

Surface Stimulation for Female Sexual Dysfunction  
NCT02692417  
Study Protocol  
October 15, 2016

## Research Design and Methodology

### Design overview

We have planned a randomized pilot study to evaluate the use of two skin-surface electrical stimulation approaches for improving sexual arousal. Subjects will be assigned one of two stimulation approaches and will receive the experimental treatment during a twelve-week test period. Standard sexual function and quality of life surveys will be completed at key time points to evaluate the effects of the experimental stimulation as compared to before study initiation and to look for any long-term residual effect. Participants will also be given a demographics questionnaire once during the study, so that we can evaluate possible stratification among participants and stimulation responders.

### Description of methods and analysis

Patients will be randomly assigned to one of two study groups: receiving DGNS or PTNS. In this pilot study, as has been standard for prior pilot evaluations of DGNS and PTNS [1-5], we will not have a control stimulation paradigm that does not activate the nerves of interest. While this control stimulation is desired for an ultimate demonstration of this approach, its design will be outside the scope of what is feasible with these pilot funds. To date there has only been a single controlled evaluation of PTNS which also included a control stimulation paradigm [6]. We plan to emulate that approach after demonstrating feasibility here. See Figure 1 for the study paradigm.

For subjects assigned to the dorsal genital nerve stimulation test group, electrodes will be placed as in Figure 2. Electrodes will be standard TENS skin-surface electrodes that are 2 cm in diameter. Test electrodes will be placed on either lateral side of the clitoris, with not more than 5 mm to each electrode edge, with cathode indifferent. At the first stimulation session, the pudenda-anal threshold ( $PA_T$ ) for driving reflex closure of the anal sphincter will be determined by starting with a 5 mA, 1 Hz stimuli through the test electrodes and increasing in 5 mA steps until sphincter closure is observed. Thereafter, test stimulation will be applied at 20 Hz and  $2 \times PA_T$  or below a level at which the subject notes discomfort, whichever is lower. The anticipated test amplitude is within 30 – 60 mA [7-9]. After placement of electrodes and draping of the region, stimulation will be applied for 30 minutes in each session.

For subjects assigned to the posterior tibial nerve stimulation test group, the same electrodes as for DGNS will be placed as in Figure 3. The test electrodes will be placed just above the medial malleolus (cathode) and the ipsilateral calcaneus (anode). At the first stimulation session, the test electrode stimulation level will be determined with 1 Hz stimulation at 5 mA and increased in 5 mA levels until a rhythmic flexion of the toes is observed or the patient notes discomfort. Thereafter the test stimulation will be a level just below that at which the motor or discomfort responses occurred [2]. After placement of electrodes and draping of the region, the appropriate stimulation will be applied for 30 minutes in each session. Dr. Berger will place the electrodes on subjects at each appointment.

Stimulation effects on sexual arousal are unlikely to be observed in the clinic. If this study is successful, future proposals to investigate underlying mechanisms may evaluate in vivo effects with animal models. We will have subjects complete four standard surveys as has been done for other

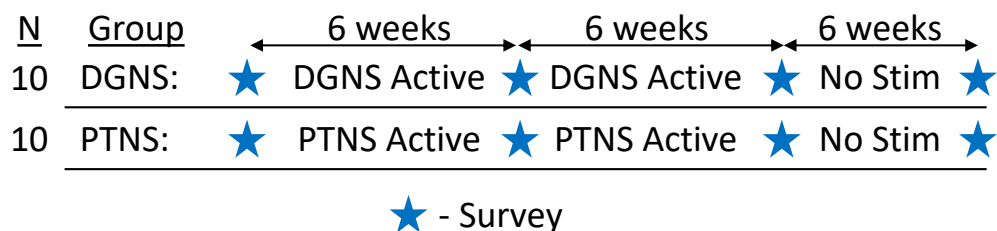


Figure 1. Study paradigm. Subjects will be randomized into one of two test groups (DGNS/PTNS). Sexual Function and Quality of Life surveys will be taken at study initiation and at 6-week intervals afterwards. The final 6-week period of no stimulation will look for long-term carry over.

neuromodulation studies [1], [6], [10-12]. The Female Sexual Function Index (FSFI) is a standardized survey with 19 questions on sexual health that provides a maximum score of 36 [13] (See Appendix 1 for survey). The short form 36-question (SF-36) quality of life survey was designed for general use in clinical practice [14] and will be used here to assess overall impact (See Appendix 2 for survey). The Measure of Symptoms - American Urological Association Symptom Index is a standardized 8-question survey assessing urologic concerns. The Patients' Global Impression of Change (PGIC) Scale is a 1-question survey designed to assess patients' feelings of improvement after intervention. Subjects will take the four surveys before study initiation (baseline), after each of concurrent 6-week stimulation sessions in the clinic (6weeks; 12weeks), and six weeks after study completion (long-term).

