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Chronic Electrical Stimulation to Reduce Bladder Hyperreflexia
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Steven Brose, DO

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List of Abbreviations

AD: autonomic dysreflexia

EMG: electromyography

FES: Functional Electrical Stimulation

GNS: genital nerve stimulation

LSCDVAMC: Louis Stokes Cleveland Department of Veterans Affairs Medical Center

SCI: spinal cord injury

SVAMC: Syracuse Veterans Affairs Medical Center

UTI: urinary tract infection

Protocol Title: Chronic Electrical Stimulation to Reduce Bladder Hyperreflexia

Study Personnel:

PI: Steven Brose, DO, Chief of the SVAMC SCI Unit

Co-Investigators: Dennis Bourbeau, PhD, Investigator and Biomedical Engineer at Cleveland FES center and LSCDVAMC.

Study Purpose

The goal of the proposed study is to determine the clinical effectiveness of chronic genital nerve stimulation (GNS) in persons with spinal cord injury (SCI) and neurogenic bladder overactivity. By using take-home stimulation devices, the long-term effectiveness of GNS for increasing bladder capacity and decreasing incontinence episodes can be tested. If effective, chronic GNS has the potential to serve as a non-invasive treatment alternative in the management of bladder overactivity and increase quality of life for those with SCI and neurogenic bladder. This project was initiated at the Louis Stokes Cleveland Department of VA Medical Center (LSCDVAMC) and has been extended to the Syracuse VA Medical Center (SVAMC) by Dr. Brose.

Literature Review and Study Objective

Neurogenic bladder is among the most common complications associated with spinal cord injury, multiple sclerosis and stroke. Neurogenic bladder frequently leads to urological complications, such as incontinence, urinary tract infection, renal damage and subsequent renal dialysis or transplantation. “Turning off” the bladder (i.e. reducing reflex voiding and spasticity of the bladder, decreasing bladder pressures and increasing bladder capacity) has the potential to reduce the number and severity of these complications. Current methods for improving bladder function in persons with neurogenic bladder, including pharmacologic and surgical interventions, are incompletely effective. The objective of this work is to decrease bladder hyper-reflexia using electrical stimulation of the genital nerve.

This work is directly applicable to the health, well-being, and functional independence of the disabled veteran. Although about 11% of Americans are veterans, 25% of all individuals with spinal cord injuries in the United States are veterans (Berkowitz & Harvey et al., 1992). In addition to being a debilitating and costly condition, paralysis compromises the ability to work, engage in social or leisure activities, pursue an education, or participate in other activities associated with an independent and productive lifestyle (Berkowitz & Harvey et al., 1992). Multiple sclerosis and stroke can also result in neurogenic bladder, with incidence rates of approximately 3,000 new cases of multiple sclerosis per year in the veteran population (Wallin et al. 2012) and

610,000 new cases of stroke per year in the general population (American Heart Association 2012).

Bladder inhibition and continence have been demonstrated using genital nerve stimulation (GNS) in acute studies. Wheeler et al. used surface electrodes to stimulate the genital nerve and showed significant increases in bladder filling volume during cystometrography (Wheeler & Walter et al., 1992) and this was confirmed by Previnaire and colleagues (1996) who further discussed carry-over benefits from the stimulation, even after stimulation was terminated (Craggs & McFarlane, 1999). Goldman, Gustafson, Grill and colleagues (2008) performed a 7-day GNS series with percutaneous electrodes in women with overactive bladder and found it to be helpful for reducing overactive bladder symptoms with minimal side effects of bruising and irritation at the penetrating electrode sites. A meta-analysis conducted by Bourbeau et al. (2017) further supports the ability of GNS to strongly inhibit bladder contractions and improve bladder capacity in clinically significant levels.

Study Objective. *Determine the long-term ability of GNS to reduce incontinence and improve quality of life in individuals with SCI.*

Cleveland Functional Electrical Stimulation (FES) Center investigators have chronically tested GNS in one individual with SCI and neurogenic bladder overactivity, using skin surface electrodes connected to a portable battery-powered stimulator. Stimulation was applied by the subject for 30-60 seconds whenever he sensed a bladder contraction. He kept a voiding diary for three weeks recording bladder sensation, incontinence, and volumes obtained by intermittent catheterization. Stimulation increased bladder capacity, resulting in more time between catheterizations, improved continence, allowance of the user to increase his fluid intake, and reduced usage of an external device for collecting urine when going out of the house (Lee & Creasey, 2002). The subject continued to use the device after the study and anecdotally reported that his bladder management improved over a few months of use.

