Behavioral or Solifenacin Therapy for Urinary Symptoms in Parkinson's Disease

PI: Camille Vaughan, MD
Protocol Version 7-28-2022

Background: The number of persons with Parkinson Disease (PD) in the United States is expected to double by 2030 as the population ages[1,2]. Importantly, this increase in the prevalence of PD will have greater impact within the Department of Veterans Affairs (VA)[2] because the Veteran population is older than the general population and Veterans with PD are more likely than those without PD to rely solely on VA for their health care[3]. While PD is often characterized by the motor symptoms of the disease (tremor, bradykinesia, rigidity), **non-motor symptoms such as urinary symptoms correlate more closely with impaired well-being as the disease progresses[4].** The urinary symptoms of overactive bladder (OAB), including urgency, frequency, and nocturia, with or without urinary incontinence, are the most common urinary symptoms of PD[4,5]. Because OAB symptoms, such as incontinence and nocturia, are associated with falls[6,7 8] (a cause of increased mortality in PD[9]), spouse/caregiver stress[10], and, ultimately institutionalization[11,12], it is critical that we optimize the care of urinary symptoms for Veterans with PD. This proposal directly addresses VA Rehabilitation R&D RFA RX-17-002 that calls for "…new approaches to improving…aspects of physical functioning that result from PD…that jeopardize patients' safety, independence and well-being."

Several studies suggest abnormal central nervous system processing of sensory input from bladder afferent nerves contributes to OAB symptoms in PD, possibly because of delayed recognition of bladder fullness[5,13,14]. This mirrors findings in non-PD populations with OAB[15,16]. In the non-PD population, pelvic floor muscle contractions diminish bladder muscle contraction and recent evidence demonstrates that behavioral training with pelvic floor muscle exercises improves the cortical integration of bladder afferent signals[16]. **Because of its effectiveness compared to drugs, pelvic floor muscle exercise-based behavioral therapy is recommended first-line in men and women without PD who have OAB [17-23].**

Pelvic floor muscle exercise-based behavioral therapy for urinary symptoms requires individuals to learn a motor skill and implement an adaptive behavioral strategy incorporating pelvic floor muscle contraction to delay the need to void when urgency strikes. The PI's research group demonstrated the feasibility and preliminary efficacy of pelvic floor muscle exercise-based behavioral therapy to treat urgency incontinence in adults with PD[24]. However, the most recent clinical guidelines for the treatment of urinary symptoms in PD recommend treatment with anticholinergic drugs[25]. While some anticholinergic drugs are effective in reducing symptoms of OAB, it is important to note that there is a glaring lack of an empirical evidence base to promote these drugs in the setting of PD given that they add to the anticholinergic burden of antiparkinsonian therapy, and may worsen the cognitive and autonomic burdens of the illness. Therefore, **randomized controlled trials (RCTs) are needed to optimize treatment paradigms for urinary symptoms in PD.**

Multiple studies in other areas of rehabilitation medicine demonstrate adults with PD can learn and implement a motor skill as part of a strategy to address symptoms that impair independence and well-being (e.g. balance, voice training[26-28]). Despite the potential for cognitive decline, which occurs in up to 75% of PD patients within 10 years of diagnosis[29], there is evidence of neuroplasticity in patients with PD and structural benefit from learning motor skills as demonstrated through functional imaging studies[30,31]. Our preliminary studies suggest adults with PD and mild cognitive dysfunction can successfully implement behavioral therapy for urinary symptoms. Understanding the neural mechanisms for this phenomenon would greatly inform adapting rehabilitation-based interventions for patients with both motor dysfunction and declining cognitive functioning. Aim 2 will build on this line of inquiry and *set the stage for mechanistic studies* of central nervous system control of bladder function in PD. For Aim 2 we include a detailed evaluation of cognitive function, which will inform future studies and practice paradigms in this vulnerable Veteran population.

The *long term goal* of the PI's research group is to alleviate urinary symptoms as a contributor to disability among Veterans with PD and contribute to understanding of the brain-bladder connection in the setting of neurodegenerative disease. We propose the following specific aims:

Specific Aim #1: Using a RCT, determine non-inferiority of pelvic floor muscle exercise-based behavioral therapy versus drug therapy for urinary symptoms in PD. We hypothesize that pelvic floor muscle exercise-based behavioral therapy will reduce urinary symptom severity with a difference compared to

drug therapy that does not exceed the non-inferiority margin of a validated OAB questionnaire. The primary outcome, OAB severity, will be measured using the OAB symptom questionnaire (International Consultation on Incontinence-OAB (ICIQ-OAB) symptom score) with a non-inferiority margin of 15%.

Specific Aim #2 (mechanistic aim): Determine if domain-specific cognitive function impacts the response to exercise-based behavioral therapy or drug therapy for urinary symptoms.
Aim 2.a. Do higher baseline motor skill learning capacity and executive function scores predict better outcomes in the exercise-based behavioral therapy versus drug therapy group?
Aim 2.b. Compared to exercise therapy, does anticholinergic drug treatment for urinary symptoms worsen executive function and PD motor symptom severity?

Research Design and Methods
We propose a three-site, RCT conducted at the Atlanta (lead site), Birmingham and Richmond VA medical centers to establish non-inferiority of pelvic floor muscle exercise-based behavioral therapy compared to drug therapy for urinary symptoms in adults with PD. Groups will be stratified by OAB symptom severity, PD motor symptom severity, gender, and site. We will randomize 90 participants in order to complete the study in 80 participants, assuming 85% power and a non-inferiority margin for the OAB symptom score of 15% at 12-weeks. **The primary outcome measure will be urinary symptom severity as measured by the ICIQ-OAB symptom score[32,33]** collected at 3 time points during the study: baseline, 6 weeks, and 12 weeks. PFME-based behavioral therapy will occur over 3 visits conducted during the first 6 weeks as was performed in the BETTER2 PD study. Participants in the drug therapy group will also have 3 visits during the first 6 weeks in order to individually titrate solifenacin drug therapy according to a validated symptom scale. Solifenacin has been selected because this bladder-selective anticholinergic drug (less risk of cognitive side effects) is the only drug with published evidence of potential efficacy in PD[34]. At baseline, randomized participants will undergo a brief neuropsychological battery adapted from our current study to assess cognitive factors that may predict a preferred treatment strategy. At the 12-week assessment, the brief neuropsychological battery and MDS-UPDRS will be repeated in order to assess any change associated with treatment allocation. Follow-up visits will occur at weeks 4 and 8 to ascertain side effects and assess treatment adherence.

Participants: Participants will be men and women with PD. Based on our experience in the BETTUR PD and BETTUR2 pilot studies, we anticipate screening 180 participants to account for attrition and achieve the intended sample size. During FY16, 541, 399, and 112 unique Veterans with PD were seen at the Atlanta VA, Birmingham VA, and Richmond VA PADRECC, respectively. We anticipate up to half of the participants for the proposed trial will be Veterans; however, based on our extensive experience in recruiting for clinical trials focused on urinary symptoms, we propose recruiting Veterans and non-Veterans at study initiation. In order to meet recruiting targets for two recent, multi-site GRECC continence studies (ProsTel, and BETTUR2), recruitment was extended to non-Veterans in order to achieve the intended sample size. Additionally, university affiliates in Atlanta (Emory), Birmingham (University of Alabama at Birmingham), and Richmond (Virginia Commonwealth University) have active movement disorders programs, which enhance the overall resources available to the study. With the approval of the IRB and VA Research and Development Committees following a partial HIPAA waiver, we will perform a computer-based screening using the VA Corporate Database Warehouse to screen afore-mentioned veterans who live close to the Medical Center. Also, we will use data pull with real Social Security Numbers (SSNs) from VA's Information and Computing Infrastructure (VINCI) to enhance recruitment goals within the VISN. Subject eligibility is dependent upon a confirmed diagnosis of Parkinson's disease by a movement disorder neurologist. After viewing the records in CPRS or in the academic affiliate health system electronic medical record, the coordinator will make contact with the neurologist of potential subjects. With neurologist approval, an IRB-approved letter will be sent to the patient informing them of the study and providing a phone contact for study staff. The letter will include information that if study staff do not hear from the patient within 10 days, they will contact them by phone to inquire about interest in the study.

