Official Study Title: Capsaicin 8% Patch for Spinal Cord Injury Neuropathic Pain

NCT number: NCT02441660

IRB Approval Date: 07.24.2019

Unique Protocol ID: HSC20150322H

Protocol Template Form

Item 1 UTHSCSA Tracking Number	15-322H

Item 2 Abstract / Project Summary	Provide a succinct and accurate description of the proposed research. State the purpose/aims. Describe concisely the research design and methods for achieving the stated goals. This section should be understandable to all members of the IRB, scientific and non-scientific. **DO NOT EXCEED THE SPACE PROVIDED**.

Purpose/Objectives: Current pharmacologic agents for neuropathic pain (NP) in Spinal Cord Injury (SCI) provide 20-30% pain reduction at best; so there is clear need for research studies on new promising evidence-based therapeutic agents. Animal spinal cord injury models show the Transient Receptor Potential Vanilloid subfamily, member 1 (TRPV1) defunctionalization with capsaicin decreases nociceptor hyperactivity. Human trials are needed to substantiate this effect. Most systemic effects of oral agents often limit tolerability, especially as doses are titrated up to achieved maximum clinical effect. Analgesics that can be applied topically have the potential to largely overcome this problem; the only published study of a topical analgesic in persons with SCI examined low dose capsaicin cream in 8 SCI persons and found efficacy. Thus more studies on topical analgesics are needed in persons with SCI. We propose to conduct the first prospective trial of Capsaicin 8% (C8P) in persons with SCI, with hopes to provide SCI patients and clinicians with evidence for a much-needed alternative topical therapeutic without the systemic effects that often limit tolerability.

Research Design/Plan: Randomized dual balanced 2-sequence 2-treatment, 2-period (each period is 12 weeks long), crossover study; with an additional prospective trial arm

Methods:
Randomized control trial: We will recruit 25 patients with chronic SCI and chronic focal neuropathic pain (>6months) below level of injury who have failed multiple pharmacological agents. Pre-study data collection will include subjective description of pain, baseline visual analog scale (VAS) and numeric pain rating scale (NPRS) values, LANNS pain score survey to accurately determine source of pain is neuropathic in origin, a numerical scale such as World Health Organization Quality of Life- (WHOQOL) brief survey (WHOQOL-BREF) that measures quality of life parameters, subjective SCIM (spinal cord independence measure) scores, SCI specific pain measures (MPI-SCI), and pain diagrams will be obtained on each participant. Written informed consent will be obtained. Each participant will be randomized to one of two sequences:

Sequence 1: C8P application followed by one reapplication of a low dose capsaicin control patch (0.025% Well Patch) (available over the counter)

OR

Sequence 2: Control patch (0.025% Well Patch) followed by one replication of C8P. as indicated in Table 1.

Measurements of the primary outcome of pain (VAS) will occur every 2 weeks and all secondary outcomes will be measured at 4,8 and 12 weeks within each period in each sequence.

Substudy: Non-randomized, non-controlled sub-study: We will also have a non-randomized non-controlled sub-study to increase data obtained to help calculate Number needed to treat and minimal clinically important difference for the RCT.. Patients with SCI undergoing patch as routine medical treatment for refractory neuropathic pain will be recruited and enrolled immediately after patch application. Subsequently, they will be be followed for a 12 week period using the identical protocol of sequence 1 in the RCT, without reapplication of a control patch.

Clinical Relevance: Potentially giving analgesic pain relief for spinal cord focal peripheral neuropathic pain without the hand strength or dexterity required to open bottles, take oral tablets/capsules, or apply a transdermal patch, cream or ointment on a daily basis.

Item 3 Background	
Describe past experimental and/or clinical findings leading to the formulation of your study. *For research involving unapproved drugs, describe animal and human studies.* *For research that involves approved drugs or devices, describe the FDA approved uses of this drug/device in*	Capsaicin 8% patch (Qutenza) is an FDA approved treatment for neuropathic pain in post herpetic neuralgia (PHN). After the FDA approval of Qutenza several studies have been published assessing the efficacy and safety in patients with HIV autonomic neuropathy and PHN. In a meta-analysis examining 2057 persons with PHN and HIV-AN, the proportion of responders with relief (>30% improvement in pain lasting from 2-12 weeks) over a 12-week treatment period was 43% in the C8P group and 34% in the control group, a statistically significant difference. A retrospective review by Dr. Trbovich and Dr. Huiqing Yang pending publication in the American Journal of Physical Medicine and Rehabilitation also supports that Capsaicin 8% patch provided all three patients in the study had complete relief of pain on average after 2 weeks for an average duration of 169 days.

relation to your protocol.	
Item 4 Purpose and rationale *Insert purpose, objectives and research questions/hypotheses here. If you cut and paste from another document, make sure the excerpted material answers the question*	While low dose capsaicin cream has shown efficacy with minimal side effects in radicular pain of 8 SCI persons, short dosing intervals (every 1-4 hours) and poor manual dexterity of persons with SCI (e.g., tetraplegia) can impair efficacy and adherence. Thus the novelty of high dose capsaicin is that a single topical application of the C8P for only 1 hour could potentially provide pain relief for 8-12 weeks.