More recently, Cleveland FES Center investigators chronically tested GNS in 3 subjects over the course of 1 year. These subjects were involved in a study initially testing take-home GNS over a 1-month period and opted to continue using the take-home stimulation device for 1 year. Subjects returned at 6-months and 12-months for follow-up urodynamics examinations. Before GNS, all 3 subjects averaged 1-2 leak events per day and after 1 year of GNS they reported almost complete urinary continence. GNS was consistently effective when tested during each urodynamics visit and stimulation settings did not change over the course of the study (Bourbeau, Gustafson, & Brose, 2017). The subjects stated that GNS gave them more freedom and independence. Subject 3 reported that some of his experienced benefits included going for longer car rides and attending his grandson's football games sitting in the bleachers remaining

continent instead of sitting in the car with a urinal. All 3 subjects expressed a desire to continue using GNS and were interested in implanted GNS.

The proposed study aims to further investigate the effectiveness and feasibility of chronic GNS using take-home stimulators. Tracking the effectiveness and complications associated with chronic home stimulator use will advance our long-term goals of optimizing home stimulator design and developing an implantable GNS system as an alternative treatment method for neurogenic bladder. This work is a continuation of the work done by Cleveland FES Center investigators at the LSCDVAMC.

Proposed Hypotheses

Study Objective: Determine the long-term ability of GNS to reduce incontinence and improve quality of life in individuals with SCI.

Hypothesis 1.1: GNS will increase bladder capacity and decrease incontinence episodes over one year of extended testing

Hypothesis 1.2: Subjects will need to catheterize less frequently and will be able to intake more fluids than they did before GNS

Hypothesis 1.3: GNS will have a beneficial effect on quality of life, as shown by periodic standard surveys taken by subjects

Resources and Personnel

All urodynamics testing will occur at the SVAMC, in a designated private room in the SCI wing. All other study activities will take place outside of the SVAMC, as the participants will be using the stimulator in the course of normal day-to-day activities. All equipment used for urodynamics testing will be VA clinical equipment.

Recruitment of subjects will be done by the PI, who will identify potentially eligible participants receiving SCI treatment at the SVAMC. Once potential subjects are identified, informed consent will be obtained by a research assistant or nurse. A research assistant will also be responsible for administering questionnaires and maintaining ongoing contact with participants. All urodynamics testing will be done by the PI and SCI nurses approved on the study.

Study Procedures

1. Study Design

Experiments will be conducted in up to 40 individuals with suprasacral SCI. 140 subjects can be screened and up to 40 subjects enrolled to ensure that 16 complete the study between the SVAMC and the LSCDVAMC. Due to the nature of this study, no

control group will be implemented. All participants will undergo the same acute urodynamics testing and will receive fully functional take-home stimulators programmed to the parameters determined during acute testing. The LSCDVAMC has its own approved IRB protocol, which will cover all participants run at that location.

Risks/Benefits of Participation

Risks (in relative decreasing order of significance):

a) Elevated blood pressure or Autonomic Dysreflexia (AD)

There is a risk in subjects with spinal cord injury of elevation of blood pressure when the bladder is distended or contracting. This is due to autonomic dysreflexia and the risk is dependent on the neurological level of spinal cord injury, being of relatively little significance with lesions below T6 but of increasing significance with higher lesions, and is well-known in clinical urodynamic testing. The elevation of blood pressure is occasionally asymptomatic but is usually associated with symptoms such as flushing of the face, nasal congestion, and headache and is well-known to most subjects with spinal cord injury. If untreated it can result in stroke or death.

This risk will be minimized by ensuring that subjects are familiar with the condition and its prevention and management and if necessary providing them with the standard medications used for its management. During urodynamics testing in this study, the risk will be minimized by monitoring blood pressure with automatic measurement at least every five minutes, by stopping bladder filling and emptying the bladder in the event of substantial rises in blood pressure, and by utilizing the standard AD protocol in place in the SCI outpatient clinic. If emptying the bladder does not sufficiently lower blood pressure, the SCI nurses and physicians present during testing will have medication on hand for rapid treatment (e.g. sublingual nifedipine or cutaneous nitropaste).

