



Protocol for a multicenter randomized, double blind, controlled pilot trial of higher neural function in overactive bladder patients after anticholinergic, beta-3 adrenergic agonist, or placebo

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ABSTRACT

Introduction: Overactive bladder (OAB) syndrome has a negative impact on quality of life and prevalence increases with advanced age. Anticholinergics (AC) and beta-3 adrenergic agonists (β 3a) are commonly prescribed medications for treatment of OAB. AC medication has been associated with dementia in population studies and with cortical atrophy in imaging studies. Higher neural effects of both classes of OAB medications have not been evaluated with functional neuroimaging. Longitudinal clinical assessments of cognition after OAB therapy with AC has produced conflicting results. β 3a medication is has not been associated with dementia in clinical studies; however, higher neural effects are unknown.

Our multicenter, double blind, randomized, placebo-controlled trial uses functional magnetic resonance imaging (fMRI) and cognitive testing to evaluate the effects of AC and β 3a on brain functional connectivity in females with non-neurogenic OAB.

Methods and Analysis: and analysis: Female patients with OAB symptoms ages 50–90 years old without baseline cognitive impairment, moderate to severe depression or anxiety, neurologic disorders, or significant incomplete bladder emptying are invited to participate. Subjects are randomized to one of three interventions for 29 ± 1 day: AC (Solifenacin succinate, Teva), β 3a (Mirabegron, Myrbetriq, Astellas), or placebo. Functional neuroimaging data at baseline and post-intervention will be analyzed accordingly. Clinical cognitive assessments will be compared from baseline to post-intervention.

Ethics: All qualifying patients are properly consented before enrolling in this study that has been approved by the Institutional Review Board of participating institutions.

1. Background & rationale

Overactive bladder (OAB) is a clinical diagnosis characterized by bothersome urinary urgency, usually accompanied by urinary frequency, nocturia, with or without urgency urinary incontinence [1]. OAB prevalence increases with age; 36.6–43.1% of women in the United States report symptoms [2]. OAB has significant negative effects on quality of life and psychosocial functioning [3,4]. The prevalence of cognitive decline parallels OAB which imposes the great challenges in management of OAB [2,6,7].

If behavioral modifications & therapy fail to improve symptoms, pharmacologic therapy (oral AC or β 3a medication) is next line of treatment [5]. These medications significantly improve quality of life for many patients [5]. AC medications are used with caution and careful dosing in the elderly population, as increased permeability of the blood-brain barrier occurs with age [7], yet polypharmacy is an issue. The prevalence of AC medication use has increased in the past fifteen years [8]. Medications for OAB are among the most commonly prescribed AC drugs in the elderly [8–11]. Concern over increased risk of incident dementia with use of AC has been raised in multiple population-based studies [9–12].

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Abbreviations

OAB	Overactive bladder
AC	Anticholinergic medication
β 3a	β –3 adrenergic agonist medication
fMRI	Functional magnetic resonance imaging
BOLD	Blood oxygen level dependent
rsFC	Resting state functional connectivity
MOANS	Mayo Clinic's Older Americans Normative Studies
RAVLT	Rey Auditory Verbal Learning test
DTI	Diffusion Tensor Imaging
MD	Mean diffusivity
FA	Fractional anisotropy
ANOVA	Analysis of variance
BSW	Baylor Scott and White Health
HMH	Houston Methodist Hospital
MOANS	Mayo Older Adult Normative Scale

Further complicating OAB therapy, OAB may be a sign of early neurodegeneration [13,14]. Lower urinary tract symptoms (LUTS) such as OAB, are a prodromal symptom of dementia; a diagnosis of dementia frequently follows LUTS diagnoses by 1–5 years [13–16]. LUTS remain a risk factor for dementia after controlling for age, gender, and multiple comorbidities [13].

Clinical measures of cognition in OAB patients follow AC medication have shown mixed results. Prospective studies of the cognitive effects of OAB medications have been measured with clinical testing. Thus far there are conflicting results, with most finding no significant cognitive effects with shorter term (1–3 months) use of AC OAB medications [17–20]. A broad range of screening and diagnostic test for cognitive impairment exist, but it is possible they were not sensitive enough to detect early clinical effects [20]. In the clinical setting, an assessment of cognitive function is recommended prior to initiating AC therapy [5,21]. Without screening, it has been estimated that up to 50% of dementia cases are undiagnosed at any given time [22]. Mild cognitive impairment may not be evident during standard evaluation for OAB.

