Title: **Improving functions in Veterans with Post-traumatic Peripheral Neuropathic Pain**

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Specific Aims

Traumatic peripheral nerve injury is a common occurrence in the Veterans due to service or surgically related trauma. Over 30% of neuropathic pain conditions in Veterans are due to peripheral nerve injury (VASDHS internal survey). Peripheral nerve injury often results in the formation of neuroma/nerve entrapment, a persistent neuropathic pain state with ectopic neuronal activity at the site of injury and/or at the dorsal root ganglion (DRG) of the injured axons [1]. Invasive measures such as surgical resection, venous transposition or local injections of steroid and local anesthetics at the injury/neuroma site are often ineffective in alleviating the symptoms. On the other hand, the invasive nature of these interventions frequently further exacerbates pain associated with the pre-existing hypersensitive neuropathic pain states [2]. Therefore, there is a need in the field of pain management in developing means of non-invasive therapy in treating post-traumatic peripheral neuropathic pain (PTP-NP) states. The pain service at the VA San Diego Healthcare System (VASDHS) has recently adopted the use of transcutaneous magnetic stimulation (tMS) in treating PTP-NP and noticed encouraging pain relief benefit in patients with PTP-NP [3]. The PI also completed a mechanistic nerve conduction study and showed that this treatment method can potentially restore lost neuronal functions associated with pain modulation [4]. Our initial pilot data from a randomized controlled study support the feasibility of conducting a larger scale clinical trial to adequately assess the effect of tMS in treating PTP-NP and improving patients' function. The proposed study will set the foundation for future phase II/III multi-center studies. To validate tMS as a non-contact and non-invasive pain treatment option for reducing pain in Veterans with PTP-NP and improving their overall functions, the proposed study consists of the following hypotheses and specific aims:

Aim #1) Assess the effect of transcutaneous magnetic stimulation (tMS) in alleviating post-traumatic peripheral neuropathic pain (PTP-NP);

Hypothesis #1: Active tMS will significantly reduce symptoms of PTP-NP more than sham tMS as reflected by change of the spontaneous and evoked pain scores, and area of allodynia;

Aim # 2) Assess the effect of tMS in improving quality of life and functions in Veterans with PTP-NP;

Hypothesis #2: Active tMS will significantly provide more improvement in quality of life and functions for Veterans with PTP-NP than sham tMS

Background:

Post-traumatic peripheral neuropathic pain (PTP-NP) is a common debilitating condition in Veterans after peripheral nerve injury due to either physical or surgical trauma. In certain type of physical trauma or surgical procedures, the prevalence of PTP-NP can exceed 60% [5-7]. Unfortunately, current available treatment options such as surgical exploration, injections or medications have not been adequately addressing this debilitating condition, which often casts a profound negative impact on the patients' quality of life [8]. Preclinical studies have demonstrated that after peripheral nerve injury, large myelinated pain modulatory A-beta afferent fiber firing diminished over time whereas smaller pain transmitting fibers including A-delta and C-fibers had enhanced firing [9]. Clinically, a significant degree of pain with altered sensitivity at the area of the scar or within the distribution of the peripheral nerve has been the hallmark of PTP-NP. This chronic pain state is frequently accompanied by a condition known as allodynia in which noxious perception occurs with non-noxious stimuli such as light stroking [10] and with morphological changes including the formation of neuroma [11, 12]. In addition, spontaneous electrical (ectopic) activities at the site can also enhance the sensitivity of the nociceptors and augmented conduction of the nociceptive impulses toward the central nervous system. Therefore modulating afferent sensory input at the site of injury without physically irritating or contacting the area of neuronal injury provides an excellent alternative in managing PTP-NP with a potential long lasting analgesic effect.

Non-invasive neuromodulation for PTP-NP

While non-invasive peripheral neuromodulation provides a great alternate treatment option for pain, not all peripheral neuromodulatory modalities are applicable to PTP-NP. For example, low frequency TENS (≤5 Hz) appeared to undiscrimitively diminish both large and small afferent fibers input as it diminished mechanical pain and tactile thresholds. On the other hand, high frequency TENS at 250 Hz appeared to predominantly activate pain transmitting A-delta afferent inputs [13, 14]. The analgesic effect of low frequency (≤5 Hz) TENS is usually not sustained once the stimulation is stopped [15]. While TENS reduces hyperalgesia and pain, tolerance to the treatment effects may develop with prolonged stimulation and a high intensity of stimulation is required to counteract the tolerance effect and produce optimal analgesia [16]. In patients with PTP-NP, a direct high intensity electrical stimulation via the TENS electrodes over the site of injury is often not tolerated by patients with allodynia, thus making direct skin contact electrotherapy not an appealing therapeutic option for this patient population.