Potential subjects may also be referred to the study by their physician either at the host VAMC or academic affiliate. The study will use an approved flyer as advertisement. Potential subjects may contact study staff by phone to determine eligibility or to inquire more about the study. Staff will respond to phone inquiries from patients who self-identify as interested, explain the study, and pre-screen them for eligibility. Those who qualify

preliminarily will be scheduled for a full evaluation and will be mailed an advance copy of the consent form along with a "first appointment letter." Informed Consent discussion will be conducted during the first visit and if the potential participant consents to participate in the study they will be further evaluated clinically for eligibility based on specific inclusion/exclusion criteria per study protocol.

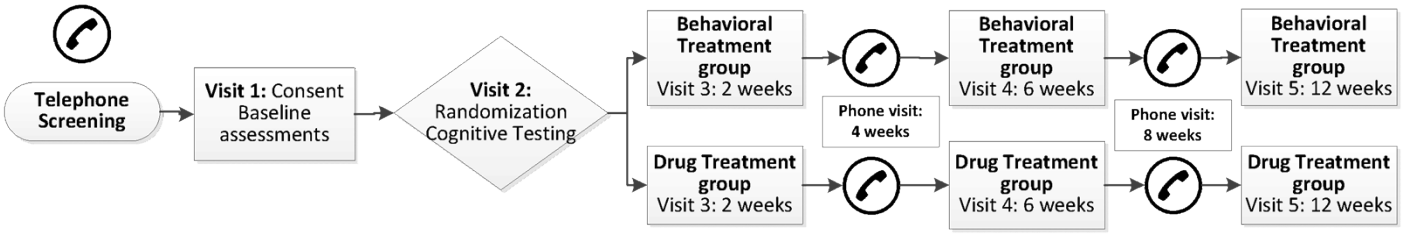
Inclusion criteria:

- Clinical diagnosis of PD determined by a board-certified neurologist with specialty training in movement disorders
- An ICIQ-OAB Symptom Score of ≥ 7, which indicates clinically significant symptoms of OAB, defined as *presence of urinary urgency with or without urgency incontinence usually with increased daytime frequency and nocturia in the absence of infection or other obvious pathology*[32,35].

Exclusion criteria:

- Significant cognitive impairment, as indicated by a Montreal Cognitive Assessment[36] (MoCA) score of < 18 (or <14 for the MoCA Blind), which is the recommended diagnostic cutpoint for dementia in PD[37].
- Previous intensive pelvic floor muscle exercise training
- Clinically significant depression as measured by a Geriatric Depression Scale-Short Form[38] score ≥ 10 which could affect motivation to fully engage in the intervention
- Use of an indwelling urinary catheter
- Post-void residual (PVR) urine measurement by bladder ultrasound of ≥ 150 mL
- Severe uterine prolapse past the vaginal introitus
- Poorly controlled diabetes defined by a hemoglobin A1c (HgbA1c) of >9.0% within the last 3 months. Participants with poorly controlled diabetes will be offered enrollment if the OAB symptoms persist after improvement in diabetes control
- Chronic renal failure and on hemodialysis
- Genitourinary cancer with ongoing surgical or external beam radiation treatment
- Previous artificial urinary sphincter, sling procedure or implanted sacral neuromodulation device
- History of bladder-injection of botulinum toxin in the last 12 months
- Any unstable health condition expected to result in hospitalization or death within in the next 3 months as determined by site principal investigator.
- Hypersensitivity to drug class
- Contraindication to the study drug (solifenacin) including: narrow angle glaucoma, history of gastric retention, history of acute urinary retention requiring catheterization
- Current use of a bladder relaxant – permitted to enroll after one-week washout
- 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
- If on diuretic, dose should be stable for at least 4 weeks
- If taking an alpha-blocker, dose should be stable for at least 4 weeks
- If taking dutasteride or finasteride, dose should be stable for at least 6 months
- Women who are pregnant, or breast-feeding, or planning to become pregnant. *Women of child-bearing age must agree to use of birth-control while enrolled

Figure 1: Schematic of the Study Design



*Visits 1,2,and 7 will require in-person procedures. All other visits may be conducted by phone/telehealth.

During the first visit, potential participants will receive an explanation of the study procedures and complete informed consent to participate. Baseline assessments will include the following:

Baseline assessments:

1. **Seven-day bladder diary** includes daily participant-reported voids and incontinent episodes, with ratings of associated urgency, and wake time and bedtime to assess daytime frequency and nocturia. A single 24-hour frequency-volume chart will be included in the 7-day diary at baseline, week 6, and week 12. Participants will measure their urine output with each void for a 24-hour period (first void after rising until the first morning void the following day) using a receptacle marked in 25 mL increments.
2. The **Movement Disorder Society – Unified Parkinson Disease Rating Scale** (MDS-UPDRS) includes 40 items which are a combination of questions regarding activities of daily living and a physical examination of motor function by the investigator[39]. This updated UPDRS includes a question about urinary symptoms. A modified Hoehn and Yahr (H&Y) scale is included as part of the MDS-UPDRS. The modified H&Y scale provides a score determined during the physical examination. These instruments will be completed during the *second* clinic visit in order to be performed during a 'defined on' period.
3. The **ICIQ-OAB questionnaire** is a 4-question assessment of OAB symptoms and the degree to which they bother the respondent (urgency, frequency, nocturia, UI)[32,33]. The ICIQ-OAB questionnaire requires about 5 minutes to complete and will serve as the primary outcome for the study. The participants will complete the ICIQ-OAB-QOL questionnaire[40] at home, which requires about 20 minutes. The ICIQ questionnaires have been validated in men and women, but not in Parkinson's disease specifically. These questionnaires will be completed at baseline, 6 weeks and 12 weeks.
4. The **UAB Study of Aging Life Space Assessment** will be used to assess individual mobility and need for assistance within the participant's home and community, thus providing a validated assessment of individual independence[41]. It is designed to identify the distance through which a person reports moving during the 4 weeks prior to the assessment. Life-Space 0 indicates movement restricted to one's bedroom increasing to Life-Space 5 indicating travel outside of one's town. A score is generated by assigning a value to each Life-Space level based on the frequency of travel to that Life-Space level and degree of independence in getting there. The assessment, which can be performed in less than 5 minutes, leads to a score ranging from 0 ("totally bedbound") to 120 ("traveled out of town every day without assistance").
5. The **MoCA** test is more sensitive to detect mild cognitive impairment than another brief screening measure, the Mini-Mental Status Exam, in PD patients[37] and is recommended by the Parkinson Study Group[42]. The MoCA test is designed to assess executive function, higher level language abilities, memory, and complex visuospatial processing, which are areas that may be affected more commonly in PD dementia.
6. The **Geriatric Depression Scale-Short Form** is a 15-question assessment that has been validated in older adults and is recommended as a screening test for depression in adults with PD[43].
7. The **Self-Efficacy for Managing Chronic Disease** questionnaire is a 6-item questionnaire developed through the Stanford Patient Education Research Center. It covers several domains that are common across many chronic diseases, symptom control, role function, emotional functioning and communicating with physicians[44].
8. **Physical Exam and Laboratory testing**
    - Urinalysis (for all participants) and pregnancy test (for women of child-bearing age). If bacteriuria is suggested by screening urinalysis[45], a culture will be sent and bacteriuria (>100K colony forming units) will be eradicated by a 7-day antibiotic course with permission/notification sent to their primary care provider. Participants will be re-assessed for UI following treatment. Participants with unexplained, persistent hematuria will be referred for an appropriate evaluation.
    - HgbA1c if the participant is diabetic and has not had an HbgA1c in the 3 months prior to enrollment.
    - Basic metabolic panel if the participant has not had an assessment in the 6 months prior to enrollment.

Enrollment and Neuropsychological Assessment:

One week later, potential participants will return for visit two. Study staff will review the completed bladder diary, questionnaires, and PVR and will determine if the participant qualifies for the study. Once enrolled, participants will undergo a brief neuropsychological battery and a motor task of procedural learning. These tests will be administered by a research assistant so that the principal investigator is blinded to baseline performance on the SRTT and cognitive function. The selected tests correspond with the battery piloted in the PI's current Rehab R&D CDA-2 study and are manageable for participants with PD. These assessments will

allow for exploratory analyses beyond the planned tests of implicit memory and executive function to assess for correlation between baseline cognitive function and ability to implement the behavioral therapy intervention. For instance, if the implementation of the behavioral intervention correlates with tasks of motor procedural learning, we might not expect it to correlate with tasks of declarative memory, thus providing further evidence that the task is one of implicit memory. Further, several of the tests have been linked with specific neuroanatomical regions of the brain and could provide preliminary data to support future studies involving functional imaging. The neuropsychological assessment will be repeated at visit 7 (12 weeks) in order to determine any change from baseline.