Functional magnetic resonance imaging (fMRI) can be used to assess resting state functional connectivity (rsFC) and regional activation during tasks [23]. Performance on cognitive testing correlates with activation of the hippocampus in fMRI studies [24–26]. In healthy subjects, intervention with intravenous AC cause changes in hippocampus and prefrontal cortex activity [27]. Serum anticholinergic activity has correlated with reduced function in the prefrontal cortex [28]. In older adults with clinically normal cognitive function, AC medication burden has been correlated with severity of cortical atrophy and brain hypometabolism on neuroimaging [29].

An alternative oral medication for OAB is β 3a; users may have a lower risk of dementia (vs AC users) [12] β 3a is an option for eligible patients who may be considered high-risk with use of AC [21]. Beta-adrenergic receptors types 1, 2, and 3 are found in high levels in rat cortex, and blockade has shown influence on prefrontal cortex neuron activity [30]. β 3a medication is assumed by many clinicians to not affect cognitive abilities; however, there are no studies of higher neural effects of this medication. Changes in rsFC and activation on fMRI have been seen with therapies for OAB which do not likely cross the blood-brain barrier [31–34]. This is the first study to compare the effects of two types of oral medication therapy for idiopathic OAB on rsFC and activation during a cognitive task.

The primary objective of this study is to compare the effects of AC versus β 3a versus placebo on resting state functional connectivity and activation during a visual recognition test in women with OAB. Cognitive function and OAB symptoms will be compared following AC versus β 3a versus placebo using clinical measures.

2. Methods

2.1. Participants, interventions, and outcomes

This investigator-initiated study is an exploratory, randomized, double-blind, placebo controlled, parallel clinical trial. The trial initiation was in August 2019 and is being conducted at two academic medical centers following approval in each institutions' review board. Subjects are allocated in a 1:1:1 ratio to one of three groups, namely: (Group 1) AC medication (solifenacin succinate, Teva), (Group 2) β 3a medication (mirabegron, Myrbetriq, Astellas), and (Control group) placebo.

2.2. Patient selection & recruitment

Female patients with OAB are recruited from clinics affiliated with two hospital systems in Texas. Potential subjects are screened by a clinical research coordinator or investigator after completion of a full history and physical examination by their provider. Full screening is performed following patient review and signature of informed consent. Eligibility criteria are found in Table 1.

Males are excluded to eliminate prostate pathology and urethral strictures, as well as possible bias of gender differences on fMRI and cognitive testing [20,37]. Subjects with moderate to severe depression on the Personal Health Questionnaire-9 (PHQ-9) or moderate to severe anxiety on the Hamilton Anxiety Rating Scale (HAM-A) are excluded [38,39]. Patients with mild cognitive impairment as measured by the Montreal Cognitive Assessment (MoCA) are excluded [40]. Those who have absolute contraindications to the study drugs [35,36] as per the manufacturers warning are excluded. The participant timeline is outlined in Fig. 1.

All participants receive a stipend payment for their time and travel as incentive to assist in reaching the target sample size. Subjects will be enrolled until 30 are randomized. See exclusion criteria for exclusion prior to randomization.

2.3. Interventions

Subjects from all recruitment sites have baseline and post-intervention testing performed at the Houston Methodist Hospital (HMH) translational imaging center. The day of baseline testing, patients receive 30 capsules in a vial from the HMH Investigational Drug Service pharmacy. Tablets are contained in identical capsules for each of the three arms. The AC anticholinergic tablets and the β 3a tablets as manufactured are placed intact within a methyl-cellulose in an opaque

Table 1
Inclusion and exclusion criteria for participants.