Innovative non-contact treatment for PTP-NP

Transcutaneous Magnetic Stimulation (tMS) offers an innovative, non-invasive and non-contact (skin) means of neuromodulation in managing PTP-NP via the use of dynamic magnetic flux, which can affect neuronal functions by inducing localized neuronal depolarization [17]. This innovative technology derives from the use of transcranial magnetic stimulation (TMS), which uses electromagnetic principles to produce small electrical currents in neurons without skin contact or anesthetics [18-21]. This method of pain neuromodulation without skin contact provides a major advantage in treating patients with tactile allodynia. When a current is passed around the coil, a dynamic magnetic flux will pass through the skin and into the first few centimeters of the skin without attenuation. A figure-of-eight coil is commonly used because it gives a focused dynamic magnetic flux stimulation from the center of the coil to the target site which can be marked with an extended cross-hair for alignment [3]. This dynamic magnetic flux induced neuronal stimulation is far more focused than other available direct current based electrotherapies. Recently,TMS has been shown to be beneficial in managing intractable central neuropathic states and headaches [22, 23]. TMS is also known to facilitate nerve repair/regeneration [24]. While high frequency TMS (>1hz) results in neuronal excitation, low frequency TMS (≤1 Hz) results in neuronal inhibition [25]. Therefore, knowing that PTP-NP is associated with enhanced A-delta and C afferent fibers firing, and ectopic activities, low frequency tMS can be applied as a treatment option for managing the state of neuronal hypersensitivity known to exist in PTP-NP.

Preliminary data

1) Initial clinical observation reported in a case series [3]

In an earlier case series, the investigators reported the effect of tMS on neuroma/nerve entrapment in five patients with PTP-NP. Their pain conditions have failed both steroid injection and conventional pain medications prior to tMS (MagPro B65; MagVenture, Atlanta, GA). 400 pulses of stimulation at .5Hz were delivered per treatment session. Each patient received 3-4 sessions of treatment over a period of two months. Pre- and post-intervention spontaneous pain levels were assessed with a numerical pain rating scale (NPRS). Average pre and post scores (±SD) on the NPRS were 5.00 (±1.41) and 0.80 (±1.10) respectively with an average pain reduction of 84 (±21.91) % in the NRS after three to four treatments within two months. This analgesic effect appeared to be sustainable with repeated treatment delivered at a 6- to 8-week duration. Pre-treatment tactile allodynia found in three patients resolved after the initial 2-month treatment sessions. This published case series provides the initial clinical evidence that tMS offers a non-invasive treatment option for PTP-NP. The PI has since treated over 70 Veterans with PTP-NP with a similar protocol and noticed comparable encouraging outcomes. Additional randomized controlled studies are warranted to further validate the efficacy of this treatment modality.

2) Modulatory effect of tMS on peripheral sensory and motor transmission [4]

In a published mechanistic study, the investigators assessed the effect of tMS on peripheral sensory thresholds, nerve conduction properties and TENS induced fast afferent slowing effect as measured by motor and sensory conduction studies at the ulnar nerve. The investigators found that sham tMS with TENS (Sham+TENS) significantly ($P=0.02$ and 0.007 respectively) reduces sensory conduction velocity (CV) and increases sensory onset latency (OL), and motor peak latency (PL) whereas, real tMS with TENS (Real+TENS) reverses the effects of TENS on sensory CV and OL, and significantly ($P=0.036$) increases the sensory PL. tMS alone significantly ($P<0.05$) elevates sensory PL and onset-to-peak latency. The result of this mechanistic study suggests that tMS can reverse the TENS induced slowing effect on the fast conducting fibers and casts a selective peripheral modulatory effect on the slower conducting pain afferent fibers. Given that PTP-NP is often associated with aberrant neuronal activities with reduction of fast conducting pain modulatory fiber firing and enhancement of small pain conducting fiber activities, tMS can play a non-invasive neuromodulatory role in reversing this post-injury aberrant neuronal behavior and restoring normal peripheral neuronal modulatory function.

