Project Title: A randomized controlled trial investigating the efficacy of percutaneous tibial nerve stimulation (PTNS) in the treatment of female sexual dysfunction (FSD)

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NCT04122703

Document date Approved: 6/2/2022

Approved: 6/2/2022
Expiration Date: 6/1/2023
Stony Brook University Human Subjects Committee (IRB)

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A randomized controlled trial investigating the efficacy of percutaneous tibial nerve stimulation (PTNS) in the treatment of female sexual dysfunction (FSD)

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A. SPECIFIC AIMS

Aim 1: To evaluate the effect of percutaneous tibial nerve stimulation (PTNS), compared to a validated sham, on sexual functioning in women with female sexual dysfunction (FSD).

Aim 2: To compare the effect of PTNS on lower urinary tract symptoms versus sexual functioning in patient with FSD.

B. BACKGROUND AND SIGNIFICANCE

Female Sexual Dysfunction (FSD), affecting approximately 40% of women in the United States, is characterized by pain or discomfort with intercourse, diminished sexual desire and impaired arousal (Allahdadi et al. 2009; Sifren et al. 2008). The resulting symptoms are often embarrassing for the patients and negatively impact their self-esteem (Basson 2005). Sexual functioning is affected by both the emotional and physical aspects of sexual experience, making FSD a multifaceted disorder. Despite the prevalence of FSD, there are few FDA-approved treatments available, and the ones that do exist have limitations and adverse side effects. Current treatment options for FSD include hormonal therapy, benzodiazepines, hypnotherapy, botulinum toxin type A injections and pelvic floor muscle exercises (Rogers, 2013; Ghazizadeh et al. 2004). Flibanserin, a serotonin receptor agonist that increases sex drive in patients, is the only FDA-approved drug for FSD. Although Flibanserin mitigates symptoms of FSD, it has many common adverse side-effects including drowsiness and dizziness. As there are multiple contributors to FSD, and the treatment options are limited, women with sexual dysfunction are often undertreated (Clayton et al. 2017).

Given the need for more treatment options for FSD, one potentially beneficial therapy is Percutaneous Tibial Nerve Stimulation (PTNS). PTNS is a minimally invasive treatment which works by delivering small amounts of electrical current through a percutaneous electrode inserted near the ankle. PTNS is currently FDA-approved for the treatment of Overactive Bladder (OAB). Interestingly, many patients with FSD suffer from comorbid OAB (Shaw 2002). In fact, patients with OAB who received PTNS treatment reported an improvement in their overall satisfaction, libido and frequency of sexual activities (Balken et al. 2006). in one study, 43% of OAB patients were more satisfied and more sexually active after receiving PTNS, as

evidenced by an increase in mean Female Sexual Function Index (FSFI) score from 18.11 to 31.04 (Musco et al., 2016). This improvement in FSD as noted by FSFI score is comparable to those seen in the trials of Flibanserin where the treatment group had improvements in FSFI score of 5.3 versus the 3.0 improvement of the placebo group (Katz et al. 2013). Additionally, it has been suggested that the improvements in sexual functioning seen in these studies were a direct result of the neuromodulation therapy, and not the secondary result of OAB treatment (Musco et al. 2016). However, a randomized controlled trial is required to further investigate the viability of PTNS as a treatment option for patients with sexual dysfunction.

In this study, we will assess the efficacy of PTNS, compared to a validated sham intervention, in treating patients with FSD. We will utilize the previously established placebo model for PTNS used in the Study of Urgent PC vs Sham Effectiveness in Treatment of Overactive Bladder Symptoms (SUmiT) (Peters et al. 2010). Given that PTNS has improved FSD symptoms in patients with OAB, we hypothesize that PTNS treatment will have a greater efficacy in treating FSD than the placebo (Balken et al. 2006; Musco et al. 2016). This study is the first of its kind, using a randomized placebo-controlled design to study the effect of PTNS on FSD. If proven effective, PTNS can be an additional therapy for sexual dysfunction in women, a condition for which not many treatment options exist. PTNS can be an extremely attractive alternative to the current FDA-approved treatments, as PTNS only has rare and transient side effects such as minor bruising or bleeding at the needle site.

C. RESEARCH DESIGN AND METHODS

1. Rationale/overview

The goal of this study is to evaluate the efficacy of PTNS in treating patients with FSD. We will be recruiting 66 patients, who will be randomized (1:1) to either the PTNS group or the Sham group. The patients in the PTNS group will receive one PTNS treatment per week for 12 weeks. The patients in the Sham group will receive one sham treatment per week for 12 weeks. Patients in both groups will be asked to complete questionnaires before the start of the treatment, as well as after 12-weeks of treatment to assess the changes in the severity of their symptoms.

2. Research Site

All patient evaluations and procedures are to be taken place in an outpatient clinic setting.