b) Urinary tract infection

There is a risk of approximately less than 10% that a subject will develop a urinary tract infection (UTI) following urodynamics in this study as a result of catheterization for this study. This risk will be minimized by performing catheterization with sterile technique. If the subject experiences signs or symptoms of a UTI (such as blood in the urine, frequency, urgency, increased spasms, fever, chills, and/or pain in the lower back) after the study, they will be instructed to contact a member of the study team. The subject will be examined and treated, if necessary, with the appropriate antibiotic. Possible side-effects of antibiotic treatment include infection such as clostridium difficile colitis, allergic reactions, diarrhea, nausea, kidney injury, or inadequate treatment of the infection. The PI will monitor antibiotic treatment and any side effects will be addressed with standard of care treatment.

c) Urethral trauma

There is a small risk, which we estimate at approximately 2%, that a subject will experience mild trauma to the urethra as a result of catheterization for this study. Such trauma might result in a small amount of bleeding from the surface of the urethra,

similar to that seen from the gums on vigorous tooth-brushing. This risk will be minimized by lubricating the catheter with sterile water-soluble gel and by careful catheterization technique. Many individuals catheterize themselves multiple times per day and therefore the risk in these subjects is not significant.

d) Tissue burn

There is a very small risk that skin electrodes for electrical stimulation or recording could cause a tissue burn. This risk is very low because of the level of electrical stimulation and safety testing of the equipment. The safety of the complete electrical set up will be tested and documented before any testing is done. Periodic biomedical safety checks will be performed for the intended use of all equipment used during these studies. There have been no burns associated with application of this variety of electrical stimulation in approximately 50 years of experience; however, in the rare instance that a burn does occur, the participant will be examined by the PI and an SCI nurse in the outpatient clinic, where an appropriate topical burn treatment will be selected – typically consisting of a topical antimicrobial agent with a moisture-retaining dressing.

e) Skin irritation

There is a slight risk of skin irritation from the electrodes applied to the skin for electrical stimulation or from the gel used to assist in conducting the electricity. This will be minimized by using electrodes that are not known to be allergenic, and by using gel that is commonly used for other types of electrical stimulation and recording. The electrodes applied to the skin surface do not come into contact with the saline solution or urine.

f) Exposure to uncomfortable electrical stimulation.

Subjects with pelvic sensation may be exposed, during acute experiments, to stimulation levels that are uncomfortable. This risk is small and manageable because stimulus amplitude will be increased slowly and discontinued if desired. Previous GNS studies, in neurologically intact women with pelvic sensation and overactive bladder, to determine maximum tolerable stimulation levels have been conducted, therefore we do not expect tolerance to stimulation to be a limitation.

g) Incontinence after ceasing bladder relaxing medication

There is a risk of increased incontinence due to increased bladder capacity in patients who are asked to discontinue their usual anticholinergic medication (or mirabegron) 1 week before the study and for the duration of the study. This risk will be managed by describing it to the subjects and by offering them alternative methods of managing incontinence during this period, such as a condom and leg-bag system, pads, diapers, or catheterization. Ceasing these medications should cause no other side effects beyond increased risk of incontinence before stimulation begins.

h) Audio recordings

Over the course of the study audio recordings may be made. For example, if the participant is not able to physically fill out the voiding diary an audio voiding diary may

be recorded. Participants will be identified in these recordings. The recordings will be used for data collection (research) purposes only. The recordings will be stored in locked cabinets in the locked room designated for data storage. Only study staff will have access to these recordings.

i) Breach of confidentiality

There is a small risk of breach of confidentiality of subject data and protected health information. This risk will be minimized.

Benefits: This study is a step toward a human feasibility study of an implanted system that has the potential to make a significant improvement in the lives of people with SCI and neurogenic bladder overactivity. For the current study, patients will be preferentially selected if they would be considered possible future candidates for an implanted future device – and therefore potentially benefit from the overall study in the future. Additionally, subjects may experience an increase in quality of life for the duration of the experiment if the intervention successfully manages neurogenic bladder activity, as we expect.

2. Recruitment Methods

Veterans will be recruited from Dr. Brose's patient population at the SVAMC SCI unit. Names of potential subjects will be obtained from the attending physicians of SCI unit or using an Excel database of all the SCI patients at the SVAMC. The Excel database will be used in conjunction with CPRS to screen patients using the eligibility criteria, and a log will be made to keep track of which patients are potentially eligible and which are not. A physician will briefly discuss the study with the patient during outpatient clinic visits, during rounds on the inpatient unit, or a follow up phone call; the study will only be discussed with patients who have been screened and were found to be preliminarily eligible. The physician will then ask permission for the research team to contact the patient. After permission is obtained, the subject will be given a copy of the consent form to look over. The research team will follow up with the patient by phone at a later date to answer and questions the patient might have. The researcher will then set up an appointment to fully obtain informed consent and set up an initial testing session.