3) Preliminary data a randomized control study

Aside from the initial prospective case series observation, the investigators have conducted a pilot randomized sham-controlled study in which, 10 patients (12 nerve sites) with PTP-NP received three daily (>24 and <48 hours apart) sessions of real tMS at .5hz (400 pulses per session) at the side of nerve injury, and 10 patients(10 nerve sites) with PTP-NP received the sham treatment using the method as described in a previously published study [4]. % of reduction (±SD) in both spontaneous and evoked pain, and allodynic area from the pre-treatment assessments were evaluated. For the average spontaneous pain, the real treatment group demonstrated reductions on the mechanical visual analogue scale (M-VAS) from 60.7±14.7 to 36.7±25.5 and 44.6±32.9 at the post-treatment one- and four-week assessments respectively, whereas the sham group reported 60.0±20.2, 47.3±16.5, and 47.7±27.2 spontaneous pain M-VAS at pre- and post one and four-week assessments respectively. For the average evoked pain to punctate stimulation (5.18 von Frey Filament) the real treatment group demonstrated 40%% and 37% reductions at post-treatment one- and four-week assessments respectively, whereas the sham group only reported 20% reductions respectively at both post-treatment time points. In addition, the average evoked pain to stroking stimulation, the real treatment group demonstrated 44%% and 25% reductions at post-treatment one- and four-week assessments respectively, whereas the sham group only reported 2% reduction at post-treatment one week and 23% increase of pain at

post-treatment 4 week assessment. These initial observed trends of efficacy with the real tMS treatment group in both pain and allodynia reductions support the feasibility of the proposed randomized study.

These preliminary data support the feasibility of the current proposed study with the following aims and corresponding hypotheses:

1) Assess the effect of transcutaneous magnetic stimulation (tMS) in alleviating post-traumatic peripheral neuropathic pain (PTP-NP); Hypothesis #1: Active tMS will significantly reduce symptoms of PTP-NP more than sham tMS as reflected by change of the spontaneous and evoked pain scores, and area of allodynia.

2) Assess the effect of tMS in improving quality of life and functions in Veterans with PTP-NP; Hypothesis #2: Active tMS will significantly provide more improvement in quality of life and functions for Veterans with PTP-NP than sham tMS

Methods: 68 Veterans with PTP-NP will be randomized to receive either real (Group T) or sham (Group S) tMS treatments. Post-treatment assessments of pain and functions will be conducted at one week, and four week after the completion of the treatment. Each subject will receive 4 treatments at the injury site at >24 and <72 hours apart. Treatment intensity will be based on the patients' sensing thresholds to the stimulation amplitude. Pre-treatment assessments will consist of spontaneous and evoked pain rating, peripheral quantitative neurosensory testing, mapping of allodynic area and overall functional and quality of life assessments. At Visit 1, aside from careful chart review, a detailed history and physical exam will be conducted by one of the clinical investigators to identify the cause of injury and the specific peripheral nerve(s) involved. This study will be carried out according to the following schedule:

	VISIT 1	B1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	B2	VISIT 6	B3	VISIT 7
Informed consent	x									
Medical History	x									
Physical Examination	x							x		x
Daily Pain Log		x					x		x	
QST	x							x		x
Spontaneous Pain M-VAS	x		x	x	x	x		x		x
Evoked Pain M-VAS	x		x	x	x	x		x		x
Allodynic Area	x							x		x
tMS Treatment			x	x	x	x		x		
Medication Assessment	x	x					x	x	x	x
Side effect Assessment				x	x	x	x	x	x	x
BPI-sf	x							x		x
C-SSRS	x							x		x
Hamilton Depression Scale	x							x		x
PGIC	x							x		x
WPAI-SHP	x							x		x
Daily Sleep Interference		x					x		x	
Phone assessment							x		x	
Blinding efficacy assessment								x		

Visit 2 occurs one week after Visit 1; Visits 2,3,4 & 5 occur consecutively at >24 and <48 hours apart; Visit 6 and Visit 7 occur one week and four weeks respectively after Visit 5; B1 is the study period between the Visit 1 and Visit 2; B2 is the study period between Visit 5 and Visit 6; B3 is the study period between Visit 6 and Visit 7.

Primary efficacy assessment:

Spontaneous pain rating: Spontaneous pain level will be measured by using a sliding algometer, known as the Mechanical Visual Analog Scale (M-VAS). The device has been well validated, and is anchored at the left by "no pain sensation" and at the right by "the most intense pain sensation imaginable." The corresponding length of the red bar with a scale from 0 to 100, which can be read on the back by the tester, represents the subject's intensity of pain [26].