3. Study Sample

The study sample will be 66 women (18 years of age and older) with FSD. Our inclusion criteria will be patients with an FSFI score of ≤ 26.55, which is the clinical cutoff point for patients with

FSD (Wiegel et al. 2005). Patients must be sexually active within one month prior to the study and plans to continue to be sexually active for the next 12 weeks. Sexual activity can include masturbating, vaginal intercourse, caressing, and foreplay. Our exclusion criteria will be patients with anatomical limitations preventing successful placement of the electrode (bleeding disorders, peripheral vascular disease, ulcers, or lower leg cellulitis), medical disorders precluding stimulation (cardiac pacemakers, current use of Holter monitor, known history of neuropathy), pregnant women or women intending to become pregnant during the course of the study.

Patients will be recruited from the patient population with FSD seen at Stony Brook Medicine Women's Pelvic Health and Continence Center. We do not foresee any problems with recruiting patients, as this highly specialized center has 6 urologist and gynecologists who are fellowship-trained in female pelvic medicine, a colorectal surgeon and a pelvic floor physical therapist, performing more than 1500 PTNS sessions annually.

4. Screening

All interested patients will be screened based on the eligibility criteria.

5. Consenting

Explanation of the study and informed consent for the study will be obtained in a clinical setting by either the principal investigator or the co-investigators. Consent forms detailing the research protocol will be provided to patients who are eligible for the study in Dr. Jason Kim’s clinic. All questions and concerns regarding the study will be discussed with a clinician prior to signing of the consent. The clinician will also ensure the patient demonstrates an ability to use the information in a rational manner. The subject will verbalize that this study is research, that their decision to participate will not affect his or her care, and they can withdraw at any time.

As per standard of care (SOC) all patients will undergo procedural consent for receiving PTNS treatment. Patient coexisting therapy is evaluated, and they receive counseling on available treatments for FSD including Flibanserin, hormonal therapy, benzodiazepines, hypnotherapy, botulinum toxin type A injections, and pelvic floor muscle exercises. If any subject is currently on any alternative treatments, they will not be eligible to participate. Therefore, there is no need to control for treatments. Patients then are counseled about the benefits, alternatives and risks of PTNS. Risks are described as rare which may include needle site pain, minor bruising or bleeding, and a rare but possible risk of infection from needle insertion. Before starting the treatment, we will follow the SOC for patients who undergo PTNS including a pregnancy test, obtaining full history and physical exam, including a pelvic examination. A pelvic exam is a routine physical exam done to evaluate your reproductive organs such as your vulva, vagina, ovaries, uterus and rectum. It is done to assess your gynecological health. There is minimal risk

involved in a pelvic exam but there is a chance of infection, pain, and discomfort on examination. Patients will also be asked about pregnancy and planning to become pregnant prior to their enrolment in the study and initiating treatment. A negative pregnancy test is mandated for women of childbearing age at the point of enrolment. If a subject is post-menopausal for at least one year, they will not be required to undergo a urine pregnancy test.

6. Procedures

The patients will be randomized into two groups, the PTNS group and Sham group. The patients in the PTNS group will receive one PTNS treatment per week for 12 weeks. The patients in the sham group will receive one sham treatment per week for 12 weeks.

The PTNS and the sham treatments will be given in 30 min sessions. The PTNS treatment consists of inserting a 34-gauge needle electrode approximately 5 cm cephalad to the medial malleolus and, as well as placing a PTNS surface electrode (sticker) on the ipsilateral calcaneus. To keep the electrode placement consistent with the sham treatment, 2 inactive transcutaneous electrical nerve stimulation (TENS) surface electrodes are also added, 1 placed under the big toe and 1 on the top of the foot. The PTNS lead set is connected to the Urgent PC stimulator, and a current level of 0.5 to 10 mA at 20 Hz is delivered until the flexion of the big toe is observed or the patient reports a radiating sensation at the sole of the foot.

The sham treatment, as previously described by Peters *et al.,* involves simulating the sensation of the PTNS needle insertion at the same location using a Steritberger placebo needle that does not pierce the skin. To place the placebo needle, a washer with tape is placed behind the ankle where the needle will pierce the tape to hold it in place. A PTNS surface electrode (sticker) is also placed on the ipsilateral calcaneus, similar to the active treatment. Like the active treatment, two TENS surface electrodes (stickers) are placed, one on the top of the foot and another underneath the big toe. The two TENS surface electrodes placed in the same location as the PTNS treatment are active, and deliver stimulation mimicking the sensory effects of the PTNS. However, since there are no electrode needles were inserted near the tibial nerve, there will be no tibial nerve stimulation (Peters et al. 2009).

Participants will be compensated $200 upon the completion of the 12 weekly sessions. In the event that patient does not complete all study visits, payment will be prorated to reflect the number of sessions completed. Patients and their insurances will not be charged for anything related to the study. All visits and study-related interactions will be free of charge.

7. Outcome Measures

Our primary endpoint is the change on the Female Sexual Function Index (FSFI) from the baseline, after 6 weeks, and after 12 weeks of treatment. FSFI is a 19-item questionnaire used to assess female sexual function (Rosen et al. 2000). We define responder as a patient reporting a clinically relevant difference of 5 points on the FSFI, assuming a standard deviation of 10.

