Treatment of Low Back Pain Using Transcutaneous Magnetic Stimulation (TCMS): A Feasibility Study

TCMS Protocol Version: 1.0

Protocol Date: April 25, 2016

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1.0 PURPOSE

Preliminary evaluation of the safety and effectiveness of Transcutaneous Magnetic Stimulation (TCMS) for the relief of low back pain.

2.0 OBJECTIVE

To perform a preliminary study of the feasibility, safety, and effectiveness of TCMS for the relief of low back pain.

3.0 HYPOTHESIS

TCMS treatment will lead to a clinically meaningful reduction in lower back pain associated with degenerative lumbo-sacral spine disease.

4.0 PRODUCT

Zygood TransCutaneous Magnetic Stimulator (TCMS)

5.0 SPONSOR

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301-922-9225

6.0 SITE

University of Maryland Rehabilitation and Orthopaedic Institute
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7.0 DESIGN

Single-site, randomized, single -blind, placebo-controlled, trial

8.0 INTERVENTION

Subjects will identify the location of pain on their back. A member of the study team will note the location on a drawing. The TCMS device will be placed at the site the patient

identified. (Low back pain is defined as pain below the costal margin posteriorly, extending as low as the upper buttocks.)

With only a hospital gown intervening, the clinician will place the active or sham TCMS device on the area of pain, turn the device on, and adjust the amplitude upward from 0.24T in increments of 10%, approximately every 6-10 seconds, until the 1.2T setting is achieved or the subject reports discomfort. If the patient reports discomfort, the amplitude will be adjusted downward as necessary to maintain patient comfort.

Treatment group: TCMS device set to 1.2 Tesla will deliver a dose of 10 pulses per minute for 9 minutes (total 90 pulses). The first minute will be dedicated to adjusting the amplitude until maximum is achieved and/or the subject reports a sensation.

Placebo group: the sham TCMS device will remain on the area of pain for 10 minutes. The sham TCMS device is engineered so as to make the same sound at the same intervals as the active device. The same procedures will occur as those with the active device. The first minute will be dedicated to adjusting the "sham" amplitude. The remaining 9 minutes will be the treatment period.

9.0 ASSESSMENTS

9.1 Numeric Pain Rating Scale (NPRS):

0 to 10 numerical pain rating scale with equally spaced numerical intervals ranging from 0 representing "no pain" to 10 representing the "worst imaginable pain"

9.2 Baseline severity (Pain Diary):

Patient will document in a diary the severity of their pain on each day of the preceding week just prior to treatment.

9.3 **Severity during treatment** (immediate benefit):

At 5- and 10-minutes

9.4 **Severity after treatment is completed** (treatment durability):

1, 2, 4, 8, 12, 24, 48 and 72 hours post-treatment.

9.5 We will also follow-up with patients at 7and 30 days post-treatment,

Data collected at baseline, 7 day and 30 day follow-up:

Global Pain Scale (GPS)

Medication usage –Case Report Form

Non-drug treatment -Case Report Form
Functional Status (ADLs, Mobility, Employment)- Case Report Form

Patient satisfaction with treatment- Case Report Form
Presence of unwanted treatment effects, including paresthesia, irritation or discomfort, referred pain, and motor effects. – Case Report Form

10.0 ADDITIONAL DATA COLLECTED

Demographic information (age, sex, ethnicity, employment status) and medical history and result of physical examination, including weight, height, pain diagnosis (noting any nerve compression), pain characteristics, pain etiology, pain duration, pain location (noting any leg pain), treatment history, and results of imaging study or studies.

11.0 DEFINITION OF SUCCESS

Treatment success is a 30% reduction in mean baseline pain score on the 0 to 10 Numeric Pain Rating Scale (NPRS) that persists at least 1 hour and occurs at any time in the period from treatment through 48-hour follow-up.

Study success is at least 3 of 10 treatment patients meeting the criteria for treatment success and no serious adverse events reported in any subject related to active treatment.

12.0 EFFECTIVENESS OF ANALYSIS

Quantitative, but not statistically powered, trend-analysis of effectiveness of active treatment vs. sham.