Secondary Efficacy Assessment:

Evoked Pain M-VAS rating: Stroking evoked pain will be assessed by gently moving a paintbrush over the site of PTNP. Punctate evoked pain will be conducted by gently pressing a 5.18 von Frey monofilament against the site of PTNP. The patients will be asked if pain is felt. If so, the intensity of pain will be rated in the M-VAS [27]. **Average Daily NPRS rating:** The Daily Pain Diary consists of an 11-point numeric pain rating scale (NPRS) ranging from 0 ("no pain") to 10 ("worst possible pain"). Subjects describe their pain during the past 24 hours by choosing the appropriate number between 0 and 10. **Quality of life and functional assessments will be conducted with: 1) Daily Sleep Interference Scale (DSIS)** [28]**; 2) Brief Pain Inventory (BPI-sf)** [29, 30]**; 3) Patient Global Impression of Change (PGIC)** [31]**; 4) Hamilton Rating Scale for Depression (HRSD)** [32-35], 5) **Columbia Suicide Severity Rating Scale (CSSRS)** [36], and **Work Productivity and Activity Impairment Questionnaire (WPAI-SHP version 2)** [37]**. Other study associated assessments consist of: 1) Weekly Phone Assessment:** After the post-treatment one-week assessment, the study coordinator will conduct weekly phone contact with the subjects for pain and side effect assessments until the completion of the study. The study coordinator will also trouble shoot any potential issues that may lead to unnecessary subject dropout with the assistance of the PI; 2) **Side Effect Assessment:** During each study related visit (after Visit 2) and weekly phone assessment, side effect assessment will be conducted to monitor any study related complication. Patient will be asked to report any potential neurological side effect such as persistent numbness, tingling or increase of pain related to the treatment. Investigators will determine whether these side effects are study or non-study related and report to the Institutional Human Subject Protection Committee, VA Research and Development Committee and Data Safety Monitoring Board according to the protocol; and 3) **Concomitant Medication:** Any medication that a subject uses during the study is considered concomitant medication. This includes prescription and non-prescription treatment such as contraceptives, vitamins, topical preparations, herbal preparations, and non-pharmacological therapies. Concomitant medication information (please see Human Subject for allowable and prohibited concomitant medications during the study) will be collected for all subjects during the screening, treatment, between visits (recorded in the Daily Pain Log) and subsequent post treatment visits. Information regarding subjects' previous failed treatments will also be collected at the screening visit. Subjects will be instructed not to alter medication regimens during the study without consultation with the investigators.

For **the blinding process**, a curtain will be placed in front of the patient so that the patient cannot see the treatment field. In addition, during the treatment the patients will be required to wear a soft eye shield. Simultaneous transcutaneous electrical stimulation will be provided to enhance the blinding effect. Blinding efficacy assessments will be conducted according to the study schedule.

tMS sensing amplitude threshold will be determined by placing the center of the TMS coil over the injury site at one cm away without touching the skin. The subjects will be instructed to click a computer mouse when he or she feels the stimulation, which will be started at 10% of the maximum stimulation amplitude and increased at 5% increments. Each stimulation threshold will be deliver 10 times with various between-stimulation intervals (15 to 60 seconds) prompted by a computer indicator. A computer program linked to the mouse will record a subject's response. The lowest stimulation amplitude at which a subject responds correctly at $\geq$6/10 trials will be recorded as the tMS sensing amplitude threshold. This method of tMS sensing amplitude threshold determination used in the preliminary data collection allows a consistent way to establish the stimulation

intensity for each subject based on the sensing ability of an individual injured peripheral nerve to the stimulation.

Real tMS (T): The treatment site will be marked and additional crosshair marking will be drawn for coil alignment. The center of magnetic coil (MagPro B65; MagVenture, Atlanta, GA) will be placed one cm above the marked location in reference of the crosshair markings without touching the skin [3]. A total of 400 pulses at 0.5 Hz and 150% of the tMS sensing amplitude threshold will be delivered via the center of TMS coil. For blinding purpose, a pair of transcutaneous electrodes will be placed at least 10 cm away from the sensory or motor innervation territory of the injured nerve and greater than two centimeters away from the border of the allodynic area. The electrodes will be linked to a pulse generator (ITO-160, Japan) and synchronized stimulation at the same frequency of the tMS will be provided during the study treatment [4].

Sham tMS (S): Sham treatment will be provided with the magnetic coil treatment site turned 180 degrees and the non-treatment site (facing the injury location) covered with a magnetic shield made of Giron molded to the shape of the coil [4, 23]. The magnetic shield completely prevents any magnetic flux from reaching the skin. Similar synchronized electro-stimulation at the same frequency of the tMS will be provided for the blinding purpose [4].