While solifenacin is a bladder-selective anticholinergic drug with less risk of negative cognitive impact than other anticholinergic bladder relaxants, the 12-week re-assessment of cognitive function in this study is important to understand the potential drug impact on cognition in the PD population. Persons with PD are at increased risk of developing cognitive impairment and are more susceptible to anticholinergic side effects of these medications (such as delirium, constipation, and dry mouth[29,46-48]). Each testing session will last approximately 75 minutes, with breaks included to reduce fatigue. The measures are described below:

1. The **SRTT** is a task of motor procedural learning in which participants are asked to press one of four keys on a response box which correspond to a lighted stimulus[49]. Unknown to the participant, the light stimuli occur in a sequence and thus reaction time improves as the participant performs multiple blocks of the sequenced-based task. This learning is demonstrated by an increase in reaction time when the stimuli are presented in a random order after repetitions of the sequenced-based task. The task is typically measured in millisecond response times. The SRTT can be administered in approximately 30 minutes and has been used in multiple studies of procedural learning among PD participants[50,51]. A response box for the SRTT is available for purchase from Psychology Software Tools Inc. The software to collect, store, and analyze the SRTT reaction times is also available for purchase from this company. A standard operating system installed on a laptop computer is sufficient to allow for data collection and initial analysis of reaction time. Once reaction times for the sequenced and random blocks have been calculated, these data will be entered into the Redcap database.
2. The **CERAD Word List subtest**[52] requires the subject to recall 10 words that are presented over three trials, followed by short-delay recall and recognition memory. Left entorhinal cortex volume is significantly correlated with immediate recall on this task[53].
3. The **Nonverbal/Spatial Selective Reminding Test**[54] taps spatial memory by requiring the subject to recall a dot pattern. Performance on this measure has been found to discriminate patients with right versus left temporal lobe epilepsy[55].
4. The **Wisconsin Card Sorting Test**[56] will be used to assess hypothesis generation and response shifting. Perseverative errors on this task are related to the volume of prefrontal cortex and frontal white matter hyperintensities in adults 50-81 years old[57,58]. Perseverative errors will be residualized on the total number of errors to control for overall level of performance.
5. The **Subject Ordered Pointing Task** will assess working memory. Subject Ordered Pointing is sensitive to middorsolateral prefrontal cortex lesions in monkeys and humans, and activates dorsolateral prefrontal cortex on positron emission tomography in normal adults.

Randomization: At the second visit, eligible participants will be randomized to one of two groups: treatment with PFME-based behavioral therapy or solifenacin drug therapy. Participants will be stratified by site, gender, UI severity (< or ≥ a score of 9 on the ICIQ-OAB), and PD motor symptom severity (MDS-UPDRS < 33 on the part 3 motor score)[59]. Participants will be randomized through computer-generated block randomization in groups of six. Based on preliminary data showing these cut points approximate the means among our randomized participants, we do not anticipate four stratification variables will present a challenge to recruitment. While participants will not be blinded to treatment group, the interventionist will be blinded to the participant's performance on the neuropsychological tests and SRTT performance.

Data Management: Participants' assessment data will be kept in a locked cabinet behind a locked door at each site of the Birmingham/Atlanta GRECC and the Richmond PADRECC. Bladder diaries will be scored by a research assistant who is blinded to the assigned treatment group. Data from the Birmingham and Richmond sites will be uploaded to a secure VA server in the form of PDF documents scanned on a VA device behind the VA firewall. Deidentified data will be entered and verified in Redcap by research staff at the Atlanta site, which will ensure accuracy of the data. A standard form will be used to record the date and reason for all

exclusions and dropouts, and these data will also be entered into the master database. Four times per year the PI will meet with the Atlanta-based data manager to review accrual, data entry, and eligibility criteria and examine the database for outliers or database entry errors at each site. The Redcap database will then be converted and data analyses will be completed in SAS 9.4 (SAS Institute, Cary, NC). Additional details regarding confidentiality of patient data are included in the Human Subjects plan.

Specific Aim #1: Using a RCT, determine non-inferiority of pelvic floor muscle exercise-based behavioral therapy versus drug therapy for urinary symptoms in PD.

Rationale: The use of anticholinergic drugs for UI in PD, which are currently recommended by guidelines, increase polypharmacy and may add to the cognitive and autonomic burdens of PD. Impaired cognition and polypharmacy are recognized risk factors for medication non-adherence in PD and could lead to treatment failure for OAB[60]. PFME-based behavioral therapy, while more labor-intensive, is free of drug side effects for patients. The PI's pilot studies demonstrate that adults with PD and UI can learn and implement PFME-based behavioral therapy resulting in significant decreases in UI and OAB symptoms. Given the efficacy of the URGE PD drug trial, a comparative effectiveness trial of behavioral therapy and drug therapy for bothersome urinary symptoms is a logical next step to better inform treatment guidelines for Veterans with PD. Based on our preliminary data showing similar effect sizes between behavior and drug therapy, a non-inferiority design is proposed. A non-inferiority design provides the most critical information needed to inform clinical guidelines without exposing additional participants to drug therapy. The reason for not including a behavior therapy plus drug condition is that we wish to disentangle the contributions of baseline levels of motor symptoms and cognitive scores on outcomes, hopefully gaining an understanding of which treatment might be more effective for which patients in light of the potential of drug side effects.

Intervention: Once randomized, both groups will participate in a 12-week study (**Figure 1**). Study visits (either in-clinic or via phone) will occur every two weeks for the first 8 weeks followed by a final in-clinic assessment at 12-weeks. Participants will be compensated $50 upon completion of first visit procedures, $50 for second visit procedures and $60 for completion of visit 7 procedures with a maximum of $160 for completion of all study visits (includes screening and follow-up visits).

Primary Outcome: The ICIQ-OAB questionnaire is a previously validated symptom questionnaire that has been used in the PI's previous studies related to urinary symptoms in PD[32,33]. The ICIQ-OAB validation protocol states that a clinically meaningful improvement includes a statistically significant decrease in the symptom score paired with reduction in bother and improvement in QOL[61]. To provide additional evidence of clinical meaningfulness of the ICIQ-OAB based outcome data, the ICIQ OAB-QOL and bother scores will be re-administered at the conclusion of the trial as secondary outcome measures. Validated patient benefit and satisfaction questionnaires[62] will also be used at the fifth(midpoint of the study) and final visits. Participants in the behavioral group will also be asked to submit a daily record of their completed PFME to document adherence with recommended exercise targets. Adherence among participants in the drug therapy group will occur via pill counts. As evidenced by Tables 2-4, we have experience with all these measures and procedures.

Behavioral Intervention: Exercise-based behavioral therapy using PFME

Participants who are randomized to exercise-based behavioral therapy will receive a comprehensive training program administered individually by a trained nurse practitioner interventionist to address UI and other LUTS. Participants will be taught PFME as well as urge suppression strategies to overcome the urge to void. Initial instruction in PFME will involve rectal (or vaginal) palpation to confirm contraction of appropriate muscle groups. The proposed method for teaching PFME and urge suppression strategies and reinforcing these techniques is based on the protocol used by Burgio et al[20,23,24]. Recommendations for PFME will include 45 exercises every day divided into manageable sessions, typically sets of 15 exercises, 3 times per day. Completing 45 exercises will require 7-10 minutes daily to complete.

Urge suppression strategies involve teaching participants to respond adaptively to the sensation of urgency. Instead of rushing to the toilet, which increases intra-abdominal pressure and leads to visual cues that can elicit incontinence, participants will be instructed to pause, sit down, if possible, relax the entire body, and contract the pelvic floor muscles repeatedly to diminish urgency, inhibit detrusor contraction, and prevent urine loss ("freeze and squeeze"). This technique typically leads to the diminution of urgency within 1 minute. When the urgency subsides, participants are instructed to proceed to the toilet at a normal pace. Participants

with stress-related urine loss will also be instructed how to contract pelvic floor muscles immediately prior to precipitants of stress leakage (sneezing, coughing, or laughing). Other **behavioral techniques** introduced at the randomization visit for participants in the behavioral therapy group will include instruction on the management of constipation, fluid intake modification, or scheduled voiding (attempting to void on a predetermined schedule). Participants in the behavioral therapy group will maintain a 7-day bladder diary for eight weeks after randomization to mirror the behavioral intervention in the BETTUR and BETTUR2 studies.