Participants will be reimbursed \$50 per session to cover costs of transportation, food, and the inconvenience of coming to the SVAMC. Payment will be given in the form of a check mailed to the participant's home address after participation in a session. Because there are three sessions overall, participants may earn \$150 overall.

3. Informed Consent Procedures

Informed consent will be obtained by one of the investigators, study nurses or research staff after verbal explanation and provision of time for the subject to study the consent form and ask questions. The informed consent process will involve meeting with a potential subject in a quiet, private area (on the SCI Unit or in a physician's private

office), finding out whether he or she is capable of giving consent, and discussing the purpose, risks, and benefits of participation. We will ensure that the subjects genuinely understand the study. The researchers will convey information to subjects in an appropriate manner so that the subjects are able to understand what they are consenting to. The consent form will include a section about the collection and use of audio recordings. These recordings will be for the purposes of data collection, especially if the subject is physically unable to fill out a paper voiding diary and, for example, opts instead to record an audio voiding diary. The participant will also check a box indicating whether or not they consent to having their data stored in a research repository, and whether or not they consent to contact about future studies. Subjects will also give HIPAA authorization at this time.

Inclusion/Exclusion Criteria

To be included in the study, veterans must meet the following criteria:

Inclusion Criteria

- Suprasacral neurogenic bladder following spinal cord injury
- Neurologically stable
- Skeletally mature, over 18 years of age
- Reflex bladder contractions confirmed by cystometrogram
- At least 1 year post spinal cord injury
- Willingness to perform intermittent catheterization or volitional voiding for the duration of the study
- Able to understand and comply with study requirements
- Able to understand and give informed consent.

Exclusion Criteria

- Active sepsis
- Open pressure sores on penis
- Significant trauma, erosion or stricture of the urethra
- Bleeding diathesis
- Indwelling catheterization for > 1 year and bladder capacity < 100cc
- Pregnancy
- Individuals who do not speak English.

4. Materials and Measures

Questionnaires

Demographics Questionnaire: We will collect demographic information (e.g. age, date of spinal injury, level of spinal injury, gender, medical record number, current

medications, previous bladder or urinary tract interventions, current medical status). If any subject is over 89 years of age, “>89” will be recorded instead of their precise age.

Quality of Life Questionnaire: The effect of GNS on quality of life will be measured with the *Qualiveen*. The *Qualiveen* consists of 40 questions in 4 sections as follows; *what bothers you* (9 questions), *what are you restricted or forced to do* (8 questions), *what you worry about* (8 questions), and *what you feel* (15 questions). Answers are on a 5 point scale from 0 (not at all) to 4 (extremely).

Exit Questionnaire: At completion of the study, subjects will complete a GNS satisfaction survey about: their reliance on GNS, approval of the system, whether or not they would recommend it to others, desire to continue using the system, whether sexuality was affected by the system, and comments for improvement.

Voiding diary

A take-home voiding diary will track intake and output of fluids, providing information that is clinically relevant. Subjects will be asked to record daily bladder emptying times and amounts, fluid intake, and leakage events. Subjects will also record stimulation use, duration, and amplitude. These diaries will be physical, not electronic, except in the case a participant would prefer to complete a recorded audio voiding diary. Subjects will be provided with a Federal Information Processing Standard (FIPS) approved audio recorder if they choose to complete an audio diary instead of a paper diary.

Urodynamic Instrumentation and Documentation for Acute Testing

A dual-lumen Foley catheter will be inserted into the bladder via the urethra and the bladder will be emptied. One lumen of the catheter will be connected to a pressure transducer and amplifier to record bladder pressure, and the second lumen will be used to control bladder volume by filling and emptying with sterile saline. A balloon catheter inserted in the rectum will be used to determine detrusor pressure by subtracting rectal from vesical pressure. Surface EMG electrodes will be applied to the anal sphincter to monitor pelvic floor activity; signals will be amplified and filtered (10Hz-1kHz). Infused volumes will be measured both via a force transducer and infusion pump. Signals will be monitored on a urodynamic system (Medtronic) and stored on a strip chart and digital tape. Electrical stimulation will be applied using a Digitimer benchtop stimulator.