Due to the relatively small sample sizes planned for this study, we will use non-parametric statistical testing. We will use a two-sided Wilcoxon rank sum test to make comparisons of the survey scores among the different subject groups [1], [6], [8], [15], with a significance level of 0.05. FSFI and SF-36 scores will be compared for each of the potential comparisons among the baseline, 6-week and 12-week study time points and at long-term time point, for DGNS and PTNS groups separately.

We plan for a total study size of 30 subjects. 15 subjects will be assigned to each stimulation group – DGNS and PTNS. As this is a pilot study that has not been performed before, we do not have an effect size from which to calculate a target sample size. This study size of 15 subjects for each stimulation approach was selected for two reasons. Our primary factor was that prior pilot studies using these stimulation approaches for other patient groups used similar study sizes of 9-10 subjects [3-4], [8-9]. Our secondary factor was that given the one-year time frame of our planned study, larger sample sizes may not be feasible. If one or both stimulation approaches are successful, larger sample sizes will be performed in subsequent studies.

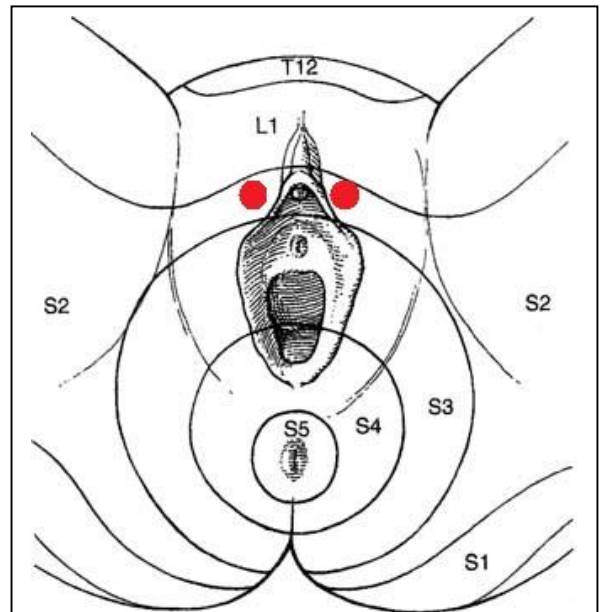


Figure 2. DGNS electrode locations. For experimental DGNS, the TENS unit will be connected to electrodes placed on either side of the clitoris.

### Potential difficulties

We anticipate several potential difficulties with these planned studies. Patient compliance may be an issue, as the need to visit the clinic for 12 consecutive weeks may be a burden. We may adjust the study budget (or draw from Dr. Bruns' startup funds) to allocate funds to pay for daily parking (~\$7) and to give a lump sum upon completion of the study (\$50) to each subject. As other PTNS studies use weekly study durations, sometimes with much larger sample sizes, we expect that a similar willingness will occur here.

It is possible that patients find the planned stimulation amplitudes (e.g.  $PA_T$  or  $2 \times PA_T$ ) to be uncomfortable. As it is not our goal to explore optimal stimulation parameters here, we will keep current levels as low as necessary to maintain subject comfort.

It is possible that transient genital arousal or pain may occur in the clinic directly as a result of the applied electrical

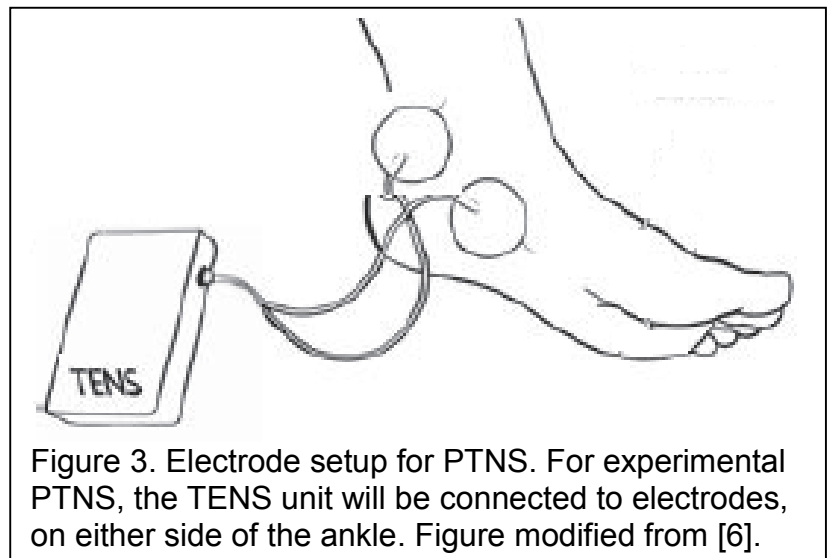


Figure 3. Electrode setup for PTNS. For experimental PTNS, the TENS unit will be connected to electrodes, on either side of the ankle. Figure modified from [6].