Quantitative Neurosensory Testing and Determination of Allodynic Area: Tactile threshold in the affected area will be measured by von Frey and non-noxious thermal sensations including cold, warm, and noxious thermal sensations such as cold and hot pain thresholds will be measured by using a Thermal Sensory Analyzer (Medoc Advanced Medical Systems, Minneapolis). This method of peripheral sensory testing has been well established in literature and used extensively in previous pain-related studies conducted by PI [27, 38]. The region of allodynia will be established with a 5.18 von Frey hair and a foam paint brush gently stroked on the skin. The stimuli will be initialed away from the allodynic area and marched towards the center of the area from different angles at half of a centimeter interval. The periphery of the allodynic area will be marked with a felt tip pen. At least eight points, at about 45 degrees apart and in a range of 360 degrees, will be established to mark the border of the allodynic area. The border will then be outlined onto a transparency. The area (cm2) will be determined by using a compensating planimeter (Keuffel & Esser, Germany) [27].

General approach in Data Analysis and Power Calculation

Descriptive statistics will be obtained for all variables, test of normality of continuous and homogeneity of variance will be performed. The statistical method such as log or square root transformations will be employed to correct for any abnormalities. The comparability of the groups on demographic data at the pre-treatment level will be tested with analyses of variance or Chi-square analyses. If we identify any significant differences in these variables between the groups, we will modify our analyses by adding those covariates to the model. Dr. Shahrokh Golshan, the study statistician, will perform statistical analysis. All analyses will be performed using the SPSS version 21. Missing data values will be minimized by intensive training of the interviewers in techniques of clarifying answers and checking questionnaires while the participants are on-site. When missing values are identified, several approaches to acquire the necessary data will be employed: 1) if at all possible, participants will be rescheduled within 24 hours of completion of tests or interviews; 2) if a participant cannot be rescheduled, an effort will be made to send a tester to the individual's place of residence within the same period; 3) The pattern of missing data will be examined according to the procedure recommended by Little and Rubin [39] which includes comparing group differences in the primary outcomes of subjects with versus without missing data. We will also test whether the dropouts are random or systematic by comparing the dropouts with the study completers on the baseline data. An absence of significant differences will support the random nature of dropouts. The following steps will minimize effect of dropouts: First, selected data analysis method allows the inclusion of subjects who dropout or are terminated early in the study, without relying on data imputation procedures. Second, effect of any systematic differences between the dropouts and completers will be explored by including the variable of concern to the model as a covariate. Finally, we will use pattern-mixture models to assess if there is bias due to drop out or missing data.

Hypothesis #1: Active tMS will significantly reduce symptoms of PTP-NP more than sham tMS as reflected by change of the spontaneous and evoked pain scores, and area of allodynia; **Independent Variables:** Treatment Groups with two levels (Groups T&S), Visits up to 7 levels; **Dependent Variables:** Primary outcome: Spontaneous Pain Scores; Secondary outcome: Evoked Pain Scores; Area of Allodynia;

Statistical Analysis: Data will be analyzed using mixed effects model [40-42]. The influence of missing data is reduced since this analytical approach maximized number of subjects by allowing the inclusion of subjects with missing data, dropouts or early termination without relying on data imputation procedures. We will use pattern-mixture models to assess biases due to drop out or missing data. The mixed effects model method provides an estimate of the individual variability around the population trend, the variability of the individual intercepts (baseline values) and slopes (changes across time), and the correlation between them. A fully saturated treatment by time model will be utilized for inference. Co-variance structure will be chosen and random group level treatment effects will be evaluated based on Akaikes Information Criterion. Analyses will be conducted within and across nested levels of the study design; this will involve within-subject analyses (comparison of occasions of measurement nested within an individual), as well as between-subject analyses (comparison of two groups). In addition, any treatment group comparison can be adjusted for subject-specific characteristics and adjustments for changes in these characteristics over the course of the study can be incorporated into the single-subject analyses. Based on the pilot study, we expect a dropout rate of <10% throughout the study. All analyses will be two-tailed, where applicable, with $\alpha = .05$. Correction for family-wise Type I error rates will be made using the Westfall-Young randomization maxTprocedure, which adjusts p-values for significance while taking into account the correlation of the outcomes [43]. In this way we can control for an overall family-wise error rate of .05 while achieving more power than Bonferroni adjustments.

Power Calculations: Sample size estimation was done using the RMASS program provided by Hedeker et al. [44, 45]. Based on these calculations a sample size of 68 would provide 80% power to detect a large effect size. This effect size was selected based on the observations reported in the preliminary data #1 and #3. Large effect size is defined as a between-group difference increasing linearly from 0 at baseline to .8 SD units at the last time point. The minimum power estimation is based on sample size calculation for 10% attrition rate, correlations of 0.6 between the repeated measures, and for large effect size.