Inclusion	Exclusion
50 to 90-year-old females	Mild cognitive impairment on the Montreal Cognitive Assessment (MoCA)
OAB diagnosis (experiencing at minimum "somewhat" bothered on OAB-q symptom bother scale)	History of neurologic disorders, dementia, prior cerebrovascular accident, neurogenic bladder
English primary language	Contraindication for MRI (metal implants, claustrophobia)
Post-void residual volume < 250 mL	Positive pregnancy test or breastfeeding
	OAB therapy in the past 6 months with: oral medication or pelvic floor physical therapy by a licensed professional
	Moderate to severe anxiety on the HAM-A
	Moderately severe or severe depression on PHQ-9
	Response of yes to "Do you experience pain in your urethra or bladder with filling that is relieved after you empty?"
	Contraindications for the study medications [35,36]

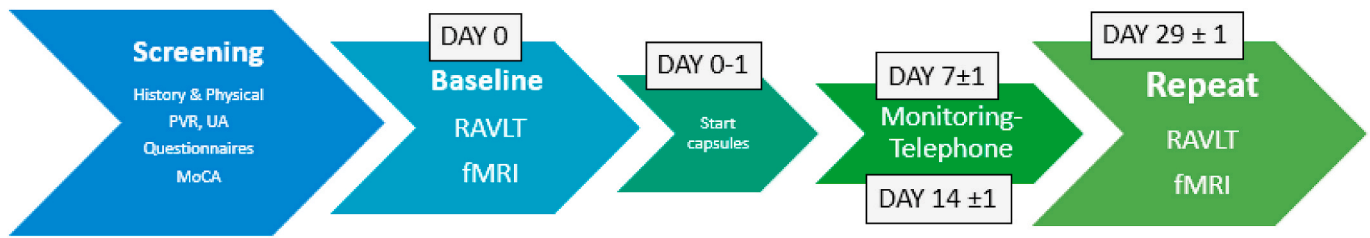


Fig. 1. Sequence of visits during which data will be collected.

locking 2-piece gelatin capsule. Placebo capsules contain only methylcellulose. Subjects have a telephone interview 7 ± 1 and 14 ± 1 days after initiating treatment. During that interview, side effects and compliance by pill count are assessed.

2.4. Outcomes

2.4.1. Primary

Compare changes in activation and resting state functional connectivity of patients' cognitive network after exposure to AC versus β 3a versus control. Activation is measured as blood oxygen level dependent (BOLD) responses in cognitive networks during a visual word recognition task. Compare resting state functional connectivity (rsFC) after exposure to AC versus β 3a versus control. The intrinsic brain functional connectivity is computed as functional correlations in cognitive networks in a resting state.

2.4.2. Other

1. Compare Mayo Clinic's Older Americans Normative Studies (MOANS) calculated from Rey Auditory Verbal learning test (RAVLT) scores
2. Compare lower urinary tract symptoms using the overactive bladder questionnaire (OAB-q) and Patient Perception of Bladder Condition (PPBC) questionnaire.

2.5. Randomization & allocation concealment

Permutated block randomization with 1:1:1 allocation is computer generated by the independent pharmacy. Two blocks of 15 subjects are stratified by recruitment site. Thirty vials (each containing thirty tablets) are numbered from 1 to 30, prepared by an independent pharmacy in Houston, TX, USA. Records with concealed allocation are maintained by the independent pharmacy. The numbered vials are stored at the HMH Investigational Drug Services pharmacy where vials are distributed to patients on the day of baseline testing. The dispensing pharmacy keeps record of the vial number dispensed to each subject number.

Subjects, practitioners, investigators, and outcome assessors are blinded to the allocation sequence. Subject ID numbers are known to subjects, practitioners, investigators and documented in the medical record. Unblinding will be done by the independent pharmacy if indicated. Indications for unblinding include severe adverse events.

2.6. Rey auditory verbal learning test (RAVLT)

RAVLT is a validated cognitive test which assesses immediate memory span, new learning, susceptibility to interference, delayed recall, and recognition [38]. This trial includes a modified administration of the RAVLT in which the recognition task is performed with a 30-min delay. In a private exam room, blinded assessors give standardized verbal instructions. Word lists are read by a standardized recording for immediate recall and interference trials. Different word lists [38,41] are used at baseline RAVLT and post-intervention RAVLT.

Subjects are transferred to the next room for positioning in the

scanner prior to an anatomic scan (Fig. 2). Each subject's head is stabilized with foam pillows to minimize head movements. A screen display is behind them, which they view easily by looking up at a mirror. Subjects are asked to read a line displayed on the screen to assist with fitting MRI approved visual correction if needed. A push button is placed in the dominant hand of subjects and they are instructed to push the button when they recognize a word displayed later.

An anatomic scan is obtained, followed by resting state image acquisition while the subjects are asked to stare at a white cross on a black screen. The visual recognition task begins 25 min later (30–35 min after last exposure to the word list).