The information collected during acute testing—such as bladder capacity, threshold for the pudendo-anal reflex, and stimulus parameters—will be recorded on a *urodynamics checklist* designed for the experiment. This checklist contains all the steps for setting up and conducting acute testing to guarantee accurate acute testing of all subjects. The researcher will also use this checklist to record notes about each participant for the duration of the acute testing session. Some basic demographics like age, gender, and

medication usage will be recorded on this document as well. If any subject is over 89 years of age, “>89” will be recorded instead of their precise age.

Acute Genital Nerve Stimulation

Two surface electrodes (1 cm x 1 cm) will be placed on the dorsum of the penile shaft 2 cm apart, the cathode proximal. The anode will be placed distally to avoid any possibility of anodal block of the sensory axons. The electrodes will be connected to the stimulator.

Take-home Stimulator System for Chronic GNS

The stimulator system will be a two-channel stimulator, like a transcutaneous electrical nerve stimulation (TENS) unit, that attaches to the waist using a belt clip. The model used will be the Ultima NEO. The TENS/EMS/MIC/IF Model Ultima NEO combines the systems of a TENS (Transcutaneous Electrical Nerve Stimulator) device, an EMS or NMES (Neuro-Muscular Stimulator), a MIC (Microcurrent) stimulator and an IF(Interferential) stimulator. The Ultima NEO pack includes the stimulator unit, 2 Leads, 4 self adhesive Pads with connectors, a 3.7V rechargeable lithium Battery (BL-6F), 1 charger with an adaptor and a charging cradle, and an instruction booklet.

At some point during the study, a wireless transmitter and a rechargeable battery powered stimulator may replace the basic wired stimulator. Details about each component of the stimulator system and the safety testing it will undergo are provided below.

Wireless Transmitter/Controller: A wireless “fingerswitch” controller for implantable devices was developed by the LSCDVAMC Advanced Platform Technology (APT) Center and is approved for use to transmit user commands (e.g., Go, Stop, Scroll) to the UECU (universal external control unit) for control of stimulation for implanted neural stimulation devices for standing and walking. The Control/Transceiver Board contains a Texas Instruments CC430 (MSP430 microcontroller with integrated 902-928 MHz wireless transceiver). The VA APT Center wireless controller consists of a pushbutton circuit board plugged into a wireless transceiver board housed in a small “fingerswitch” enclosure. Our proposed system will make use of one of these wireless “fingerswitch” transmitters as well as another one of these transceiver boards which will receive the button press information and be plugged into the wearable surface stimulation board.

Stimulator:

The stimulator board design is a reduced version of the surface UECU stimulator developed by the FES Center that has been used at Case Western Reserve University and the LSCDVAMC for ~10 years in human subjects research. This system will allow full control over the stimulation parameters including pulse width, pulse amplitude, and stimulation frequency

Stimulator Safety Testing: The Cleveland FES Center has a standardized electrical safety testing protocol that is accepted by local institutions. The prototypes and final design will be tested to ensure leakage currents are below established safety levels (lead leakage <10 μ A and chassis leakage <100 μ A). Each device will be electrical safety tested, certified and documented by Cleveland VA Center of Excellence in Functional Electrical Stimulation staff.

5. Study Evaluations

The duration of this study is 1 year, though subjects may choose to continue their use of the device beyond this period and will be monitored *clinically* for the duration of their usage. Participation in research activities will cease at the 12 month mark. Subjects will engage in study procedures both within and outside of the SVAMC. The study will involve three in-person testing sessions at the SVAMC. The rest of the study activities will take place remotely. Please see Figure 1, at the bottom of this section, for a full chart of study procedures for an individual participant.

A description of each stage of the study is provided below:

Informed Consent:

Informed consent will be obtained and HIPAA authorization will be discussed with the potential participant at the time the patient is interviewed and a copy of the authorization will be given to them for their review. Participants will be asked to cease taking any anticholinergic medications for 1 week before undergoing the first urodynamics testing session.

Initial Urodynamics and Stimulus Parameter Selection: To manage the known risk of urinary tract infection in SCI and in association with urodynamics, the standard of practice in clinical urodynamics for persons with SCI will be followed, entailing provision of antibiotics for three days (starting the day before the urodynamics) in the event of non-sterile pre-procedure urine.