Comparison of mean magnitude of treatment effect (change in NPRS) between sham and active treatment (cumulative responder analysis)
Medication usage
Non-drug treatment
Global Pain Scale (GPS)
Patient satisfaction with treatment
Presence of unwanted treatment effects, including paresthesia, irritation or discomfort, referred pain, and motor effects.

13.0 SUBJECT SAFETY

Board-certified anesthesiologists are immediately available.

The risk level to subjects is considered minimal. The device shares technology with an FDA-approved TMS with which no adverse events (AEs) have been associated (http://www.gpo.gov/fdsys/pkg/FR-2014-07-08/html/2014-15876.htm).

The "dose" of magnetic stimulation is comparable to that delivered during magnetic resonance imaging (MRI) but is transient and localized to the area of pain. Based upon clinical experience, viz. with MRI, AEs are not anticipated with this application of magnetic stimulation.

14.0 SAFETY ANALYSIS

Qualitative tabular record of any AEs.

15.0 SAFETY ENDPOINTS

Any undesirable sign or symptom (specific narrative documentation is required for abnormal motor activity, pain of different modality or location, somatic sensations of any kind occurring during treatment)

Serious adverse event (SAE) from any cause precipitating inpatient and/or invasive medical evaluation/treatment

Human factors: detailed evaluation regarding usability, especially

- Misinterpretation of display
- Mistaken entry of intended prescription
- Injury to device operator
- Significant interference with operation of other medical monitoring devices external to the patient

16.0 SAMPLE SIZE

20 (10 control and 10 intervention) subjects who complete treatment/sham based on an estimate that this number will be sufficient to reveal whether this therapy is safe and whether further studies are warranted to investigate the level of any clinically meaningful pain relief.

17.0 RECRUITMENT, ENROLLMENT, AND ELIGIBILITY CONFIRMATION

All potential subjects identified through standard clinical practice at the site will be listed on a Screening Log and provided with detailed study information, including a description of TCMS.

We anticipate that 350 patients will be screened and 20 patients will be randomized to either placebo or intervention

If the subject is willing to participate, written informed consent will be obtained.

A subject is considered provisionally enrolled upon completion of the informed consent process.

Subjects provisionally enrolled will be taught how to complete a 7-day diary recording low back pain and will complete this diary before randomization (Self-Report).

Subjects will not be told the pain scores are needed for study inclusion.

The principal investigator or a member of the study team will review the diary to confirm that the subject's mean pain intensity score meets the inclusion criteria. Subjects who do not complete the diary or who fail to meet preliminary pain eligibility requirements will not be randomized, are ineligible for participation in the study and will not be counted in the number of enrolled patients. In such cases, the principal investigator or an authorized designee will log this into the data collection system.

If a patient is unable to tolerate at least 50% of the max 1.2T they will be excluded from the study.

> ***** *A significant change for this study is defined as a 20% increase or decrease in dosing of the patient's opioid dose and/or or a change in the medication class (adding or removing other types of medicine used to treat pain).*
>
> ****** *This exclusion is restricted to opioids, benzodiazepines and psychotropics.*

18.0 INCLUSION /EXCLUSION CRITERIA

18.1 INCLUSIONS

1. Age ≥ 18 years of age
2. Prescription pharmacologic treatment is insufficient for treatment of pain
3. Pain duration of ≥ 6 months
4. Pain limits physical activity

5. Pain occurs daily
6. Chronic low back pain, with or without leg pain, associated with MRI or other imaging study consistent with lumbo-sacral spine disease with or without nerve compression
7. Failed back surgery patients without metal implant
8. Pain intensity ≥ 5 at the time of enrollment and a self-reported pain score of ≥ 4 over the 7 preceding days.