Instructions for the task with sample words are displayed. Thirty words (of which 15 should be recognized from the list administered verbally) are displayed to the patient one at a time for 5 s in blocks of 6 words. Thirty second resting state periods are between blocks of words. Correctly identified words, missed words, and incorrectly recognized words are noted.

Scores for domains of learning over trials, short and long-term percentage retention, recognition percentage correct, and raw recognition score will be converted to age normalized scores using the Mayo Older Adults Normative Scale (MOANS) score [42].

2.7. MRI procedures

MRI scans are performed on a 3.0 T S Vida full body MRI scanner (Siemens Healthineers, Erlangen, Germany) with a standard 20-channel head coil. Three dimensional structural images are obtained from a T1-weighted sequence; ($0.86 \times 0.86 \times 1.00 \text{ mm}^3$ resolution).

Diffusion Tensor Imaging (DTI) images are acquired (64 directions, one B0 image) using the standard MRI pulse sequence available on the Siemens 3.0 T Vida scanner. The original DTI images as well as the fractional anisotropy (FA) and mean diffusivity (MD) calculated on the scanner will be transferred to an offline workstation for further processing. The software packages TackVis (version 0.6.0.1) and the Diffusion Toolkit (version 0.6.3, trackvis.org) will be used to calculate and extract selected white matter tracts of interest. This software also enables calculating FA and MD values for the segmented white matter tracts.

Resting state BOLD fMRI are collected during a 6-min quiet rest when subjects focus on a white cross with a black background (axial echo-planar, repetition time = 2,000 ms, 3.0 mm slice thickness, 2.98 mm in-plane resolution).

Task BOLD fMRI is acquired afterwards during a visual word recognition test. Structural and functional images will be registered and motion-corrected. Patients with rapid motion ($>4.5 \text{ mm}$) will be excluded from analysis. Voxel activation will be identified at the time when patients indicate word recognition and significant differentially-activated voxels will be identified at this time point under the generalized linear model. Group level analysis will be performed by transforming data into MNI 152 space, and significantly activated voxels will be identified using a Student's t-test after the correction for multiple comparisons.

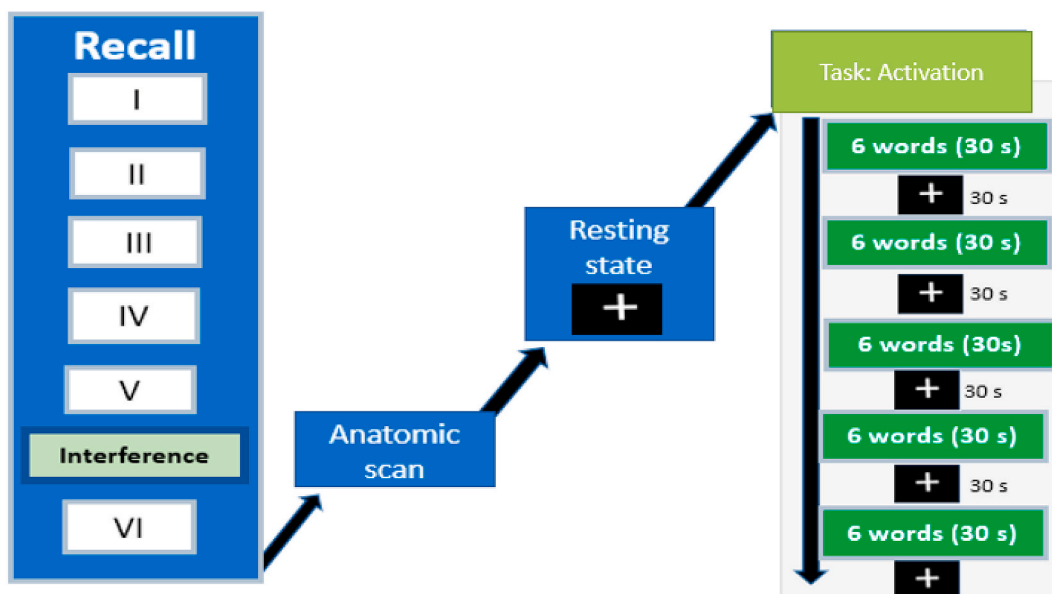


Fig. 2. Flow chart of RAVLT trials integrated with the imaging protocol. After resting state images are acquired, the visual recognition task is performed. Resting state periods of 30 seconds separate word exposure into blocks of 6.