The intervention will be initiated at the 2nd clinic visit (randomization visit). Participants will complete the Patient Global Symptom Control instrument at the 5th visit (week 6 - midpoint of study) to assess whether behavioral therapy is providing control of OAB symptoms; responses to the statement, "This treatment has given me adequate control of my overactive bladder symptoms" range from 1 (disagree strongly) to 5 (agree strongly). Participants will be offered an additional session of PFME training if they meet at least one of the following criteria: a) the participant desires further reinforcement of the pelvic floor muscle techniques, or b) the participant reports a Patient Global Symptom Control score of 1 to 3.

Drug Intervention: Solifenacin

Participants who are randomized to drug therapy will receive solifenacin at visit 2 (randomization visit). The starting dose will be 5 mg by mouth once daily. Participants in the drug therapy group **will not receive any of the educational or exercise components of behavioral therapy.** Participants will complete a 7-day bladder diary at baseline, 6 weeks, and 12 weeks post-randomization, which will include a single 24-hour frequency volume chart at each time point. At visit 5 (week 6 – midpoint of study) solifenacin dose escalation to 10 mg will be allowed if the Patient Global Symptom Control score is 1 to 3, indicating inadequate symptom control, and the participant reports that the side effects of drug therapy are tolerable. Individual titration of drug therapy mirrors the study design from Urge PD, which was the first pilot randomized controlled trial of a bladder relaxant drug in a Parkinson's patient population[34,63]. Additionally, individual titration of drug therapy mirrors clinical practice and the methodology for behavioral therapy implementation, which also involves individual titration of exercise-based strategies depending on symptom response. Failure to individually titrate drug therapy could bias the results of the study toward behavioral therapy. An assessment for adverse drug events will occur at each in-clinic or telephone visit after randomization using a standardized checklist. If any participant experiences adverse events after the dose increase, he/she may return to the 5mg daily dose or discontinue the medication. If the medication is discontinued, the participant will be offered the opportunity to continue the study for data collection only.

Power Analysis: The power analysis is informed by the ICIQ-OAB symptom score reduction observed in the BETTUR PD and BETTUR2 studies of behavioral therapy for urinary symptoms in PD. Based upon the bladder diary-derived UI frequency data (consistent measure used in both behavioral and drug trials), the effect of behavioral therapy and drug therapy to reduce UI frequency is similar. The ICIQ-OAB symptom score range is 0-16, with higher scores indicating worse symptoms. A score ≥ 7 would indicate clinically significant OAB symptoms (urgency, frequency, urgency UI, nocturia) occurring on average at least *sometimes*. In our previous studies, we have observed a 2-3 point reduction in the symptom score, which represents a 12%-19% reduction from baseline[24,64]. The minimally clinically important difference for the ICIQ-OAB is defined as a statistically significant reduction in the symptom score that is accompanied by a reduction in bother and improvement in OAB-specific QOL. Because the observed reduction **≥ 2 points** represents a statistically and clinically meaningful difference, we propose a non-inferiority margin of 15%. Thus, we will randomize 90 participants in order to complete the interventions in 80 participants, which assumes 85% power and a non-inferiority margin on the OAB symptom score of 15% at 12-weeks post-randomization. **Table 6** indicates that the proposed sample size will permit an assessment of non-inferiority within a range of potential non-inferiority margins that correspond to outcome assessments in our pilot studies.

Table 6: Sample Size per Group to Declare Non-Inferiority with 85% power

Standard Deviation of 12 week ICIQ-OAB Symptom Score	Margin of Non-Inferiority Between Groups at 12 weeks (Assumes OAB Symptom Score at baseline of = 8.1)			
	10%	12.5%	15%	20%
1.0	23	16	11	7
2.0	89	59	40	24
3.0	198	131	88	52

Table 7: Summary Outcome Assessments						
Outcome Assessment	**Baseline Visit 1/Visit 2**	**2 weeks Visit 3**	**4 weeks Visit 4**	**6 weeks Visit 5**	**8 weeks Visit 6**	**12 weeks Visit 7**
ICIQ-OAB	X			X		X
7-day Bladder Diary (drug)	X			X		X
7-day Bladder Diary (behavioral)	X	X		X		X
7-day PFME Record (behavioral)		X				
ICIQ-OAB QOL	X			X		X
Benefit & Satisfaction				X		X
Life Space Assessment	X			X		X
Self Efficacy for Chronic Disease Management	X					X
Patient Global Symptom Control Score				X		X
Adverse Event checklist	X	X	X	X	X	X
Adherence Questionnaire		X		X		X
Neuropsychological battery	X					X
MDS-UPDRS	X					X

Data Analysis:

Primary Outcome for Aim 1: To evaluate the impact of treatment within group, we will first use a random effects mixed model with adjustment for baseline OAB symptom severity to compare mean ICIQ-OAB symptom scores across the three time points. In order to test for non-inferiority of behavioral therapy compared to drug therapy, we will assess the difference in the mean 12-week post-randomization ICIQ-OAB symptom score between groups using a two-sample t-test, assuming a non-inferiority margin of 15% and a standard deviation of 2.0 points. The significance level of the test will be set at an α of 0.025 for a one-sided test of significance.

Secondary Outcomes: The pre-treatment and post-treatment frequency of UI based on the bladder diary will be used to calculate a percentage change for each participant ([pre-treatment frequency – post-treatment frequency]/[pre-treatment frequency] x 100%). Based on pilot study results, non-normality of the diary data is anticipated and thus the Wilcoxon rank sum test will be used for bladder diary-reported outcomes (UI, urgency, nocturia). Questionnaire-based secondary outcomes (ICIQ-OAB bother score, ICIQ-QOL, benefit and satisfaction, self-efficacy, voided volume, and the Life Space Assessment) will be assessed between groups using a t-test. Twenty-four hour voided volume measures will permit an evaluation of nocturnal urine production as a confounding factor for response to treatment among persons with nocturia. Nocturnal urine production includes the sum of all voided volumes after going to bed with the intention of sleeping and the subsequent first voided volume the next morning. Additionally, an evaluation of change in mean voided volume provides an objective measure of functional bladder capacity.

Self-assessed adherence to exercise or drug therapy will be assessed through questionnaires (both groups) and with exercise records or pill counts depending on group allocation. Data will be calculated as medians (and inter-quartile range), and compared using Kruskal-Wallis test for continuous variables or chi-square test (Fisher's exact when expected cell counts were <5) for categorical variables. Adverse event questionnaires will be administered at each in-clinic or phone visit after treatment allocation. The number of times a specific side effect is reported after the baseline assessment will be summed and presented as a continuous variable. Comparisons between groups of the proportion of participants reporting specific side effects will be performed by Fisher's exact test.

[Specific Aim #2 (mechanistic aim): Determine if domain-specific cognitive function impacts the response to exercise-based behavioral therapy or drug therapy for urinary symptoms.

Aim 2a: Do higher baseline motor skill learning capacity and executive function scores predict better outcomes in the exercise-based behavioral therapy versus drug therapy group?

Rationale: In spite of the potential for cognitive impairment, which occurs in up to 75% of PD patients within 10 years of diagnosis[29], some PD patients demonstrate evidence of neuroplasticity and benefit from learning motor skills as demonstrated through functional imaging studies[30,31]. Understanding whether baseline domain-specific cognitive function is associated with successful implementation of behavioral therapy among adults with PD is important to understand the central control of bladder function and identify new targets to augment rehabilitation therapy in the setting of a neurodegenerative disease. While participants with significant cognitive impairment (MoCA < 18) will be excluded, this exclusion criterion will not eliminate participants with mild cognitive impairment. The range of MoCA scores among current completers of the BETTUR2 PD study (n=26) is 18 to 29 (mean=24.6 ± 2.9). Among the 11 participants randomized to behavioral therapy in the BETTUR2 PD study who had a MoCA score between 18-26 (includes the screening cutpoint for mild cognitive impairment in PD[37]), the median reduction in weekly UI frequency eight weeks after randomization was 88% (IQR 42%-100%), suggesting that even mild cognitive impairment does not interfere with learning a behavioral therapy intervention.