An initial urodynamics test will be performed to verify that GNS is effective, select stimulus parameters that effectively inhibit reflexive bladder contractions, and train subjects how to use GNS. The pudendo-anal reflex stimulation threshold and tolerable limits will be determined. Blood pressure will be monitored continuously during urodynamics with a non-invasive monitor over the course of the urodynamics. Subjects will be fitted with catheters to determine bladder pressure, bladder volume, and detrusor pressure.

Subjects will also be fitted with surface EMG electrodes applied to the anal sphincter and 2 surface electrodes (1 cm x 1 cm) applied to the dorsum of the penile shaft 2cm apart. Single biphasic rectangular stimuli of 200 μ sec pulse width and a range of

amplitudes will be applied to determine the stimulation threshold for producing visible (or EMG) reflex contraction of anal sphincter (the pudendo-anal reflex threshold). The threshold stimulation amplitude for the pudendo-anal reflex will be used to normalize stimulation amplitude between subjects.

Serial cystometrograms will be conducted with a 10-30 minute rest between each trial by filling the bladder at a rate of 50ml/min with normal saline at room temperature and recording the volume and pressure in the bladder up to the point capacity is determined. Fills will occur either 1) without stimulation (to verify reflexive bladder contraction – control runs); 2) with stimulation conditionally based on visualized bladder reflex; and 3) with continuous stimulation. The first cystometric fill is performed without stimulation and the second cystometric fill is performed with conditional stimulation. Each successive cystometric fill will be randomized to be performed either without stimulation, with conditional stimulation, or with continuous stimulation. At the end of each cystometrogram, the bladder will be emptied and the volume added to any voided volume to determine total bladder volume. Subjects will be turned every 20 minutes on the well-padded custom-designed urodynamics table.

Acute Testing Sessions: Acute urodynamics testing will occur at 6 and 12 months after the initial testing session. Thus, urodynamics testing will occur three times overall and will be performed similarly each time. Testing follows the protocol described above for initial testing.

For a designated period of time surrounding these acute testing sessions, participants will keep a diary log of their stimulator use, urinary habits, and leakage events—either using a paper diary template provided or an audio recorder provided. Voiding diaries will be collected at the acute testing time points. The voiding diary will be recorded the first week after the first urodynamics testing session. Subsequently, the diary will be recorded for the week *before* the testing session. Thus, subjects will record a voiding diary for 1 week before the second session (occurring 6 months into the study) and 1 week before the third session (occurring 12 months into the study). During these 1 week periods, the diary will be completed daily. The research staff responsible for maintaining ongoing contact with participants will provide a reminder at these time points. Please see Figures 2 and 3, which indicate the timeline for acute testing sessions, diary recording, and participant contact.

Subjects will also complete the OAB-q and have a brief interview with a researcher about their experiences during each acute testing session.

Chronic GNS Stimulation: Subjects will take home a stimulator for daily use and maintain a diary detailing fluid intake and output, as well as leakage events. This diary will only be maintained for select months during the study, not daily for the entire duration of the 1 year study period. With the home stimulator, GNS occurs in a 60

seconds on, 60 seconds off pattern except when showering or bathing (in which case the stimulator will be turned off), and for the first hour after each catheterization. Subjects will push a button on the stimulator after each catheterization which will inactivate the stimulator for one hour after catheterization. Subjects will use intermittent catheterization at least 3 times per day. While subjects without pelvic sensation will generally keep the stimulator on constantly, those with pelvic sensation may choose to turn the stimulator on only when they feel the need to hold their bladder. Thus, subjects will have the ability to turn the stimulator on and off at will, as well as alter the amplitude of the stimulation to fit their needs. Details regarding their stimulator use will also be recorded in the voiding diary. Please see Figure 4, which indicates what a typical week without acute testing will look like for the participant.

Ongoing Study Communication: Subjects will remain in weekly contact with the research staff throughout the length of the study (and daily contact during data collection periods) to ensure that voiding diary recording is occurring properly and the device is functioning correctly. Phone discussions will also allow for close monitoring of complications such as autonomic dysreflexia or any discomfort due to the stimulator.

After the 12 Month Study Period: Because the proposed stimulators are designed to reduce incontinence, participants may find that their quality of life is increased if the stimulators are effective. After the conclusion of the official study period of 12 months, participants may decide whether they would benefit from continued use of the stimulator. Participants will be given a stimulator free of charge for personal use and will receive clinical checkups to monitor stimulator usage and safety. These checkups will be considered standard of care and not research procedures. Additionally, the PI and nurses will stay available for questions about the stimulators and stimulator use may be discussed if the individual wishes.