Our secondary endpoints are the changes on the Prolapse/Urinary Incontinence Sexual Function Questionnaire(PISQ- 12), Arizona Sexual Experiences Scale (ASEX), and Urogenital Distress Inventory (UDI-6) from the baseline, after 6 weeks, and after 12 weeks of treatment. PISQ-12 is a 12-item questionnaire used to assess sexual function in women with pelvic organ prolapse or urinary incontinence (Rogers et al. 2003). ASEX is a 5-item questionnaire scored used to quantify sex drive, vaginal lubrication, and satisfaction from orgasm (McGahueyet al. 2000). UDI-6 is a 6-item questionnaire used to assess lower urinary tract symptoms in women (Lemack et al. 1999).

D. STATISTICS

A sample size estimate of approximately 66 subjects, 33 per study arm, was calculated using a 2-sided Fisher's exact binomial test based on an estimated 85% responder rate for the PTNS group and a 50% responder rate in the sham group, with a 5% significance level and 80% power. We define responder as a patient reporting a clinically relevant difference of 5 points on the FSFI after treatment, assuming standard deviation of 10. T-test will be used to compare the mean change from the baseline in FSFI score in the PTNS group versus the sham group.

E. FUNDING STATUS

This is an investigator-initiated study funded by a grant from the Society of Urodynamics, Female Pelvic, and Urogenital Reconstruction (1159437-1-87301).

F. DATA AND SAFETY MONITORING PLAN

Oversight Responsibilities

This is a randomized controlled trial involving application of an intervention with minimal risk. The oversight of the trial is provided by the Principal Investigator (PI), Dr. Jason Kim, and co-investigator, Sina Mehraban Far.

Monitoring Procedures

The PI, Dr. Jason Kim, assures that informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan.
Study data are accessible at all times for the PI and co-investigator to review. The PI reviews study conduct including accrual, drop-outs and protocol deviations on a monthly basis. The PI reviews AEs individually real-time and in aggregate on a monthly basis. The PI reviews serious adverse events (SAEs) in real-time. The PI ensures all protocol deviations, AEs, and SAEs are reported to the IRB according to the applicable regulatory requirements.

Collection and Reporting of SAEs And AEs
For this study, the following standard definitions are used:
Unanticipated problems involving risks to participants or others refer to any problem, event, or new information that:
1. Is unexpected (in terms of nature, severity, or frequency) given the research procedures that are described in the protocol-related documents, such as the CORIHS-approved research protocol and informed consent documents; and the characteristics of the subject population being studied; and
2. Indicates that subjects or others are at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

An Adverse Event (AE) is defined as any untoward physical or psychological occurrence in a human subject participating in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom or disease associated with the research or the use of a medical investigational test article.
A Serious Adverse Event (SAE) is defined as death; a life-threatening experience; hospitalization (for a person not already hospitalized); prolongation of hospitalization (for a patient already hospitalized); persistent or significant disability or incapacity; congenital anomaly and/or birth defects; or an event that jeopardizes the subject and may require medical or surgical treatment to prevent one of the preceding outcomes.

AEs are graded according to the following scale:
Mild: An experience that is transient, and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. This includes transient laboratory test alterations.
Moderate: An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes laboratory test alterations indicating injury, but without long-term risk.
Severe: An experience that requires therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment it becomes an SAE.

The study uses the following AE attribution scale:
Not related: The AE is clearly not related to the study procedures (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).
Possibly related: An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.
Related: The AE is clearly related to the study procedures.

Potential AEs are identified during each weekly visit as the subject undergoes PTNS or placebo treatment.
The PI will follow the guidelines, procedures and reporting timelines as stated in section 8.3 of Stony Brook University's Human Research Protection Plan (HRPP). The IRB will be notified of any unanticipated problems involving risk to subjects and SAEs (this is highly unlikely) within 24 hours. Whereas, minor AEs such as needle site pain, minor bruising or bleeding, and a rare but possible risk of infection from needle insertion will be summarized in the protocol annual report.

Management of Risks to Subjects

Expected AEs

Expected AEs associated with PTNS include:

- Needle site pain, minor bruising or bleeding, and a rare but possible risk of infection from needle insertion

AE Management

The principal investigator will be notified immediately of any adverse effects of subject participation and will insure that medical attention is provided either through the subject's personal physician or through UHMC.

Data Analysis Plans

The PI or the co-investigator will review all data collection forms on an ongoing basis for data completeness and accuracy as well as protocol compliance. Review of the rate of subject accrual and compliance with inclusion/exclusion criteria will occur monthly to ensure that a sufficient number of participants are being enrolled and that they meet eligibility criteria. Data on adherence to the treatment protocol will be collected weekly by the co-investigator and reviewed monthly by the PI. Adherence of participants will be evaluated by monitoring the rate of attendance at the required weekly visits. This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention (this is highly unlikely); (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

Patient Confidentiality

All investigators have completed all the required Human Subject Training and will observe HIPAA regulations regarding patient health information. Patients may choose to withdraw from the study at any time without affecting their treatment.
The patients will fill out the questionnaires on a digital interface administered on Apple iPads. The data collected will be stored on REDCap, which is a HIPAA-compliant and secure web application for building and managing online surveys and databases.

G. LITERATURE CITED

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