STOMP: **S**exual function **T**rial of **O**veractive bladder: **M**edication versus **P**TNS

Research Plan

Specific aims:

Primary aim:

Aim 1: To determine if there is greater improvement in female sexual function as measured by the female sexual function index (FSFI) with percutaneous tibial nerve stimulation (PTNS) as compared to medical therapy (MT).
Hypothesis: We expect that there will be a greater improvement in overall FSFI with PTNS as compared to MT.

Secondary aims:

Aim 2: To determine if improvement in female sexual function with percutaneous tibial nerve stimulation or medical therapy is correlated with improvement in urinary symptoms as measured by the OAB-q questionnaire.
Hypothesis: We expect that improvement in urinary symptoms will be correlated with improvement in sexual function but that the difference in FSFI between groups will not be solely attributable to differences in urinary symptom improvement.

Aim 3: To determine if changes in sexual function are greater with beta agonist medications as compared to anticholinergic medications.
Hypothesis: We expect that beta agonists will result in improved sexual function as compared to anticholinergics.

Aim 4: To determine if those patients with female sexual dysfunction as defined as an overall FSFI score below 26.5 have greater improvements than those without.
Hypothesis: We expect that patients with female sexual dysfunction will have a greater improvement in FSFI than those without.

Research Strategy

Significance:

Female sexual dysfunction (FSD) affects approximately 45% of women with an even greater incidence reported in women with overactive bladder symptoms [1], [2], despite this there is a lack of FDA approved treatments for sexual dysfunction in this population. Female sexual function is complex and can be affected by pain, depression, and comorbidities as well as bowel and bladder function. There are numerous treatments for women with overactive bladder defined as urinary urgency, frequency, urge urinary incontinence (UUI) and nocturia. These treatments include medical therapy (MT) with anticholinergics and beta agonists and neuromodulation via implantable sacral nerve stimulator (SNM) and percutaneous tibial nerve stimulation (PTNS). Sexual function, which can be measured by the Female Sexual Function Index (FSFI) has been shown to improve with both medical therapy and neuromodulation.

Medical therapy (MT) with both oral and transdermal anticholinergics has been shown to have a positive effect on female sexual function in overactive bladder patients [3]–[5]. Sand et al. found improvement in responses to questions about sexual function in the King's Health Questionnaire with tolterodine [5]. Hajebrahimi et al. showed improvement in sexual desire, arousal, vaginal lubrication and orgasm as measured by the Arizona Sexual Experience Scale [3]. In a randomized trial of placebo versus tolterodine, Rogers et al. showed improvement in the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire and found this improvement to be correlated with improvement in overactive bladder symptoms [4]. Beta agonist therapy is a

relatively newer treatment for urinary urgency and there is a lack of literature regarding the effects of this treatment on sexual function.

There are multiple hypotheses regarding the association between overactive bladder/urge incontinence and sexual dysfunction, including low self-esteem related to incontinence and fear of incontinence during sexual activity. It has been suggested that improvement in sexual function is a result of improvement in urinary function. This has been shown to be the case in a number of studies that have found improvement in sexual function correlates with improvement in urinary function [4], [14] however other studies have shown that the two are not correlated [6], [7], [12]. In addition to the effects of treatment on overactive bladder symptoms, treatments may affect sexual function in other ways. Anticholinergics may have a negative effect on sexual function. The human sexual response is mediated by various neurotransmitters, including acetylcholine. Acetylcholine's actions on muscarinic receptors result in parasympathetic activation that leads to vasodilation in the erectile tissues of the clitoris, and in the lining of the vagina [15]. In fact, bethanecol has been used to reverse the anticholinergic properties of tricyclic antidepressants that result in sexual dysfunction [16]. Improved understanding of the effects of these medications on sexual function would be valuable in counseling patients about options for medical therapy.

There are a number of hypotheses regarding the improvement in sexual function with neuromodulation. Neuromodulation may strengthen pelvic floor muscle tone with bulbocavernosus contraction placing pressure on the deep dorsal vein of the clitoris preventing venous escape and resulting in clitoral engorgement. Arterial flow may also be affected by neuromodulation as studies of male animals as well as human subjects have shown electrical stimulation of the cavernous nerve results in an erection by causing increased arterial flow in addition to relaxation of the cavernous muscles, and venous outflow restriction [17], [18]. In women, sacral nerve stimulation has been shown to result in increased vaginal pulse amplitude on vaginal plethysmography [19]. Understanding the comparative effectiveness of PTNS and MT may shed light on the mechanisms by which these treatments improve female sexual function.