The neuropsychological assessment in the proposed study is a unique approach to further characterize domain-specific cognitive function as a predictor of the ability to use exercise-based behavioral therapy. The baseline neuropsychological battery will provide additional domain-specific measures of cognitive function (SRTT, executive function, word retrieval) that will be analyzed in the context of the ability to learn and implement the exercise-based behavioral strategy. These preliminary data will provide further evidence to support or refute the hypothesis that learning the PFME-based adaptive strategy is a procedural task and that implementation of the task uses implicit memory rather than explicit memory systems. Further, because several of the selected tests have neuroanatomical correlates, these data could support the design of future studies involving functional brain imaging to understand mechanisms of learning in the context of neurodegenerative disease, thus building on imaging studies in non-PD populations with OAB[15,16].

Measures: Participants in both groups will complete the SRTT (task of procedural learning) in addition to a neuropsychological battery that will include evaluations of executive function and explicit memory at baseline. These assessments mirror the evaluation included in the BETTUR2 study, which will ultimately increase the power of the evaluation to determine mediators impacting implementation of behavioral therapy for urinary symptoms in persons with PD.

Data Analysis: The analysis for Aim 2a will determine if baseline cognitive function scores mediate successful outcome in the behavioral therapy group. Based on previously published research and our pilot studies, successful implementation of behavioral therapy will be defined as achieving at least a 2-point reduction in the ICIQ-OAB symptom score[24,61,64]. Cognitive function will be evaluated as a continuous and categorical measure (MoCA 18-24 vs 25-30).

To explore other potential characteristics of successful behavioral therapy implementation, we will examine baseline characteristics that differ between those in the behavioral therapy group who demonstrate at least a 2-point improvement (reduction) in ICIQ-OAB symptom score versus those who report less improvement. Baseline characteristics will include gender, age, PD severity as measured by the MDS-UPDRS motor part 3 score (mild vs. moderate), depression as well as the pre-specified measures of cognitive function (SRTT and Wisconsin Card Sort Test). Baseline characteristics will be compared using chi-square or t-tests as appropriate.

We will examine the correlation between cognitive function tests of procedural learning and executive function with change in ICIQ-OAB score after behavioral therapy. Performance on the SRTT will be assessed as the mean change in time (milliseconds) between random and sequential tasks. Performance on the Wisconsin Card Sort Test will be assessed using the perseverative errors score. We will correlate these measures with the change in ICIQ-OAB score between baseline and 12-weeks post-randomization.

Baseline characteristics which are significantly associated with successful implementation of behavioral therapy will be included as part of a multivariable logistic regression model including SRTT performance, Wisconsin Card Sort Test perseverative errors score in order to determine if these cognitive domains are important in the central nervous system control of OAB symptoms in response to behavioral therapy.

Aim 2b: Compared to exercise therapy, does anticholinergic drug treatment for urinary symptoms worsen executive function and PD motor symptom severity?

Rationale: The standard treatment recommendation for urinary symptoms in PD is anticholinergic drug therapy, despite the fact that, guidelines for OAB in older adults *without PD* recommend an initial trial of behavioral therapy, which is free of any drug side effects[17,18]. Anticholinergic bladder relaxants block the action of acetylcholine by competitively binding the muscarinic receptors in the bladder, leading to bladder smooth muscle relaxation. Muscarinic receptors are also involved in cognitive functioning and the use of older antimuscarinic bladder relaxants has been associated with an increased risk of cognitive side effects such as delirium and confusion[65]. Chronic use of anticholinergic medications is associated with accelerated cognitive decline in PD[48]. Newer anticholinergic bladder relaxants, such as solifenacin, are designed to have less risk of cognitive side effects because they specifically antagonize bladder muscarinic receptor subtypes instead of those in the central nervous system[65]. As shown earlier in the URGE PD data, solifenacin reduced urgency UI in persons with PD and symptoms of OAB in a RCT; however, no cognitive assessments were conducted thus precluding a careful assessment of the impact of this drug on potential cognitive side effects[34]. The proposed neuropsychological battery will include domain-specific assessments that will provide a unique opportunity to assess if bladder selective anticholinergic drug therapy has any measurable effect on cognition in PD.

It is well established that anticholinergic drug therapy also reduces the motor symptoms of PD[66]. Anticholinergic drugs are used alone and in combination as treatments for motor symptoms in PD, particularly tremor[66]. However, there is increasing concern that the overall burden of anticholinergic therapy paradoxically can have significant negative impacts on motor symptoms, by increasing the risk of falls, fractures, and postural instability[47,67]. Indeed, one study found that adding a central cholinesterase inhibitor decreased the risk of falls by 50% among persons with PD and a history of frequent falls[68]. The addition of anticholinergic drug therapy for urinary symptoms leads to an overall increase in anticholinergic burden, particularly for conditions impacted by muscarinic receptors.

Regardless of whether behavioral therapy proves to be inferior or non-inferior to drug therapy, understanding the potential association of drug therapy with cognition or PD motor symptom severity are important factors for patients and providers to determine next steps for treatment[69].

Measures: Participants in both groups will complete a baseline and 12-week neuropsychological battery as previously described including the MoCA test, SRTT, CERAD Word List subtest, Nonverbal/Spatial Reminding Test, Wisconsin Card Sort Test, and the Subject Ordered Pointing task. We will use the Anticholinergic Risk Scale[47] to calculate an overall anticholinergic drug score for participants in both groups based on medications listed at the randomization visit as a potential effect modifier. The MDS-UPDRS will be repeated at the 12-week visit. Thus, the behavioral therapy group will serve as a control group to assess the potential impact of solifenacin drug therapy on domain-specific cognitive function and PD motor symptom severity.

Data Analysis: [The analysis for aim 2b will generate data informing how central cognitive control of sensory integration and motor function are involved in the response to drug therapy.**]** Baseline and 12-week post-randomization cognitive tests will be evaluated using paired t-tests to assess for change within the drug group and two-sample t-tests for differences across groups (the behavioral therapy group will serve as a control for this analysis). Because cognitive impairment in PD most often manifests as impaired executive function, we will focus on tests of this domain, such as the Wisconsin Card Sort Test or the Subject Ordered Pointing Task in our evaluation of impact on cognition. The clock-draw test, as a component of the MoCA, is another assessment of executive function that is often performed in clinical practice. If changes are noted on domain-specific assessments of the neuropsychological battery, we will also examine correlation with clock draw scores obtained through the MoCA test. The Anticholinergic Risk Scale will be assessed based upon medications at randomization. The Anticholinergic Risk Scale score will be included in a multivariable model including baseline characteristics associated with changes in cognitive function in bivariable analyses.

To assess the potential impact on motor symptoms, we will assess the change in the motor symptom subscale of the MDS-UPDRS (part 3 score). Similar to the cognitive testing, baseline and 12-week post-randomization assessments will be evaluated using paired t-tests to assess for change within the drug group and two-sample t-tests for difference across groups, with the behavioral therapy group serving as a control for this analysis. Previous research suggests an increase in the MDS-UPDRS part 3 score of 4.6 points is associated with clinically relevant decline in motor function[70].

Visit Schedule
Visit 1: Baseline (One phone/telehealth session and one in-person session)

Explanation of study procedures and consent to be a participant
Interview: Demographics, continence and medical history, MoCA, LSA, GDS
Physical: Height, weight, vital signs, cardiac, pulmonary, and abdominal exam, genital and rectal exam, basic neurologic exam, MDS-UPDRS, determination of post-void residual by bladder ultrasound
Laboratory Examination: Urinalysis and BMP and HgbA1c if indicated
Education: How to complete bladder diary, handout take-home questionnaires (ICIQ-OAB and OAB-QOL)

Visit 2 (Part 1) : Randomization
Interview: Collect and review 7-day bladder diary, ICIQ questionnaires
Physical: Vital signs; review laboratory results; determination of post-void residual by bladder ultrasound if not conducted at first visit;
Procedure: **Randomization (Behavioral Therapy or Drug Therapy)**