2.8. Sample size

This pilot trial is the first to compare these 3 interventions and is not powered for the primary outcome. Additionally, this is the first trial to characterize changes within groups after oral OAB therapy. Resting state FC, DTI, and activation results from this exploratory sample will be used to guide a larger program of research assessing cognitive effects of pharmacologic OAB therapy.

Group size of 10 subjects was a convenience sample in this trial; this sample should be adequate to detect regional activation during the visual recognition task. Desmond et al. used simulation to generate power curves from percent signal change during a verbal working memory task [37]. Authors estimated a need for 11–12 subjects to achieve 80% power with 95% confidence, at the single voxel level for typical activations. We estimate that 10 subjects in each group will permit detection of regional activation.

2.9. Outcomes analysis

The primary outcome measures of regional activation and rsFC will be analyzed and reported separately. Analysis of variance (ANOVA) will compare the difference between baseline and post-treatment measures across groups. Baseline characteristics and secondary outcomes (clinical data) comparison across groups will be performed with ANOVA. All analyses will be performed at a two-sided type 1 error rate of 0.05AFNI software will be used for analysis of images [43]. SPSS (v19.0) will be used to perform statistical analysis of clinical data. Clinical data (demographics, RAVLT scores, symptom scores) will be correlated to BOLD signal changes as well as to structural markers (e.g., integrity of white matter tracts) using regression analyses.

2.10. Data collection & management

Clinical data is collected in REDCap® [44], hosted by Baylor Scott and White Health (BSW). Patient identifiers will be removed and replaced by the subject identification number. Investigators involved in analysis of the images are blinded to allocation. Paper consents and data collection forms linking the subject ID number to identifiers are stored in a locked, secure office. Consent forms will be archived by the investigators for 15 years following the end of the study. Clinical and

outcome data will be electronically stored on double password protected computers.

2.11. Monitoring & safety

This study is registered at [ClinicalTrials.gov](https://clinicaltrials.gov) as NCT03817931. Baylor Scott and White is the primary institution responsible for monitoring study activities and data. A formal monitoring visit of the testing site was conducted 6 months after initiation and involved pharmacies 12 months after initiation of recruitment. This study is also monitored by the Quality Assurance committee of HMH Research Institute.

Every staff member involved in the collection of data and patient handling have been trained and evaluated regarding MRI safety before being allowed to enter the scanner room. Urine pregnancy tests are performed prior to each imaging test in patients without a documented hysterectomy, tubal ligation, or postmenopausal status. All baseline fMRI will be reviewed by a radiologist for conditions requiring urgent treatment; and if detected the subject will be discontinued before randomization. The study duration, intervention dosing, and sample size were selected with a goal to minimize risk to subjects.

All staff members involved in the collection of data and handling of patients have proper privileges and training by our research institute and MRI core. Before proceeding with fMRI testing, patients are asked to remove all clothing and items containing metal. Participants are provided with gowns during the imaging study. No minor or vulnerable individuals will be recruited for the study. If an adverse effect occurs, the principal investigator and appropriate authorities will be informed, and proper actions will be taken based on good clinical practice.

2.12. Limitations

This study protocol focused on patients with non-neurogenic OAB, thus findings cannot be generalized to all patients with OAB. The doses selected for β 3a and AC medications in this study are the lowest starting doses and may be sub-therapeutic for some patients [35,36]. In clinical practice these doses are titrated upward to reach optimal efficacy within the first few weeks of therapy in many patients. Additional studies may be required to confirm findings of this pilot study which is not powered. Patients or the public were not involved in the design, conduct, reporting, or dissemination of our research.

2.13. Ethics and dissemination

Institutional board review and full approval has been obtained at Baylor Scott and White Research Institute (# 160–362) and Houston Methodist Research Institute (Pro00019252). The funding organizations did not participate in collection, analysis or interpretation of data, writing of the protocol, or publication of this work. All authors had full access to the data (statistical reports and tables) and can take responsibility for the integrity and accuracy. The lead author (the manuscript's guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained. The informed consent notes that participation is completely voluntary, and patients can withdraw at any point and this will not affect their relationship with the physician and their treatment course. Outcomes of this research will be presented at national and international meetings and published in scholarly journals.

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