Neuromodulation has also been shown to have a positive impact on sexual function. There has been much research on the effects of neuromodulation via sacral nerve stimulator on sexual function as measured by FSFI. While the majority of studies show improvement in overall FSFI, there are variations with respect to improvement in specific domains [6]–[9]. Banakhar et al. showed improvement in overall FSFI as well as desire and orgasm, whereas Lombardi et al. showed improvement in overall FSFI as well as satisfaction [7], [9]. Pauls et al. found improvements in desire, lubrication, orgasm, satisfaction and pain, but not arousal, whereas Zahibi et al. showed improvement in all domains [6], [8]. These reports of SNM have all shown an improvement in FSFI compared to baseline. In a controlled trial comparing SNM to MT Siegel showed that among female patients, SNM had a greater improvement in sexual function as compared to MT [10]. This study however did not use a questionnaire specific to sexual function and so was unable to examine specific domains of sexual function. Fewer studies have been done looking at the effect of PTNS on sexual function. Van Balken et al., in a study of 121 men and women examined before and after PTNS, found improvement in satisfaction, libido and frequency as compared to baseline [11]. Recently Musco et al. looking at 41 women who underwent PTNS found improvement in all domains of the FSFI [12]. This study found that improvement in urinary function did not correlate with improvement in sexual function. This led the authors to suggest that sexual function improvement might be directly related to PTNS effects rather than simply due to improvement in urinary symptoms [12]. A small randomized study of PTNS versus tolterodine showed a trend towards greater improvement with PTNS but no significant difference between groups regarding FSFI was found however the study was under-powered [13].

The purpose of this study is to examine the comparative effectiveness of neuromodulation via percutaneous tibial nerve stimulation and medical therapy with anticholinergics or beta-agonists in improving female sexual function. Additionally this study will assess whether improvement in sexual function is correlated with improvement in urinary symptoms. Furthermore the effectiveness of anticholinergics as compared to beta agonists with respect to changes in sexual function will be examined. Lastly we aim to determine if patients with female sexual dysfunction have greater improvements than those without, as this may open the door to future studies using PTNS for the primary indication of female sexual dysfunction. Enhanced understanding of

the effects of neuromodulation and medical therapy on sexual function may allow for improved patient selection and better outcomes which may lead to widespread use of neuromodulation for female sexual dysfunction.

Innovation:

While MT and PTNS have both been shown to improve female sexual function as compared to baseline as measured by the female sexual function index, there is a dearth of literature regarding their comparative effectiveness. A single study compared SNM to MT with sexual function examined only using the ICIQ OAB questionnaire which contains questions regarding sexual function but is not specific to sexual function and cannot tease out dysfunctions in specific domains. SNM is also more invasive than PTNS. Less is known about the effects of PTNS on sexual function and only a single underpowered study exists comparing PTNS to MT with respect to sexual function. Additionally there are conflicting results regarding whether the improvement in sexual function seen with PTNS and MT is associated with improvement in urinary function. If as hypothesized, sexual function improves to a greater extent with PTNS than with MT although both result in a similar improvement in urinary symptoms; it suggests that there may be additional mechanisms by which PTNS affects sexual function. Improved understanding of these effects may lead to clinical use of PTNS for FSD, a condition for which few treatments exist.

Approach:

This will be a prospective multi-center cohort study comparing changes in sexual function in women undergoing PTNS or MT for OAB/UUI. Potential subjects will be adult women presenting to a urogynecology clinic for symptoms of overactive bladder such as urgency and UUI. Eligible subjects must report urinary urgency or urge incontinence and be recommended for treatment with medical therapy (with anticholinergic or beta agonist) or PTNS by the treating physician. Women meeting inclusion criteria will be asked to complete the validated OAB-q, FSFI, Beck Depression Inventory and a visual analog pain scale prior to therapy and then again after twelve weeks of therapy. Patients will also be specifically asked about the presence or absence of fecal incontinence and known side effects of therapy. Demographic data including age, comorbidities and menopausal status will be extracted from the medical record.

Women meeting inclusion/exclusion criteria will be prospectively enrolled.