Behavioral Therapy	Drug Therapy
Visit 2 (Part 2): Behavioral Therapy Randomization Procedure: Neuropsychological battery, SRTT, Pelvic floor muscle exercise training Education: specific behavioral techniques for constipation, modification of fluid intake or timed voiding	**Visit 2 (Part 2) : Drug Therapy Randomization** Procedure: Neuropsychological battery, SRTT Education: Medication
Visit 3: Behavioral Therapy (2 weeks) Interview: Review PFME record, address new problems, reinforce practice at home and verbal feedback regarding muscle control Education: Urge suppression strategy, management of stress-related urine loss (if applicable)	**Visit 3: Drug Therapy (2 weeks)** Interview: Medication Management, Medication Side Effects Education: Medication & Bladder Diary & Forms (to return at Visit 5)
Visit 4: Behavioral Therapy (4 weeks) Interview: Review PFME record, address new problems, offer additional manual training session if subject is not satisfied with treatment or has < 25% reduction in episodes of UI based on bladder diaries. Education: Reinforce strategy and PFME	**Visit 4: Drug Therapy (4 weeks)** Interview: Medication Management, Medication Side Effects Education: Medication and Reminder to complete Bladder Diary
Visit 5: Behavioral Therapy (6 weeks) Interview: Discuss new problems, Satisfaction & Benefit questionnaire Education: Reinforce PFME and urge strategy, Bladder Diary & Forms (to return at Visit 7)	**Visit 5: Drug Therapy (6 weeks)** Interview: Collect and review bladder Diary; Medication Management, Satisfaction & Benefit questionnaire Education: Medication & Bladder Diary & Forms (to return at Visit 7)
Visit 6: Behavioral Therapy (8 weeks) Interview: Review PFME record, address new problems, offer additional manual training session if subject is not satisfied with treatment or has < 25% reduction in episodes of UI based on bladder diaries. Education: Reinforce strategy and reminder to complete diary and forms	**Visit 6: Drug Therapy (8 weeks)** Interview: Medication Management & Medication Side Effects Education: Medication and Reminder to complete Bladder Diary
Visit 7: Behavioral Therapy (12 weeks) Interview: Collect and Review diary, collect follow-up questionnaires (ICIQ and satisfaction & benefit), administer LSA, constipation, self-efficacy and adherence questionnaires Procedure: Repeat neuropsychological battery	**Visit 7: Drug Therapy (12 weeks)** Interview: Collect and Review diary, collect follow-up questionnaires (ICIQ and satisfaction & benefit), administer LSA, self-efficacy, and constipation questionnaires Procedure: Repeat neuropsychological battery

Physical: Vital signsEducation: Reinforce strategy	Physical: Vital signsEducation: Medication completion

Human Subjects:

a. Risk to Subjects

Human Subjects Involvement and Characteristics: Men and women with PD recruited from the Atlanta, Birmingham, Richmond, and Philadelphia VAMCs as well as in the surrounding community. We propose randomizing 90 participants to either exercise-based behavioral therapy or drug therapy with Solifenacin. In order to complete the study in 80 participants, we anticipated having to screen approximately 180 PD patients to identify those with clinically significant OAB symptoms, and enroll approximately 45 participants in each group. These estimates are based on our experiences in the BETTUR PD and BETTUR2 pilot studies. In the BETTUR PD study, 33 individuals were screened to enroll 20 participants. Of the 20 participants who were enrolled, 17 completed the study demonstrating a 15% drop out rate once enrolled. To date, in the BETTUR2 study, we have screened 107 individuals to randomize 51 participants and have had 6 participants drop out (11.7% rate).

During FY16, 541 unique Veterans with PD were served by the Atlanta VA and surrounding CBOCs. For the BETTUR PD pilot, 14 of the 32 screened subjects were recruited from the Atlanta VA after mailing letters to 360 Veterans identified with a diagnosis of PD in the Metro Atlanta area in FY08. Recruitment was extended to a university-based movement disorders clinic to achieve the intended sample size of 20 enrolled subjects. For the BETTUR2 study, of the 65 persons who have undergone screening procedures thus far, 25 were Veterans and 40 were recruited from university-based movement disorders clinics in Atlanta and Birmingham in order to maximize the team's ability to recruit the intended sample size. Thus, we propose to recruit both Veterans and non-Veterans for the proposed study from the outset. The university affiliates in Atlanta (Emory), Birmingham (University of Alabama at Birmingham), Richmond (Virginia Commonwealth University), Philadelphia (University of Pennsylvania) all have active movement disorders programs, which enhance the overall resources available to the study.

The sample size is informed by the ICIQ-OAB symptom score reduction observed in the BETTUR PD and BETTUR2 studies of behavioral therapy for urinary symptoms in PD. Based upon the bladder diary-derived UI frequency data (consistent measure used in both behavioral and drug trials), the effect of behavioral therapy and drug therapy to reduce UI frequency is similar[24,34]. The ICIQ-OAB symptom score range is 0-16, with higher scores indicating worse symptoms. A score ≥ 7 would indicate clinically significant OAB symptoms (urgency, frequency, urgency UI, nocturia) occurring on average at least *sometimes*. In our previous studies, we have observed a 2-3 point reduction in the symptom score, which represents a 12%-19% reduction from baseline[24,64]. The minimally clinically important difference for the ICIQ-OAB is defined as a statistically significant reduction in the symptom score that is accompanied by a reduction in bother and improvement in OAB-specific QOL. Because the observed reduction (12%-19%) represents a statistically and clinically meaningful difference, we propose a non-inferiority margin of 15%. Thus, we will randomize 90 participants in order to complete the interventions in 80 participants, which assumes 85% power and a non-inferiority margin on the OAB symptom score of 15% at 12-weeks post-randomization.

Sources of Materials: The patients involved in this study will be seen in the Atlanta and Birmingham VAMC/GRECC Continence Clinics and the Philadelphia and Richmond PADRECCs. No tissue, blood, or urine samples will be stored during the study period as part of the protocol. For purposes of this research, baseline and treatment data will be stripped of all patient identifiers and each participant will be given a unique identifier for the study. Patient records will be stored in a locked cabinet in a locked office and will be accessible only to the Principal Investigator, Interventionist, Research Coordinator, Patient Recruiter, Site PI's (Markland, Lehosit, and Morley) and co-investigators (Johnson, Goode, Burgio, Baron). Computer-based records will be maintained through the Veteran's Administration Computerized Patient Record System (CPRS), a secure network with password protection.

Potential Risks: Behaviorally-based intervention and treatment for urinary symptoms is both low risk and side effect free. During the course of a study in which questionnaires are used and bladder diaries are a source of outcome measure, some participants may find questions uncomfortable or find documenting voiding habits burdensome. Rectal or vaginal manual biofeedback occurs during a physical exam. The participant is instructed to squeeze against the interventionist's finger to isolate their pelvic floor muscles through a contraction. Similar techniques have been utilized in previous studies of exercise-based behavioral training for

urge incontinence and have shown clinically significant improvement with minimal discomfort[20,23]. The discontinuation rate for enrolled subjects was 15% or less.

Solifenacin has been FDA-approved for OAB symptoms since 2004[71]. The most common side effects include dry mouth and constipation[71]. In a small study of adverse events among older (> 65 yrs old) versus younger (≤ 65 yrs old) adults taking solifenacin or oxybutynin, solifenacin was associated with lower incidence of side effects than oxybutynin[72]. Older and younger adults taking solifenacin had similar rates of treatment-emergent dry mouth. Another study of solifenacin or oxybutynin versus placebo among older adults with mild cognitive impairment showed no impact of solifenacin at a dose of 5 mg daily (10mg daily was not tested) on tests of executive function, working memory or reaction time compared to placebo[73]. In the Urge PD study, which evaluated solifenacin in persons with PD, 1/9 individuals reported constipation, 2/9 reported dry mouth and 1/9 experienced urinary retention[34].

b. Adequacy of Protection from Risks

Recruitment and Informed Consent: Subjects for the current study have been recruited through the Movement Disorders clinics at the Atlanta VAMC, Birmingham VAMC, Philadelphia, and Richmond VAMC, where each site has at least one board-certified movement disorders neurologist. For the BETTUR PD pilot, recruitment was extended to the Movement Disorders clinic at Emory University because of slow recruitment at the Atlanta VAMC. For the BETTUR2 study, although an additional recruitment site was added at the Birmingham VA, both sites requested permission to recruit non-Veterans through their university-affiliated movement disorders program in order to reach the target sample size.

Fliers are posted in the medical center as well as a PowerPoint slide ad that is broadcast throughout the medical center closed circuit television system. Per VA procedures and with permission from the primary neurologist, letters are sent to Veterans with a diagnosis of PD, who are identified in the corporate data warehouse and confirmed through chart review, to inform them about the study and offer contact information for study staff. Study teams have also partnered with the Michael J Fox Foundation Fox Trial Finder and local Parkinson Support Groups in order to let the local community know about the study. All patients will have the opportunity to give informed consent after discussion with the study PI or research assistant in a private examination room. As a three-site VA study, study procedures and the informed consent form will be approved by the Central VA Institutional Review Board and the VA Research and Development committee at each site. All subjects will be given a copy of the consent to keep for their records.