stimulation. To protect subject privacy and modesty, we will ensure that subjects are located in private rooms and left alone for the duration of applied stimulation. Subjects will be given a method to report uncomfortable side effects if they should occur. At the conclusion of each session, we will survey subjects as to any transient pain or arousal to compare effects over time.

It is possible that patients attending Dr. Berger's clinic do not have intercourse frequently enough to be eligible for the study ( $\geq 1$  time per month). If we observe that occurrence through the first month of recruitment (3 clinics) then we will relax the criteria to be a desire to have intercourse several times per month. Conversely, it is possible that subjects who have intercourse 1-2 times a month may not provide sufficient perspective on the efficacy of the stimulation for improving arousal. We will observe for this potential trend during the first 5-10 patients and will adjust the inclusion criteria threshold upwards as necessary.

It is possible that patients may develop psychological discomfort during the research intervention. To reduce this risk, patients will be fully informed about the treatment regimen, such as the fact that they may have a doctor placing leads on their genitals every week. They will also be reminded that their continued participation is voluntary. If psychological trauma is raised, patients will be referred to our sexual health therapists for treatment. Casey O'Gara is a registered nurse and sexual health therapist who does such therapy and is part of the study team.

### Collection, analysis and interpretation of results

Each study subject will be assigned an identification number. Only this number will be used to identify subjects in any individual tabulation. It is expected that only group data will be published. If individual subject data is to be published, no identifying information will be included. The study files will be maintained in a secure location. Access to computerized data will be restricted to IRB-approved study personnel. Password authorization will be enforced.

The study coordinator or other research team staff will provide both the FSFI and the SF-36 surveys to each subject, in paper form, upon their initiation into the study. Subjects will be given up to an hour to complete the survey by circling their responses on the paper form. The form for each subject will have the identification number as the only identifying piece of information on it. This same sequence will be performed at the other data collection points – after 6 weeks of testing (in the clinic before the 7<sup>th</sup> stimulation session) and after the 12<sup>th</sup> session. For the 6-week post-trial follow-up, a research staff will contact each subject to complete the survey over the phone, or will allow the subject to complete the survey and mail back in if they will not be visiting the clinic during that time.

As described in the appendices, each survey has a scoring method that yields a total quality of life score and a total sexual satisfaction score. These scores will be compared across the different time points as discussed above. The study team will meet with a statistical consultant (UM Center for Statistical Consulting and Research) to confirm correct approaches and conclusions. The study team will also compare the results found to other reported studies in the literature that used similar methods and analysis approaches for consistency. As described in the appendices, each survey has sub-sections that we may compare individually, if the data suggests any sub-section trends.

Data collection will be limited to the investigators and the research staff. All study personnel who have access to the data will be educated regarding the need to protect confidentiality and the procedure to be followed to ensure such protection. All staff will also be required to sign a standard medical record confidentiality agreement.

### Description of any new methods and why an improvement

Currently there are no neuromodulation therapies available to address sexual arousal. Our approach of translating an approach validated for other pelvic organs represents a new direction in this field. Furthermore, these periodic clinic stimulation sessions, if efficacious, may lead to novel non-regular sessions that reduce the load on patients or potentially to small minimalist implants that provide more user control. Either of these approaches would represent a novel approach in the field.

## Recruitment & Retention Plan

### Population characteristics

The proposal involves a 30-subject prospective study of surface electrode stimulation (dorsal genital nerve or posterior tibial nerve) weekly sessions for improving sexual arousal. As described below, adult women over the age of 18 who are neurologically stable and have intercourse at least once a month will be candidates. Typical patients will likely be in excess of 40 years of age. During each stimulation session, subjects will be reclined in a chair or examination table and will have electrodes placed at the appropriate location. After setting of parameters, stimulation will be applied for 30 minutes in duration.

We will be recruiting patients primarily from Dr. Berger's pelvic pain clinic as described below. The characteristics of the patients include dyspareunia (pain with intercourse), and/or pelvic or bladder pain. The bulk of Dr. Berger's pain in this clinic (~5 new patients each session, plus similar numbers of return visits) have pain with intercourse and pelvic pain as major components of their complaints. There is a sexual health therapist present in the clinic who sees most of the new patients, so we will have a psychosocial evaluation for many of them.