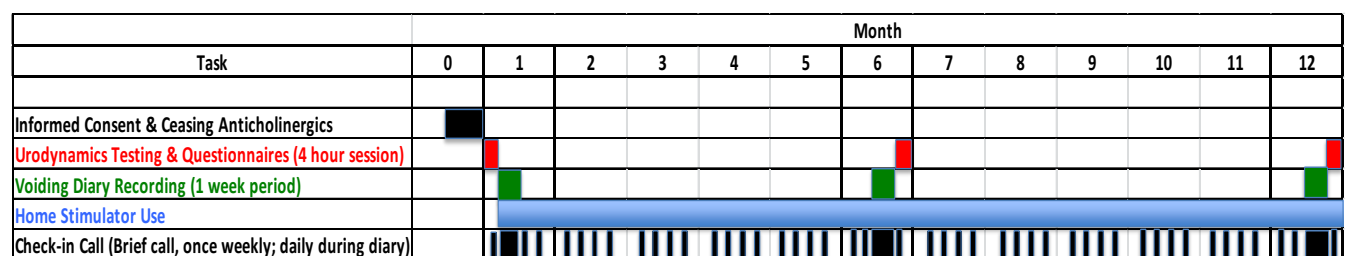


Figure 1. A timeline indicating the study procedures for an individual participant. Informed consent and ceasing of anticholinergic medication occurs 1 week before initial testing. The initial testing session will take 4 hours and the participant will record their voiding diary the week after. Subsequently, the diary will be recorded the week before acute testing. The researchers will keep in weekly phone contact with participants, except during diary collection, where daily phone calls will occur.

	First Urodynamics Testing (1st week of 1st month)							
Task	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Monday
Initial Urodynamics Testing	4 Hours							
Voiding Diary Recording								
Home Stimulator Use								
Check-in Call (<30min)								

	Second & Third Urodynamic Sessions (6 Months & 12 Months)							
Task	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Monday
Urodynamics Testing								4 Hours
Voiding Diary Recording								
Home Stimulator Use								
Check-in Call (<30min)								

Figures 2 & 3. These figures show a snapshot of the weeks that involve acute urodynamics testing. After the first session, participants will complete their voiding diary the week after. For the second and third sessions, the diary will be completed the week before. Daily phone contact will occur during diary collection week. All acute testing sessions will involve urodynamics testing and questionnaires.

	Week without Acute Urodynamics Testing						
Task	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Urodynamics Testing							
Voiding Diary Recording							
Home Stimulator Use							
Check-in Call (<30min)							

Figure 4. A snapshot of a week in which acute testing does not occur. These weeks involve only home stimulator use and 1 weekly check-in call.

6. Data Analysis

Outcomes, including bladder capacity, will be used to determine the effect of chronic GNS on reducing bladder hyperreflexia. Differences in the average number of leak episodes per week per subject will be examined at each time point using the non-parametric Wilcoxon signed-rank test. Similarly, the bladder capacities with and without GNS measured during acute urodynamics visits will be compared using an ANOVA. In addition, to identify any potential habituation, the pudendo-anal reflex threshold and the stimulation amplitudes used to achieve effective bladder inhibition will be recorded during each acute testing session and compared.

If the data provide an opportunity for more sophisticated analyses, we shall use various random coefficient mixed linear repeated measures ANOVA models to determine the effect of each testing period (0 months, 6 months, 12 months) as a factor on each outcome measure. We will include subject as a factor in our analysis and consider starting levels as potential covariates. Outcome measures will be plotted as a function of day number throughout the trial, and baseline characteristics such as age and SCI location may indicate possible future covariates for consideration in future studies. This analysis would allow us to identify trends in daily responses that are significant or of practical application.

Our primary variable is urinary incontinence, which will be used to power the study. Based on our preliminary data and average values observed in the literature, we determined that we can expect an effect size of 0.8 UI/day and a SD of 2.7 UI/day. A pair-sampled, one-sided t-test with $n=16$ subjects would have a statistical power of ~ 0.8 .

7. Withdrawal of Subjects

Participants may choose to withdraw from the study at any time. Participants may be withdrawn from the study without their consent if the PI decides that it is against the patient's best interest to continue in the study (i.e. patient experiences an injury or health problem, either related or unrelated to the study, that affects their participation).