Item 5 Study Population(s) Being Recruited In your recruitment plan, how many different populations of prospective subjects do you plan to target? Provide number: 2 *e.g., a population can be individuals with type 2 diabetes controlled with diet and/or a population of healthy controls. Or a population can be individuals attending an education program, etc.* <u>List each different population</u> on a separate row and provide a short descriptive **label**: *(e.g., normal-healthy, diabetics, parents, children, etc.)* *To add rows use copy & paste*	Identify the criteria for **inclusion**:	Identify the criteria for **exclusion**: **4.**
Spinal cord injury patients with neuropathic pain for RCT	1. Diagnosis of SCI 2. Neuropathic pain below level of injury 3. Surface area of pain no larger than 2 patches 4. Failed or did not tolerate gabapentin 3600mg/day, pregabalin 600mg/day, capsaicin cream and/or lidocaine cream 5. Skin over painful area intact	1. Pain over open wound 2. Previously documented allergy to capsaicin 3. Superficial burn over area of pain 5. Premorbid (before SCI) neuropathic pain 6. HIV/AIDS neuropathy 7. Uncontrolled hypertension or autonomic dysreflexia 8. Previous application of capsaicin patch
Spinal cord injury patients with neuropathic pain for prospective trial arm	1. Diagnosis of SCI 2. Neuropathic pain 4. Failed or did not tolerate gabapentin 3600mg/day, pregabalin 600mg/day, capsaicin cream and/or lidocaine cream 5. Skin over painful area intact 6. have been prescribed the C8P as routine clinical care treatment	1. Pain over open wound 2. Previously documented allergy to capsaicin 3. Superficial burn over area of pain 9. Premorbid (before SCI) neuropathic pain 10. 6. HIV/AIDS neuropathy 11. Uncontrolled hypertension or autonomic dysreflexia

Item 6
Research Plan / Description of the Research Methods ***a.*** *Provide a* ***comprehensive narrative*** *describing the* ***research methods****.*
Provide the ***plan for data analysis*** *(include as applicable the* ***sample size calculation).***

Step-by-Step Methods:

RECRUITMENT:
RCT: We will identify 25 patients with chronic SCI from our VA SCI clinic, UH SCI and Rehabilitation Clinics, and/or local SCI population. We will recruit with flyers at the VA and UHS. We will utilize chart review and patient interview to ensure patients) meet inclusion criteria above and have failed multiple pharmacological agents. We will gather demographics, clinical history, and imaging on each patient via chart review. SCI attending Dr. Michelle Trbovich or one of the four residents participating in this research- Esha Lukose, Wesley Peace, Brett Helmonds, or Colby Beal- will contact patients that are appropriate study subjects regarding recruitment for the study and to invite patients to come an outpatient SCI clinic to consent to participate in this prospective study. Each patient's pain will be classified based on a taxonomy utilized by the validated and reliable International Spinal Cord Injury Pain Basic Data Set (ISCIPDS). The ISCIPDS classifies NP into three groups: "at level", "below level", and "other." 24 "At level" and "below level" pain must be directly related to SCI (central nerve injury) and are the only subjects that will be included in this study. Pain will also be validated with the LANNS pain score survey, which is an accurate tool for validation of pain which is neuropathic in origin.

Substudy: Non- randomized, non-controlled arm: The VA SCI clinic routinely applies the C8P to patients as an off-label treatment for refractory pain control. When a patient has been identified to have had the patch placed, we will consent, enroll him/her and follow him every 2 weeks to collect primary and every 4 weeks to collect secondary outcome data as described in the RCT. We aim to enroll 50 persons in this arm of the trial.

CONSENT:
RCT and substudy:
Patients will be approached in a private outpatient room in the spinal cord injury clinic or inpatient room.or via telephone. Risks, benefits, alternative options will be shared and the subjects will be allowed to ask any questions they may have to ensure they understand the risks, benefits and goal of study.

PRE STUDY DATA COLLECTION:
RCT: Pre-study data including subjective description of pain, baseline VAS, LANNS and NPRS . Pre-study data collection will include an intake form with subjective description of pain, baseline VAS / LANNS/NPRS, a numerical scale such as SF36 that measures quality of life parameters, subjective FIM scores, and pain diagrams will be obtained on each participant via the outpatient spinal cord injury clinic, or inpatient spinal cord injury unit.

Substudy: Non randomized, non-controlled arm: no pre-study data collection.