Patients will also be recruited from the OB/GYN clinic, other sex therapists' clinics, and UHS.

### Sampling plan

We will seek patients who meet the study inclusion and exclusion criteria. Due to the relative short timeframe of this study length, we will not perform any random sampling of potentially eligible patients and will approach each candidate on a first come first serve system. There are no ethnic distributions of targeted/planned enrollment.

### Inclusion criteria

- Adult women  $\geq 18$  years of age
- Sexually active  $\geq 1$  time per month ( $\geq 2$  times per month preferred)
- Having sexual dysfunction as identified by a score of 19 or less on the FSFI-6 [16].

For each question: Over the past four weeks...						
How would you rate your level (degree) of sexual desire?		Very high (5)	High (4)	Moderate (3)	Low (2)	Very low or none at all (1)
How would you rate your level of sexual arousal ("turn on") during sexual activity or intercourse?	No sexual activity (0)	Very high (5)	High (4)	Moderate (3)	Low (2)	Very low or none at all (1)
How often did you become lubricated ("wet") during sexual activity or intercourse?	No sexual activity (0)	Almost always or always (5)	Most times (4)	Sometimes (3)	A few times (2)	Almost never or never (1)
When you had sexual stimulation or intercourse, how often did you reach orgasm?	No sexual activity (0)	Almost always or always (5)	Most times (4)	Sometimes (3)	A few times (2)	Almost never or never (1)

How satisfied have you been with your overall sexual life?	Very satisfied (5)	Mod-erately satisfied (4)	About equally satisfied and dissatisfied (3)	Mod-erately dissatisfied (2)	Very dissatisfied (1)	
How often did you experience discomfort or pain during vaginal penetration?	Did not attempt intercourse (0)	Almost never or never (5)	A few times (4)	Some-times (3)	Most times (2)	Almost always or always (1)

- Neurologically stable
- Ambulatory
- Capable of giving informed consent
- English speaking
- Capable and willing to follow study procedures

### Exclusion criteria

- Pregnant or planning to get pregnant during the study period
- Clinically diagnosed neurological bladder dysfunction
- Prior experience with PTNS or DGNS
- Use of TENS on pelvis, back or legs
- Implanted pacemaker, defibrillator, spinal cord stimulator, or sacral root stimulator
- Vaginal infection
- Coagulation disorders
- Taking any investigational drug

### Recruitment and retention

Potential subjects will be recruited from an investigator’s clinic or related clinics. Only inclusion/exclusion criteria that are provided by the patient as part of their check-in procedures or prior visits will be used to make a decision to approach a potential study subject. If a patient expresses interest in the study, then eligibility based on the full inclusion/exclusion criteria list will be verified.

The study coordinator/nurse will follow up with the patient to schedule the stimulation sessions and will administer the baseline surveys (American Urological Association Symptom Index - AUA, Female Sexual Function Index – FSFI, Short Form Health Survey – SF-36) via mail or email. Informed consent will be obtained in person at the first stimulation session, prior to any intervention. After each session, the coordinator will remind subjects of subsequent meetings.

Patient personal information will be protected per HIPAA guidelines.

### Plan for recruitment, informed consent process

Eligible subjects will be identified through the treating physicians, and will be recruited in clinic by a study coordinator or team member. Dr. Berger has a pain clinic on the 1<sup>st</sup>, 3<sup>rd</sup>, and 5<sup>th</sup> Tuesday afternoon of each month at the Von Voigtlander clinic that is called the Female Pelvic and Urinary Pain clinic. Dr. Berger runs this clinic with Dr. Ann Oldendorf from Urology. In addition, Dr. Berger and his partners have general urogynecology clinics at which subjects could be recruited.

Prior to the initiation of the study, an IRB approval for the study of human subjects will be obtained. The consent form will include all of the elements required by the FDA and state, local, and institutional regulations. Comprehensive written consent will be obtained from subjects prior to participation. A study coordinator or investigator will approach subjects to obtain informed consent.

Open, witnessed and non-coercive discussion will be undertaken prior to signing of the consent document.