Reporting

Adverse Event (AE): An example of an adverse event would be discomfort due to electrical stimulation. If a subject expresses discomfort during an acute testing session, the electrical stimulation will be gradually discontinued.

Serious Adverse Event (SAE): An example of a SAE would be a subject developing high blood pressure or AD during urodynamic testing. If a serious rise in blood pressure occurs, the subject's bladder will be emptied and the standard AD protocol in the SCI center will be utilized.

An AE temporally related to participation in the study will be documented whether or not considered related to the test article or procedure. This definition includes current illnesses and injuries and exacerbations of preexisting conditions including changes to psychological state. AE will be kept in the subject tracking log and reported as a summary at continuing review. SAE, such as hospitalization for more than 24 hours, will be reported to the IRB within 5 days per SOP 151-17.

Immediate action will be taken to resolve any adverse events. If any oversight body determines that the adverse event(s) in a study is indicative of an unreasonable risk to subjects, immediate and appropriate action will be taken to minimize this risk. Within 5

days, the PI will make a determination to continue or terminate testing. This may include removing a subject from the study, or terminating the entire study.

Privacy and Confidentiality

Data Storage

All study files at the SVAMC will be kept in a locked file in a designated room in the SCI unit. Consent forms will be kept in a separate file apart from the data files. All research data (physical and electronic) will be anonymized using identifiers supplied by the experimenter. In this study, each participant will be assigned a subject number (e.g., Subject 001), which will be used to link all data provided by the participant. There will be no correspondence between the participant's subject number and other personally identifying information, such as names or contact information, which could link them to the study or their data. The subject number key will be locked away separately from any data identifiable by subject number. Privacy for patient health information will be strictly adhered to by study staff. Information will be collected during an interview in a quiet and private area (on the SCI Unit, or in a physician's private office).

Any audio files collected using audio recorders will be transcribed into an Excel database stored on the VA network, similarly to the paper diaries. Audio files will be maintained on the subject's encrypted recorder for the duration of their use of the recorder. Audio files will be deleted from the recorder after the subject is done making audio files as a part of the study and those files have been transcribed into the electronic study record.

De-identified electronic data will be exported from the laptop used for data collection using a VAMC encrypted thumbdrive, and uploaded to a VAMC network computer for storage and data analysis purposes. Data will be stored in a secure, encrypted network subfolder. Only approved study personnel will have access to electronic data. At such a time as study personnel are removed from the protocol, their access to the data will be terminated.

Because two VA sites will be involved in data collection (LSCDVAMC and SVAMC), data will be transferred between these locations using secure, encrypted VA email to the PI or his designated research staff. However, nothing beyond data sharing should be required between the two sites because they are operating off independent, locally-approved IRB protocols.

In the event that the security of VA research-related information (physical or electronic data) is compromised, either by unauthorized use, disclosure, transmission, removal, theft, loss, or destruction, the PI and authorized research staff will report to ACOS for

Research, Privacy Officer, and Information Security Officer within 1 hour, as specified in Research & Development Policy 151-17.

This study will include a Data Safety Monitoring Board (DSMB). Voting members will include individuals with the following expertise: an SCI physician with experience in physical medicine and rehabilitation, neurogenic bladder experience, statistics, neural engineering or electrical stimulation, and a veteran advocate. The DSMB will meet at least annually. The DSMB will review the study design, IRB documents, results, study progress, participant recruitment, adverse events, participant risk versus benefit, and any other factors the DSMB determines are appropriate. The DSMB will evaluate data from all participating sites. The DSMB will make recommendations to the PI and/or IRB, and protect the confidentiality of the data.

Study data may also be reviewed by The Cleveland FES Center Data Safety Monitoring group. This group examines FES related studies from multiple institutions to identify issues that may not be apparent from single study analyses.

Data Repository

During the consent process, the researcher will also obtain the participant's optional consent for and storing data and contact information (if provided) in a data repository. If the participant consents to both data storage and future contact, their data and contact information will enter a data repository maintained at the Syracuse VA Medical Center by the PI and will not expire/be destroyed at the end of the current study. If the participant consents only to the data repository, their data will be stored but no contact information will be obtained and future contact will not occur. If a participant consents for contact in future studies but not data repository storage, their contact information will be maintained as a part of the current study record and will not enter the data repository. Participants will agree to the data repository both in the consent form and in the HIPAA authorization form. Data entered into the data repository will be maintained in the manner detailed in the IRB protocol submitted for the data repository itself.

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