Protection Against Risk: For purposes of this research, baseline and treatment data will be stripped of all patient identifiers and each participant will be given a unique identifier for the study. Patient records will be stored in a locked cabinet in a locked office and will be accessible only to the Principal Investigator, Interventionist, Research Coordinator, Patient Recruiter, and Site PI's (Markland, Lehosit, and Morley) and co-investigators (Johnson, Goode, Burgio, Baron). Computer-based records will be maintained through the Veteran's Administration Computerized Patient Record System (CPRS), a secure network with password protection.

- Only personnel who are qualified and IRB approved and trained for maintaining the privacy of each participant will be permitted to view records.
- Each participant will be assigned a unique study ID that will be used on all study documents.
- All identified patient data will be maintained on a secure VA research server at each site.
- A separate tracking database with patient identifiers that provide a link to the unique study IDs will be stored on a secure VA research server at each study site.
- Participant study documents which are identified by the participant's unique study ID, will be scanned on a VA device behind the VA firewall and uploaded to an Atlanta VA research server that is accessible to BOSS PD study personnel from each study site who are credentialed through the VA Research service at each site.
- Only deidentified data will be entered into the Redcap database by study personnel who are credentialed through the Atlanta VA Research service.

At all visits (in-clinic and telephone) after the baseline assessment, we will incorporate a standardized side effects checklist that has been used by the Continence research team for studies involving anticholinergic bladder relaxant therapy. The most common side effects reported by persons taking solifenacin are dry mouth and constipation. The risk of acute urinary retention will be reduced by excluding those with a baseline post-

void residual of ≥ 150 mL by bladder ultrasound. All adverse events and severe adverse events will be reported to the IRB, VA ORD, and the DSMB per VA policies.

References

1. Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed MM, Chaudhuri AR, Zalutsky R. How common are the "common" neurologic disorders? *Neurology.* 2007;68(5):326-337.
2. Dorsey ER, Constantinescu R, Thompson JP, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology.* 2007;68(5):384-386.
3. Gage H, Hendricks A, Zhang S, Kazis L. The relative health related quality of life of veterans with Parkinson's disease. *J Neurol Neurosurg Psych.* Feb 2003;74(2):163-169.
4. Gallagher DA, Lees AJ, Schrag A. What are the most important nonmotor symptoms in patients with Parkinson's disease and are we missing them? *Mov Disord.* 2010;25(15):2493-2500.
5. Winge K, Fowler CJ. Bladder dysfunction in Parkinsonism: mechanisms, prevalence, symptoms, and management. *Mov Disord.* Jun 2006;21(6):737-745.
6. Balash Y, Peretz C, Leibovich G, Herman T, Hausdorff JM, Giladi N. Falls in outpatients with Parkinson's disease: frequency, impact and identifying factors. *J Neurol.* Nov 2005;252(11):1310-1315.
7. Vaughan CP, Brown CJ, Goode PS, et al. The association of nocturia with incident falls in an elderly community-dwelling cohort. *Int J Clin Pract.* 2010 Apr 2010;64(5):577-583.
8. Sakushima K, Yamazaki S, Fukuma S, et al. Influence of urinary urgency and other urinary disturbances on falls in Parkinson's disease. *J Neurol Sci.* 2016;360:153-157.
9. Fink H, Kuskowski M, Taylor B, et al. Association of Parkinson's disease with accelerated bone loss, fractures and mortality in older men: the Osteoporotic Fractures in Men (MrOS) study. *Osteoporosis International.* 2008;19(9):1277-1282.
10. Tanji H, Anderson KE, Gruber-Baldini AL, et al. Mutuality of the marital relationship in Parkinson's disease. *Mov Disord.* 2008;23(13):1843-1849.
11. Luppa M, Luck T, Weyerer S, König H-H, Brähler E, Riedel-Heller SG. Prediction of institutionalization in the elderly. A systematic review. *Age and Ageing.* January 1, 2010 2010;39(1):31-38.
12. Aarsland D, Larsen JP, Tandberg E, Laake K. Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. *J Am Geriatr Soc.* 2000;48(8):938-942.
13. Herzog J, Weiss PH, Assmus A, et al. Subthalamic stimulation modulates cortical control of urinary bladder in Parkinson's disease. *Brain.* December 2006;129(12):3366-3375.
14. Herzog J, Weiss PH, Assmus A, et al. Improved sensory gating of urinary bladder afferents in Parkinson's disease following subthalamic stimulation. *Brain.* January 2008;131(1):132-145.
15. Nardos R, Karstens L, Carpenter S, et al. Abnormal functional connectivity in women with urgency urinary incontinence: Can we predict disease presence and severity in individual women using Rs-fcMRI. *Neurourol Urodyn.* 2016;35(5):564-573.
16. Griffiths D, Clarkson B, Tadic SD, Resnick NM. Brain Mechanisms Underlying Urge Incontinence and its Response to Pelvic Floor Muscle Training. *J Urol.* 2015;194(3):708-715.
17. Gormley EA, Lightner DJ, Faraday M, Vasavada SP. Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline Amendment. *J Urol.* 2015;193(5):1572-1580.
18. Gormley EA, Lightner DJ, Burgio KL, et al. Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline. *J Urol.* 2012;188(6, Supplement):2455-2463.
19. Burgio KL, Locher JL, Goode PS, et al. Behavioral vs drug treatment for urge urinary incontinence in older women: a randomized controlled trial. *JAMA.* Dec 16

Dec 16 1998;280(23):1995-2000.

20. Burgio KL, Goode PS, Locher JL, et al. Behavioral training with and without biofeedback in the treatment of urge incontinence in older women: a randomized controlled trial. *JAMA.* Nov 13

Nov 13 2002;288(18):2293-2299.

21. Johnson TM, Burgio KL, Redden DT, Wright KC, Goode PS. Effects of Behavioral and Drug Therapy on Nocturia in Older Incontinent Women. *J Am Geriatr Soc.* 2005;53(5):846-850.
22. Johnson TM, Markland AD, Goode PS, et al. Efficacy of adding behavioural treatment or antimuscarinic drug therapy to α-blocker therapy in men with nocturia. *BJU Int.* 2013;112(1):100-108.