Hypothesis #2: Active tMS will significantly provide more improvement in quality of life and functions for Veterans with PTP-NP than sham tMS; Independent Variables: Treatment Groups with two levels (Groups T&S), Visits up to 7 levels; **Dependent Variables:** DSIS, BPI-sf, PGIC, HRSD; WPAI-SHP.
Statistical Analysis: Similar to Hypothesis #1

Human Subjects

Characteristics

Approximately 68 Veterans with PTP-NP who meet the study inclusion and exclusion criteria will be enrolled into one of the two study groups: Group T will receive real tMS and Group S will receive sham tMS.

The following eligibility criteria will be applied to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions will be taken into consideration when deciding whether this protocol is suitable for a particular subject.

Inclusion Criteria

Subject eligibility will be reviewed and documented by one of the clinical investigators in the study team before subjects are included in the study. Subjects must meet all of the following inclusion criteria and none of the exclusion criteria to be eligible for enrollment into the study:

1). Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study;

2). Subject is willing and able to comply with scheduled visits, treatment plan, daily pain, sleep and all study related assessments and procedures;

3). Subjects must be literate in the language used in the assessments and pain diary;

4). Veterans (men or women) of any race or ethnicity who are at least 18 years of age;

5). Female subjects of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 7 days after the last session of the assigned treatment . A subject is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active;

6). Subject must have chronic peripheral neuropathic pain present for more than 4 months after a traumatic or surgical event per medical history (this may include, for example, motor vehicle accident, fall, sports injury, knee or hip replacement, hernia repair, thoracotomy, mastectomy, focal/localized burns or crush injury);

7). In addition, to be eligible for inclusion in the study, all subjects must:

a. Have an average daily Numerical Pain Rating Scale (NPRS) score >3 during B1; and

b. Have a spontaneous pain intensity >30 on 0-100 Mechanical Visual Analogue Scale (M-VAS) to be eligible for randomization;

8). Must have their implicated peripheral nerve(s) identified;

9). Must meet criteria for neuropathic pain assessment to meet eligibility for the study [46]. Pain distribution across a nerve territory and history indicates relevant lesion or disease plus criteria listed in a and/or b

a. At least one negative or positive sensory sign or symptom confined to innervation territory of the lesioned nervous structure. Examples of negative or positive signs or symptoms include:

· Burning, stabbing or tingling sensation/pain;

· Numbness/paresthesia;

· Cold, heat or pressure;

· Hyperalgesia or allodynia;

· Hypoesthesia;

· Increased or decreased sharp sensation (e.g., pinprick testing);

· Decreased vibration/vibratory sensation;

b. Prior diagnostic tests confirming lesion or disease explaining neuropathic pain (Nerve conduction

studies, EMG, skin or nerve biopsy). Documentation of affected nerve(s) indicating that the subject's pain is of neuropathic origin and is a result of injury/trauma to the affected/implicated nerve(s).

Exclusion Criteria

Subjects presenting with ANY of the following will NOT be included in the study:

1). Subjects with neuropathic pain due to diabetic peripheral neuropathy, post herpetic neuralgia, Human Immunodeficiency Virus, chemo/anti-viral therapy, trigeminal neuralgia, or carpal tunnel syndrome; subjects whose post-traumatic neuropathic pain is categorized as central (e.g., spinal cord injury) rather than peripheral.

2). Subjects with pain due to Complex Regional Pain Syndrome (CRPS, Type I or Type II);

3) Phantom limb pain after amputation. However, subjects with stump pain and phantom sensation but no phantom pain will not be excluded;

4). Subjects with skin conditions in the affected dermatome that in the judgment of the investigator can interfere with evaluation of the neuropathic pain condition;

5). Subjects with other pain such as lumbar or cervical radiculopathy that may confound assessment or self-evaluation of the peripheral neuropathic pain; subjects with significant somatic pain at the site of their trauma that may confound assessment or self-evaluation of their neuropathic pain;

6). Any subject considered at risk of suicide or self-harm based on investigator judgment and/or the details of a risk assessment;

7). Use of prohibited medications in the absence of appropriate washout periods;

8). Participation in any other clinical trial within the 30 days prior to screening and/or during participation in this study;

9). Subjects with a history of a cardiac arrhythmia that has led to the placement of a cardiac pacer or defibrillator will be excluded from the study;

10). Pregnant females and females of childbearing potential not using highly effective contraception or not agreeing to continue highly effective contraception during the study;

11). Subjects with a current diagnosis of DSM-IV-TR Axis I disorder (including, for example, schizophrenia, bipolar disorder, other psychotic disorders such as schizoaffective disorder and delusion disorder, somatoform disorders or factitious disorders, or bipolar disorders, even if controlled or stable; or alcohol or substance related disorders in the past 2 years); however, diagnoses of Generalized Anxiety Disorder (GAD) or major depression (MDD) that is clinically stable are allowed;

12). Subjects with pending Worker's Compensation, Worker's Compensation, civil litigation or disability claims pertinent to the subject based upon trauma; current involvement in out-of-court settlements for claims pertinent to subject's trauma; Subjects with fully resolved litigation and compensation claims can participate;

13) Subjects who have previously received either transcranial or transcutaneous magnetic stimulation therapy in the past.