## References

1. V. Vandoninck, M. R. van Balken, E. Finazzi Agro, F. Petta, F. Micali, J. P. F. A. Heesakkers, F. M. J. Debruyne, L. A. L. M. Kiemeneij, and B. L. H. Bemelmans, "Percutaneous tibial nerve stimulation in the treatment of overactive bladder: urodynamic data," *Neurourol. Urodyn.*, vol. 22, no. 3, pp. 227–232, 2003.
2. G. Amarenco, S. S. Ismael, A. Even-Schneider, P. Raibaut, S. Demaille-Wlodyka, B. Parratte, and J. Kerdraon, "Urodynamic effect of acute transcutaneous posterior tibial nerve stimulation in overactive bladder," *J. Urol.*, vol. 169, no. 6, pp. 2210–5, Jun. 2003.
3. D. B. Vodusek, J. K. Light, and J. M. Libby, "Detrusor inhibition induced by stimulation of pudendal nerve afferents," *Neurourol. Urodyn.*, vol. 5, no. 4, pp. 381–389, 1986.
4. J. Previnaire, J. Soler, M. Perrigot, G. Boileau, P. Schumacker, J. Vanvelcenaher, and J. Vanhee, "Short-term effect of pudendal nerve electrical stimulation on detrusor hyperreflexia in spinal cord injury patients: importance of current strength," *Paraplegia*, vol. 34, pp. 95–99, 1996.
5. H. B. Goldman, C. L. Amundsen, J. Mangel, J. H. Grill, M. Bennett, K. J. Gustafson, and W. M. Grill, "Dorsal genital nerve stimulation for the treatment of overactive bladder symptoms," *Neurourol. Urodyn.*, vol. 27, no. 6, pp. 499–503, 2008.
6. K. M. Peters, D. J. Carrico, R. A. Perez-Marrero, A. U. Khan, L. S. Wooldridge, G. L. Davis, and S. A. Macdiarmid, "Randomized trial of percutaneous tibial nerve stimulation versus sham efficacy in the treatment of overactive bladder syndrome: results from the SUmIT trial.," *J. Urol.*, vol. 183, no. 4, pp. 1438–43, May 2010.
7. E. Opisso, A. Borau, and N. Rijkhoff, "Subject-controlled stimulation of dorsal genital nerve to treat neurogenic detrusor overactivity at home," *Neurourol. Urodyn.*, vol. 32, pp. 1004–1009, 2013.
8. J. Worsøe, L. Fynne, S. Laurberg, K. Krogh, and N. J. M. Rijkhoff, "Acute effect of electrical stimulation of the dorsal genital nerve on rectal capacity in patients with spinal cord injury," *Spinal Cord*, vol. 50, no. November 2011, pp. 462–466, 2012.
9. J. Worsøe, L. Fynne, S. Laurberg, K. Krogh, and N. J. M. Rijkhoff, "Electrical stimulation of the dorsal clitoral nerve reduces incontinence episodes in idiopathic faecal incontinent patients: A pilot study," *Color. Dis.*, vol. 14, pp. 349–355, 2012.
10. D. Signorello, C. C. Seitz, L. Berner, E. Trenti, T. Martini, A. Galantini, L. Lusuardi, M. Lodde, and A. Pycha, "Impact of sacral neuromodulation on female sexual function and his correlation with clinical outcome and quality of life indexes: a monocentric experience.," *J. Sex. Med.*, vol. 8, no. 4, pp. 1147–55, Apr. 2011.
11. G. Lombardi, N. Mondaini, A. Macchiarella, A. Cilotti, and G. Del Popolo, "Clinical female sexual outcome after sacral neuromodulation implant for lower urinary tract symptom (LUTS).," *J. Sex. Med.*, vol. 5, no. 6, pp. 1411–7, Jun. 2008.
12. M. S. Ingber and H. B. Goldman, "Neuromodulation and Sexual Function in Women," *Curr. Bladder Dysfunct. Rep.*, vol. 5, no. February, pp. 27–31, 2010.
13. R. Rosen, C. Brown, J. Heiman, S. Leiblum, C. Meston, R. Shabsigh, D. Ferguson, and R. D'Agostino, "The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function.," *J. Sex Marital Ther.*, vol. 26, no. March 2015, pp. 191–208, 2011.
14. J. E. Ware and C. D. Sherbourne, "The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection.," *Med. Care*, vol. 30, no. 6, pp. 473–483, 1992.
15. S. Gokyildiz, N. Kizilkaya Beji, O. Yalcin, and A. Istek, "Effects of percutaneous tibial nerve stimulation therapy on chronic pelvic pain," *Gynecol. Obstet. Invest.*, vol. 73, pp. 99–105, 2012.

16. A.M. Isidori, *et al.* "Development and validation of a 6-item version of the female sexual function index (FSFI) as a diagnostic tool for female sexual dysfunction." *J. Sex. Med.* **7**, 1139–1146 (2010).