- Women who are prescribed MT will be instructed on adherence to therapy for the twelve week duration of the trial. Therapy prescribed (anticholinergic versus beta agonist) will be based on shared decision-making between the patient and the treating physician.
- Women who are prescribed PTNS will undergo weekly 30 minute stimulation sessions for 12 weeks using a tibial nerve stimulator (Urgent® PC, Uroplasty, Minnetonka, MN, USA). The technique consists of stimulating the nerve by means of a 34 gauge needle electrode inserted approximately 2 inches cephalad and 1 inch posterior to the center of the ankle. The needle is inserted at a 60° angle pointing toward the head and advanced until approximately half of the needle is inserted into the leg. The lead wire is then connected to the stimulator and the surface electrode is placed on the inside of the arch of the foot of the treatment leg. The patient treatment level is identified by slowly increasing the current while observing the patient's foot for a motor response (usually toe flex, fan, or twitch) and asking the patient to report any sensations they feel (typically mild pulsing sensation). Once treatment level is identified, therapy mode is initiated and continued for 30 minutes.

Inclusion criteria:

- Female patients greater than 18 years of age
- Symptomatology of urinary urgency or urge incontinence planning to undergo MT or PTNS. Patients must meet a threshold bother defined by a positive response and bother of "somewhat, quite a bit, a great deal, or a very great deal" to questions #2, #3 or #8 on the OAB-q regarding urinary urgency and urgency incontinence.

- Patients may have tried other medication for overactive bladder in the past but should be off therapy for at least one month
- Patients must be currently sexually active with sexual activity within the past month and plans to continue for the duration of the study. Sexual activity, as defined in the FSFI questionnaire, may include caressing, foreplay, masturbation, and vaginal intercourse.
- Patients must be willing and able to complete questionnaires in English

Exclusion criteria:

- Contraindications to PTNS (skin, orthopedic or anatomical limitation that could prevent placement of PTNS electrode, presence of pacemaker)
- Contraindications to both anticholinergic and beta agonist therapy
- Current symptomatic UTI within past week
- Pregnant or planning to become pregnant
- Prior treatment with SNM, PTNS, onobotulinum toxin A or two medications (stopped for reasons unrelated to side effects)
- Diagnosed or suspected interstitial cystitis/painful bladder syndrome
- Diagnosis of neurogenic bladder
- Prolapse greater than Stage 2, pessary use or planned surgery for pelvic floor disorder during the study
- Planned simultaneous treatment with both PTNS and MT

Statistical analysis and Sample Size Calculation:

The proposed study will consist of two treatment groups (MT versus PTNS). The decision to conduct a two-arm prospective cohort as compared to a three-arm randomized controlled trial was based on assessment of feasibility. The primary endpoint of the study is improvement in overall FSFI score which we hypothesize to be greater in the PTNS group.

Sample size calculations were conducted using http://clincalc.com/stats/samplesize.aspx with the primary endpoint of FSFI assessed as a continuous variable. Group sample sizes of 63 per group (total 126 patients) will be necessary to detect a clinically relevant difference of 5 points in FSFI assuming standard deviation of 10 [13] and achieve a power of 80%, alpha=0.05. By incorporating a 10% loss to follow-up rate, we propose to recruit 70 patients per group, with a total of 140 patients. Because approximately 45% of patients with OAB will have FSD as determined by an FSFI score below 26.5, we aim to include up to 312 patients in the study.

Initial statistical analysis will provide descriptive statistics on the demographic and clinical characteristics of the study participants using means, standard deviations, median and range for continuous variables and frequencies and percentages for categorical variables. To examine potential differences between the study groups at baseline, descriptive statistics will be obtained for each group and compared statistically using two-sample t-tests, nonparametric rank tests, chi-square and Fisher's exact test as appropriate. All outcome variables will be summarized using similar methods for initial data and 12-week follow-up.

Wilcoxon signed rank test will be used to assess changes in FSFI before and after treatment as we expect the quantitative data from this to have a skewed distribution given the nature of the FSFI score. A subgroup analysis will be performed to determine if those patients with female sexual dysfunction as defined as an overall FSFI score below 26.5 have greater improvements in FSFI than those without. Mann-Whitney U test will be used to compare FSFI scores between the MT and PTNS groups again because of the skewed nature of the distribution. Spearman's correlation will be used to assess for correlation between urinary symptoms, and FSFI.

We will analyze both intention to treat (ITT) and per protocol (treated) samples for the primary outcome. To handle missing data, we will employ multiple imputation models for the ITT analyses. We will also examine the difference between patients who complete the study and those who were lost to follow-up based on baseline

demographic and clinical characteristics to evaluate type of missingness, adherence to therapy and limits to generalizability.