23. Burgio KL, Goode PS, Johnson TM, et al. Behavioral Versus Drug Treatment for Overactive Bladder in Men: The Male Overactive Bladder Treatment in Veterans (MOTIVE) Trial. *J Am Geriatr Soc.* 2011;59(12):2209-2216.
24. Vaughan CP, Juncos JL, Burgio KL, Goode PS, Wolf RA, Johnson TM, 2nd. Behavioral therapy to treat urinary incontinence in Parkinson disease. *Neurology.* 2011 May 10 2011;76(19):1631-1634.
25. Sakakibara R, Panicker J, Finazzi-Agro E, Iacovelli V, Bruschini H. A guideline for the management of bladder dysfunction in Parkinson's disease and other gait disorders. *Neurourol Urodyn.* 2015:epub.
26. Earhart GM. Dance as therapy for individuals with Parkinson disease. *Eur J Phys Rehab Med.* 2009 Jun 2009;45(2):231-238.
27. Ramig LO, Countryman S, O'Brien C, Hoehn M, Thompson L. Intensive speech treatment for patients with Parkinson's disease: short-and long-term comparison of two techniques. *Neurology.* 1996 Dec 1996;47(6):1496-1504.
28. Li F, Harmer P, Fitzgerald K, et al. Tai Chi and Postural Stability in Patients with Parkinson's Disease. *N Engl J Med.* 2012;366(6):511-519.
29. Aarsland D, Kurz MW. The epidemiology of dementia associated with Parkinson disease. *J Neurologic Sci.* 2010 Feb 15 2010;289(1-2):18-22.
30. Liotti M, Ramig LO, Vogel D, et al. Hypophonia in Parkinson's disease: neural correlates of voice treatment revealed by PET. *Neurology.* 2003 Feb 11 2003;60(3):432-440.
31. Petzinger GM, Fisher BE, McEwen S, Beeler JA, Walsh JP, Jakowec MW. Exercise-enhanced neuroplasticity targeting motor and cognitive circuitry in Parkinson's disease. *Lancet Neurol.* 2013;12(7):716-726.
32. Donovan JL, Abrams P, Peters TJ, et al. The ICS–'BPH' Study: the psychometric validity and reliability of the ICSmale questionnaire. *Brit J Urol.* 1996;77(4):554-562.
33. Jackson S, Donovan J, Brookes S, Eckford S, Swithinbank L, Abrams P. The Bristol Female Lower Urinary Tract Symptoms questionnaire: development and psychometric testing. *Brit J Urol.* 1996;77(6):805-812.
34. Zesiewicz TA, Evatt M, Vaughan CP, et al. Randomized, controlled pilot trial of solifenacin succinate for overactive bladder in Parkinson's disease. *Parkin Relat Disord.* 2015;21(5):514-520.
35. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn.* 2002;21(2):167-178.
36. Nasreddine Z, Phillips N, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc.* 2005;53(4):695-699.
37. Hoops S, Nazem S, Siderowf AD, et al. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. *Neurology.* 2009 Nov 24 2009;73(21):1738-1745.
38. Sheikh J, Yesavage J. Geriatric Depression Scale (GDS): Recent evidence of development of a shorter version *Clinical Gerontology: A Guide to Assessment and Intervention*. New York: Haworth Press; 1986.
39. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord.* Nov 15
Nov 15 2008;23(15):2129-2170.
40. Kelleher CJ, Cardozo LD, Khullar V, Salvatore SC. A new questionnaire to assess the quality of life of urinary incontinent women. *Brit J Obstet Gynaecol.* 1997 Dec 1997;104(12):1374-1379.
41. Peel C, Baker PS, Roth DL, Brown CJ, Bodner EV, Allman RM. Assessing Mobility in Older Adults: The UAB Study of Aging Life-Space Assessment. *Phys Ther.* October 1, 2005 2005;85(10):1008-1019.
42. Chou KL, Amick MM, Brandt J, et al. A recommended scale for cognitive screening in clinical trials of Parkinson's disease. *Mov Disord.* 2010;25(15):2501-2507.
43. Schrag A, Barone P, Brown RG, et al. Depression rating scales in Parkinson's disease: critique and recommendations. *Mov Disord.* 2007 Jun 15 2007;22(8):1077-1092.
44. Lorig KR, Sobel DS, Ritter PL, Laurent D, Hobbs M. Effect of a self-management program on patients with chronic disease. *Eff Clin Pract.* 2001;4(6):256-262.
45. Ouslander JG, Schapira M, Fingold S, Schnelle J. Accuracy of rapid urine screening tests among incontinent nursing home residents with asymptomatic bacteriuria. *J Am Geriatr Soc.* Jul

Jul 1995;43(7):772-775.
46. Cooper JA, Sagar HJ, Doherty SM, Jordan N, Tidswell P, Sullivan EV. Different effects of dopaminergic and anticholinergic therapies on cognitive and motor function in Parkinson's disease. A follow-up study of untreated patients. *Brain.* Dec
Dec 1992;115(Pt 6):1701-1725.
47. Crispo JAG, Willis AW, Thibault DP, et al. Associations between Anticholinergic Burden and Adverse Health Outcomes in Parkinson Disease. *PLoS ONE.* 2016;11(3):e0150621.
48. Ehrt U, Broich K, Larsen JP, Ballard C, Aarsland D. Use of drugs with anticholinergic effect and impact on cognition in Parkinson's disease: a cohort study. *J Neurol Neurosurg Psych.* February 1, 2010 2010;81(2):160-165.
49. Nissen MJ, Bullemer P. Attentional requirements of learning: Evidence from performance measures. *Cog Psych.* 1987;19(1):1-32.
50. Siegert RJ, Taylor KD, Weatherall M, Abernethy DA. Is implicit sequence learning impaired in Parkinson's disease? A meta-analysis. *Neuropsych.* 2006 Jul 2006;20(4):490-495.
51. Muslimovic D, Post B, Speelman JD, Schmand B. Motor procedural learning in Parkinson's disease. *Brain.* 2007 Nov 2007;130(Pt 11):2887-2897.
52. Morris J, Heyman A, Mohs R, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology.* 1989 1989.
53. Rosen A, Prull M, Gabrieli J, et al. Differential associations between entorhinal and hippocampal volumes and memory performance in older adults. *Behav Neurosci.* 2003 2003.
54. Fletcher JM. Memory for verbal and nonverbal stimuli in learning disability subgroups: analysis by selective reminding. *J Exp Child Psychol.* 1985 1985.
55. Plenger PM, Breier JI, Wheless JW, et al. Nonverbal selective reminding test: Efficacy in the assessment of adults with temporal lobe epilepsy. *J Epilepsy.* 1996;9(1):65-65.
56. Heaton R. Wisconsin Card Sorting Test. Odessa, FL: Psychological Assessment Resources; 1981.
57. Raz N, Rodrigue KM, Acker JD. Hypertension and the brain: vulnerability of the prefrontal regions and executive functions. *Behavioral Neurosci.* 2003 Dec 2003;117(6):1169-1180.
58. Gunning-Dixon F, Raz N. Neuroanatomical correlates of selected executive functions in middle-aged and older adults: a prospective MRI study. *Neuropsychologia.* 2003 2003.
59. Martínez-Martín P, Rodríguez-Blázquez C, Mario A, et al. Parkinson's disease severity levels and MDS-Unified Parkinson's Disease Rating Scale. *Parkin Relat Disord.* 2015;21(1):50-54.
60. Daley DJ, Myint PK, Gray RJ, Deane KHOL. Systematic review on factors associated with medication non-adherence in Parkinson's disease. *Parkinsonism & Related Disorders.* 2012;18(10):1053-1061.
61. Coyne KS, Matza LS, Thompson CL. The responsiveness of the Overactive Bladder Questionnaire (OAB-q). *Qual Life Res.* 2005;14(3):849-855.
62. Burgio KL, Goode PS, Richter HE, Locher JL, Roth DL. Global ratings of patient satisfaction and perceptions of improvement with treatment for urinary incontinence: Validation of three global patient ratings. *Neurourol Urodyn.* 2006;25(5):411-417.
63. Visco AG, Brubaker L, Richter HE, et al. Anticholinergic Therapy vs. OnabotulinumtoxinA for Urgency Urinary Incontinence. *N Engl J Med.* 2012;367(19):1803-1813.
64. Vaughan CP, McGwin GM, Juncos JL, Burgio KL, Goode PS, Johnson II TM. Behavioral therapy without EMG-biofeedback training is feasible to treat urinary incontinence in Parkinson disease. *Mov Disord.* 2012;27(4):E7 (abstract).
65. Kay GG, Abou-Donia MB, Messer WS, Murphy DG, Tsao JW, Ouslander JG. Antimuscarinic Drugs for Overactive Bladder and Their Potential Effects on Cognitive Function in Older Patients. *J Am Geriatr Soc.* 2005;53(12):2195-2201.
66. Anticholinergics for symptomatic management of Parkinson's disease. Wiley-Blackwell; 2002. Accessed May 2, 2016.
67. Yarnall A, Rochester L, Burn DJ. The interplay of cholinergic function, attention, and falls in Parkinson's disease. *Mov Disord.* 2011;26(14):2496-2503.
68. Chung KA, Lobb BM, Nutt JG, Horak FB. Effects of a central cholinesterase inhibitor on reducing falls in Parkinson disease. *Neurology.* 2010;75(14):1263-1269.

69. Zizzo N, Bell E, Lafontaine A-L, Racine E. Examining chronic care patient preferences for involvement in health-care decision making: the case of Parkinson's disease patients in a patient-centred clinic. *Health Expectations.* 2016:epub Sept 14.
70. Horváth K, Aschermann Z, Ács P, et al. Minimal clinically important difference on the Motor Examination part of MDS-UPDRS. *Parkin Relat Disord.* 2015;21(12):1421-1426.
71. Yamanouchi. Vesicare (solifenacin succinate) tablet prescribing information. Paramus, NJ2004.
72. Herschorn S, Pommerville P, Stothers L, et al. Tolerability of solifenacin and oxybutynin immediate release in older (>65 years) and younger (≤65 years) patients with overactive bladder: sub-analysis from a Canadian, randomized, double-blind study. *Curr Med Res Opin.* 2011/02/01 2011;27(2):375-382.
73. Wagg A, Dale M, Tretter R, Stow B, Compion G. Randomised, Multicentre, Placebo-controlled, Double-blind Crossover Study Investigating the Effect of Solifenacin and Oxybutynin in Elderly People with Mild Cognitive Impairment: The SENIOR Study. *Eur Urol.* 2013;64(1):74-81.