Concomitant Medication(s)

Medications allowed during the study will include stable (been used at least 30 days prior to the screening visit) regimens of :

1) Non narcotic analgesics such as non-steroidal anti-inflammatory, acetaminophen (≤2g per day), tramadol (≤200mg per day), Aspirin (≤325mg per day), triptans used for non-neuropathic pain conditions such as migraine;
2) Antidepressants such as Serotonin Specific Reuptake Inhibitors and Tricyclic Antidepressants used mainly for sleep only;
3) Anxiolytics/benzodiazepine hypnotics such as Alprazolam, lorazepam, triazolam used at bedtime only;
4) GABA-A partial agonists/non benzodiazepine hypnotics such as Zolpidem, eszopiclone used for sleep only.

Subjects receive any narcotic based analgesic, topical analgesics over the affected site, steroid and local anesthetic injection, anticonvulsants, and antipsychotic medications less than 7 days prior to the pre-treatment assessment will not be enrolled for the study. Non-pharmacologic treatments, including but not limited to, transcutaneous electrical nerve stimulation unit (TENS), acupuncture, acupressure, therapeutic massage, will be prohibited during the entire study. Subjects should not have elective surgery or elective interventional medical procedures for the duration of the study. Subjects are allowed to use additional acetaminophen (up to a maximum total of 3g per day) as the only rescue medication during the study. The use of the rescue and other concomitant medications will be documented in the daily pain log

Subject Recruitment Timeline and Retention Plan

Over the past few years, the PI has established a close clinical and research collaborative relationship with the VASDHS Rehabilitation Medicine and Genera Surgery Clinic. With the addition of the proposed research personnel, we plan to conduct the study with the following timeline:

	Research Activities in 6-month Increments				
Time Increments	**1**	**2**	**3**	**4**	Total
Training & Study Preparation	X				
Targeted # of Group T Subject Recruitment	8	11	11	4	34
Targeted # of Group S Subject Recruitment	8	11	11	4	34
Total # of Subjects	16	22	22	8	68
Interim Data Analyses			x		
Final Data Analyses & Manuscript Preparation				x	

Currently the VASDHS Pain Clinic evaluate more than 100 new pain consults each month. In addition, the Rehabilitation Medicine also conducts approximately 20 new consults each month for Veterans with amputation. Initial screening of potential subjects will be conducted in both clinic locations. Approximately, 25% of the patients of pain clinic new evaluation consists of patients with PTP-NP and approximately 20% of the post-amputation subjects consists of stump pain with phantom limb pain. The Pain Service has an arrangement with the VASDHS General Surgery Service to evaluate post-surgical patients with pain at or near their surgical sites after reversible anatomical or surgical causes have been ruled out. In addition to the

clinical services, recruitment flyers will be placed in various clinical services including but not limited to general surgery, neurology and primary care clinics. Potential subjects will be provided with both verbal and written information about the study. Interested subjects will then be further assessed according to the study inclusion and exclusion criteria and enrolled for the study. With close to 30 PTP-NP being evaluated per month, the proposed recruitment plan is feasible.

Before subjects are entered into this study, the purpose and nature of the study as well as possible adverse effects will be explained to them in the presence of a witness. The subject (or his/her guardian/representative if the patient is unable to sign personally) must sign a statement, which complies with the requirements of the US Code of Federal Regulations (Title 21 CFR Part 50.25<a> &<b>). Each signature is to be witnessed. A signed original should be given to the subject. All subjects will be selected based on the above criteria.

Risk to Subjects

Risks associated with transcutaneous magnetic stimulation (tMS) are minimal. A potential discomfort associated with tMS is a mild muscle stimulation at the treatment site. Typically, changing the orientation of the coil can minimize the degree of muscle stimulation. The thermal pain testing will induce some discomfort/pain. The temperature range of the thermal analyzer is internally set at 0 to 50 ºC, which is known not to cause any risk of skin injury. The use of oscillated thermal heat further minimizes the risk of skin damage. These and other risks of the intervention will be fully discussed with the subjects prior to the study and side effect will be assessed during the study as well.