RANDOMIZATION: (RCT only)
Randomized dual balanced 2-sequence 2-treatment, 3-period, crossover study (see Table 1).
Tale 1. The proposed study layout

	Period	
Sequence	1	2
1	A	B
2	B	A

Where A indicates 8% Capsaicin and B indicates Low dose capsaicin control patch [1]. Each treatment period will be 12 weeks in duration. The proposed design is a standard 2-period, 2-treatment, 2-sequence design.
Inclusion criteria: >1year post SCI, chronic neuropathic pain with VAS>3, pain below the level of injury and failure of at least 3 oral or topical pharmacological agents. Exclusion criteria: painful area >1120cm^2 (4 patches), skin breakdown over area and uncontrolled hypertension.

Methods:
RCT: Each participant will be randomized to one of two sequences:
Sequence 1: C8P application followed by one reapplication of a low dose capsaicin control patch (0.025% Well Patch) (available over the counter)
OR
Sequence 2: Control patch (0.025% Well Patch) followed by one replication of C8P, as indicated in Table 1.

Patch application method: Per manufacturers' application directions, the painful area will be treated with topical lidocaine

2.5%/prilocaine 2.5% for 1 hour prior to application of the test patch(es). Active and control patches will then be applied and left in place for one hour. After removal, the cooling gel will be applied to decrease any burning sensation from the capsaicin, per manufacturers' protocol. Blood pressure will be monitored every 30minutes after the capsaicin (control or treatment) patch over the hour of application.

Substudy: Non-randomized, non-controlled prospective arm: Patients with SCI undergoing patch as routine medical treatment for refractory neuropathic pain will be recruited and enrolled immediately after patch application. Subsequently, they will be followed for a 12 week period using the identical protocol of data collection post patch application in the RCT, without reapplication of a control patch.

Post patch application data collection (RCT and substudy): Measurements of the primary outcome (VAS) will occur every 2 weeks and all secondary outcomes will be measured at 4, 8 and 12 weeks within each period in each sequence. Every 2 week VAS scores will be collected via phone at weeks 2,6,10 and in person at weeks 4, 8, 12. All secondary outcomes surveys will be done at a face to face visit at weeks 4, 8, 12.

Outcome measures: (RCT and substudy)
: Primary efficacy endpoint is the visual analog scale (VAS) score at the end of each of the three 12-week periods (at weeks 12 and 24). Secondary outcome measures include the Multidimensional Pain Inventory (MPI) Pain Severity Subscale, MPI-SCI, International SCI Pain Basic Data Subset (SCIPBDS), WHOQOL-BREF, Spinal Cord Independence Measure (SCIM) and number of concomitant pain medications

Specific Aims:
1. Determine the effect of the capsaicin 8% patch on VAS scores.
2. Determine the effect of the 8% Capsaicin (C8P) on QOL.
3. Determine the effect of the C8P on physical function. .

UHS clinic sites: Patients will be approached by providers (who are also investigators in this study), regarding being contacted by phone to hear more about the study. If agreeable patient's name and phone number will be provided manually/verbally to the study team at the VA in order to contact interested patients. No PHI will be transferred electronically between UHS and the VA. Data for the study will be provided by patient and collected at the VA.

Data Analysis Plan:

RCT: Due to the small population of individuals with a spinal cord injury and high incidence of neuropathic pain in such persons and lack of prospective studies on the capsaicin 8% patch, we felt a small group of 25 patients was large enough to show possible potential benefits, small enough to realistically complete this study, follow patients appropriately according to standard of care, and in congruence with the small population size commonly seen in spinal cord injury studies. This study will serve as pilot data for a larger study in the future.

Substudy: Non-randomized, non-controlled arm: 50 participants will be enrolled and we will use the baseline and post patch application data to help determine the number needed to treat and minimal clinically important difference for the RCT.

RCT and substudy: Data analysis will be performed on subjective description of pain at baseline from NPRS, VAS and evaluated at 2, 4, 8, 12 weeks post application to determine efficacy of capsaicin 8% patch in regards to point value and percentage of reduction compared to baseline. Longevity as recorded by reduction in baseline NPRS and VAS scores in days, weeks, and months of relief until pain returns to baseline. We will also compare our quality of life scale (WHO-QOL) and SCIM scores from pre study to post study and evaluate for more subjective measures of improvement in quality of life and functional improvement respectively. In the RCT trial we will assess for significant differences is outcomes between the treatment and control groups over time whereas, in the non-randomized, non-controlled trial we will compare baseline scores to 12 weeks post patch application scores for all outcomes. The significance of variation in the mean outcome with treatment will be assessed with a mixed effects linear model of the outcome in terms of sequence, subject nested in sequence, period, treatment, and first order carryover. All statistical testing will be two-sided with a significance level of 5%. SAS Version 9.4 for Windows or later, SAS Instititue, Cary, North Carolina, or R will be used throughout.

Item 7 Risks Section:

Complete the following table to describe the risks of all **research procedures** listed in Step 2, Institutional Form (items 28-34). *Do not list risks of Routine care procedures here.*

☒ N/A, Risks are described in the informed consent document – do not complete this table.

Research procedures *example:* • History and physical • Questionnaire • Laboratory tests *Add or delete rows as needed*	**Risks** List the reasonably expected risks under the following categories as appropriate:
	○
	○
	○