We will conduct secondary/advanced analyses by specifying multivariate regression models of the primary outcome measures in order to estimate treatment differences adjusted by potential confounders. Specifically, multiple linear regression analyses will be used to adjust the post-treatment change scores for baseline values of the outcome variables as well as age, OAB-q and BMI. These models will be estimated using cluster options (Intercooled Stata, command cluster) to account for the correlations between patients who are treated in the same hospital/site.

A planned interim analysis will be conducted comparing patients receiving anticholinergics and those receiving beta agonists. This will be conducted once 63 patients receiving anticholinergics and 63 receiving beta agonists have completed the study. This will address Aim 3. A Mann-Whitney U test will be used to compare FSFI between patients receiving anticholinergics and beta agonists.

Data Collection and Transmission:

Potential subjects will be approached by their treating physician in the context of a private clinical visit regarding enrollment in the study. After discussion of the risks and benefits and obtaining written informed consent, each subject will be assigned a participant identification number (ID). Those patients who express interest but are unable to sign consent in the context of an office visit due to time constraints will be contacted via telephone to complete the consent process; once consent is obtained these patients will have the option of completing paper questionnaires which will be mailed to them or online questionnaires which they will receive through a secured email link. Treating physicians and investigators will monitor patients at clinic visits. Case report forms will be generated for each subject and completed by the investigator or study coordinator at each site, these will then be entered by the investigator or study coordinator into a password protected REDCap database with each patient identified only by ID. Patients will be asked to complete questionnaires in the setting of clinic visits to minimize mailings and their potential for privacy breach. Mailing of questionnaires will only be used if patients are unable to return to clinic for follow up; forms may also be returned via fax or secure email. Patients may also complete questionnaires online directly in the REDCap database. Patients will be encouraged to complete forms in REDCap to minimize the potential for transcription error and breach of privacy. For those patients who cannot mail the forms or access them online, they may be completed via phone with an investigator or study coordinator. Original case report forms and questionnaires will be securely maintained on site in a locked file cabinet within a locked office. MedStar Washington Hospital Center will be the Data Collecting Center (DCC). Copies of the case report forms and questionnaires will be forwarded by courier or fax to the DCC with participant ID number visible and personal information obscured. The following interim data will be monitored via review of the database at scheduled six-month intervals by the PI: accrual rate, patient adherence, adverse events and accuracy and completeness of the data.

Study Timeline:

	Intake Visit	Day 0	12 weeks
Assessment for eligibility	X		
Discussion of symptoms and decision regarding treatment	X		
Informed consent	X		
Medical history	X		
OAB-q		X	X
Beck Depression Inventory		X	X
Visual analog pain scale		X	X
FSFI		X	X

Follow up medical history			X

Potential Difficulties:

There may be difficulty in recruiting patients for this study as patients may not be sexually active or may think discussion of sexual function is taboo. In order to account for this, the study will be a multi-center trial organized through the American Urogynecological Society-Society of Gynecologic Surgeons Fellows Pelvic Research Network (AUGS-SGS FPRN) to have a greater population from which to recruit patients. This project was submitted and accepted for presentation at the AUGS-SGS FPRN project proposal meeting. The FPRN is a fellow-run multi-center research network created to enable fellows to conduct multi-center pelvic floor research projects. At the meeting, which was held during the annual AUGS meeting on September 28th 2016, multiple sites demonstrated interest and the network decided to undertake the project. All participants within the Fellows Pelvic Research Network are based at academic institutions with sufficient volume to support fellowship training in Female Pelvic Medicine and Reconstructive Surgery. We are currently planning to recruit patients at MedStar Franklin Square Medical Center, Indiana University, Oklahoma University and UT Southwestern Medical Center in addition to MedStar Washington Hospital Center.

There may also be difficulty in adherence to treatment as patients may develop side effects to medical therapy or difficulty in adhering to the weekly schedule for PTNS causing them to stop treatment, these patients will be analyzed with intent to treat analysis. Patients who choose to stop therapy will be asked to fill out completion questionnaires at the time they inform their physician that they would like to stop treatment.

Patients who undergo PTNS often are MT failures thus they may have higher OAB baseline scores and possibly more sexual dysfunction, as patients and their physicians choose treatment in this study, this cannot be controlled for. However, there are many patients in our practice who choose to pursue PTNS as initial treatment as well as patients who choose to pursue MT with a second medication after trying a first. By excluding patients who have failed treatment with two prior medications (stopped unrelated to side effects), we aim to minimize differences between groups.

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