Adequacy of Protection from Risk

1) All procedures will be performed under the direct supervision of the PI or qualified co-investigators. The patient will be educated regarding returning to clinic or going to an emergency department if there is any significant change in their pain symptoms.
2) Although there is no existing guideline for peripheral magnetic stimulation, the tMS setting used in the study is within the current safety guidelines for TMS and is the same as the protocol in previous case series, mechanistic and pilot studies. However, in the event that the subject feels any discomfort during the study treatments and wishes to stop the treatment, the study will be stopped immediately.
3) Only the PI and the investigators will have access to the research records. Research records will be kept confidential to the extent provided by law. During the study, the patient's name and identity will not be publicly disclosed without their written permission. The results of this study will likely be published in medical journals or presented at medical meetings. However, the authors will only use the assigned patient number in the article or presentation. All research records and data will be kept in a locked cabinet in the PI's office at the VASDHS.
4) Minor complications such as local skin irritation may occur due to the peripheral neurosensory testing, and will be managed conservatively with rest and /or oral non-narcotic analgesics. The PI and the co-investigators are either board certified anesthesiologist or Advanced Cardiac Life Support (ACLS) certified.

Potential Benefits

Patients with PTP-NP will benefit from the study with potential pain reduction, and functional and quality of life improvement. In addition, the information obtained can potentially explain the cause(s) of their symptoms and guide the development of treatments that can potentially correct the aberrant neuronal functions leading to their debilitating symptoms.

Importance of Knowledge to be gained

The outcome of the study can help understanding the pathophysiology of PTP-NP and validating the treatment effect and mechanisms of a novel, non-invasive, low-risk and low cost treatment modality to the general VA patient population.

Data from neurosensory testing and mapping of allodynic area will also provide objective evidence and facilitate other treatment development in rectifying these functional abnormalities.

Risk and Benefit ratio

Given that PTP-NP can significantly impair a patient's daily function and quality of life and conventional therapy with multiple pharmacological agents usually consist of many side effects, and the minimal risk associated with tMS treatment, the risk /benefit ratio in the current study is very low. Therefore, the proposed study can potentially gain crucial knowledge about the utilization of a novel non-invasive therapy for Veterans with PTP-NP.

Children and Women

No children will be recruited for this study. VA requires a waiver for a research on children and currently VASDHS does not offer a pediatric service. Female subjects who meet the study inclusion and exclusion criteria will be recruited. Female Subjects at childbearing age will be required to have a urine pregnancy test prior to the enrollment.

Data and Safety Monitoring

This study assesses the effect of tMS in alleviating PTP-NP. For the objectives of the study, sensitive information (SI) collected in the study will include patients' demographic information such as age and gender, patients' location, severity and duration of pain and level of disability related to the chronic pain conditions. Information regarding past medical history, co-existing diseases and current medication will also be collected and recorded in the VA computer under the PI or research coordinator's hard drive. All SI data will be encrypted and stored in separate data management system. Information regarding the study will be stored in the PI's office inside locked cabinetry. Subjects will only be identified with initials and assigned subject numbers in the data sheets. Data collected from the subjects will be encrypted and assigned a number matching the subjects. The matching list will be stored in secure locked cabinet in the PI's office.

The SI will only be assessed by the PI, and other approved study personnel. In the event of a real or suspected breach of security, the VA police, the VA information Security Office, and the VA Privacy Officer will be notified as soon as possible. SI will be accessed, stored, and destroyed according to a data security plan that will promote security and privacy. The raw data sheet will be stored in the PI's research office at building 23 in a locked cabinet and destroyed by either the PI or the study approved personnel not later than 2 years after the close-out of the study by cross-shredding or the then approved VA procedure. The analysis data file will include only de-identified data related to goals of this study and will access only by approved study personnel.

Data Safety Monitoring Board (DSMB):

The DSMB will review all unanticipated problems involving risk to study subjects, serious adverse events, and all subject deaths associated with the protocol, and provide an unbiased written report of the event within 10 calendar days. The DSMB will provide an independent evaluation of adverse events and unanticipated problems involving risk to subjects to the Human Subject Protection Committee. The DSMB will

comment on the outcomes, adverse events, and relationship of the events to the protocol. The DSMB will indicate whether they concur with the details of the report provided by the PI. The DSMB promptly reports discrepancies or problems to the Human Subject Protection Committee. They have the authority to stop a research study in progress, remove individual volunteers from a study, and take whatever steps will be necessary to protect the safety and well being of research subjects until the Human Subject Protection Committee can assess the report. The members of the DSMB for this proposal will comprise of a pain specialist, a clinical psychologist and a biostatistician who will be independent of the investigative team and possess sufficient educational and professional experience to serve as the subjects' advocate. The members of DSMB also have no apparent conflicts of interest.

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