication and aggressively manage side effects

* PGSC=Patient Global Symptom Control rating

Table 5
Possible Study Medication Regimen

	Scenario 1 (No dose escalation)	Scenario 2 (Dose escalation at step 3 only)	Scenario 3 (Dose escalation at step 2 only)	Scenario 4 (Dose escalation at step 2 and 3)
Step 1 Months 0-2	Solifenacin 5mg	Solifenacin 5mg	Solifenacin 5mg	Solifenacin 5mg
Step 2 Months 3-4	Solifenacin 5mg	Solifenacin 5mg	Solifenacin 10mg	Solifenacin 10mg
Step 3 Months 5-6	Solifenacin 5mg	Solifenacin 10mg	Solifenacin 10mg	Trospium XR 60mg