18.2 EXCLUSIONS

1. Life expectancy ≤ 6 months
2. Oral opiate doses or active ingredient has changed significantly in past 12 months*
3. Received intraspinal medication (e.g., epidural, intrathecal) in the lumbar region of the back within the past 3months
4. Use of intravenous pain medication in the past 3months**
5. Active use of transcutaneous electrical nerve stimulator (TENS) (within 30 days)
6. History of seizures
7. History of implanted medical device, cardiac pacemaker, implantable cardiac defibrillator, or other implant above the knee (Cochlear etc)
8. History of cardiac dysrhythmias
9. Member of a vulnerable population
10. Current or potential legal action of disability claim related to back pain
11. Body Mass Index (BMI) of > 40
12. Another pain condition that might confound results (e.g. back pain above the waistline)
13. Pregnant women
14. Inability to undergo study assessments or complete questionnaires independently
15. Metal objects in the body above knee(i.e. Aneurysm clip, bullet fragment)
16. Active psychological co-morbidities (i.e. uncontrolled schizophrenia)

19.0 VISITS/PHONE ASSESSMENTS

Screening process ~ 60 minutes

Eligibility confirmation (baseline), informed consent, randomization and treatment (if enrolled) visit ~ 90 minutes

48-hour reminder follow-up telephone call ~30 minutes

Final 7& 30 day assessment telephone call ~ 30 minutes

The date of treatment will be used to calculate the time for follow-up visits.

20.0 Group Allocation

Block randomization to treatment group 1 (n = 10) or 2 (n = 10). We will use the RAND function in Excel to assign a random number from 1-20 to each of our participants. Participants who are randomly assigned odd numbers will be assigned to the intervention group. Participants who are randomly assigned even numbers will be assigned to the control group.

20.0 SCHEDULE OF EVENTS (SEE TABLE BELOW)

Informed consent
7-day pain diary to confirm eligibility (Self-report)
Enrolled or deemed ineligible
Randomization
Randomized treatment
1-, 2-, 4-, 6-, 8, 12, 24, and 48-hour follow-up
24-hour follow-up (±8 hours)
48-hour follow-up (± 8 hours)
72-hour follow-up (± 8 hours)

Final assessment 7 & 30 day follow-up telephone call (+ 3 days)

21.0 STUDY DURATION FOR SUBJECT

Duration of the study for a subject, including follow-up, will be approximately 30 days

22.0 DURATION OF STUDY

Recruitment, treatment, follow-up and data analysis will require approximately 120 days.

23.0 SUBJECT DISCONTINUATION OR STUDY SUSPENSION

Eligible, randomized subjects will be replaced if lost

Study enrollment will be suspended pending principal investigator's decision in response to any SAE

Individual participation will be suspended pending physician disposition in the presence of any SAE

We will request that withdrawn subjects continue to fill out the study questionnaires and allow us to collect data.

24.0 PROTOCOL DEVIATIONS

Protocol deviations will be recorded.

25.0 DATA COLLECTION/CASE REPORT FORMS

Researchers not involved in patient clinical care will collect data. During all study phases, all data will be collected on paper CRFs and later entered into the eCRFs for storage in the secured password-protected database. This study will utilize REDCap for data collection, transmission and storage. REDCap (Research Electronic Data Capture) is a secure, web-based application for building and managing online databases. All study data will be entered via a password protected, study unique REDCap database website. REDCap servers are housed in a data center at Vanderbilt University and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines. REDCap has been disseminated for use at many institutions and currently supports > 140 academic/non-profit consortium partners and 11,000 research end-users (www.project-redcap.org).

26.0 DATA ANALYSIS

Descriptive statistics, trend analysis of endpoint means for effectiveness. Tabular collection of adverse events with narrative

STUDY SCHEDULE AND DESCRIPTION OF DATA COLLECTION

Time of data collection	Data collected						
	Log entry	Demographics	History	Informed consent	NPRS first rating or since last rating given	AE	Additional endpoints
*Eligibility screened and offered participation	X	X	X	X			
*Pain each day in 7-day period					X	X	
Day 1 (baseline = start of treatment)					X	X	X
During treatment: 5 minutes					X	X	
10 minutes					X	X	
After treatment: 1 hour					X	X	
2 hours					X	X	
3 hours					X	X	
4 hours					X	X	
8 hours					X	X	
12 hours					X	X	
24 hours					X	X	
48 hours					X	X	
72 hours					X	X	
*Final assessment 7 & 30 days (+3)		X (employment status only)			X	X	X

*Data can be collected in person, via mail, via telephone, email, or fax

LAY SUMMARY

The study will evaluate whether an experimental medical device that emits a brief, intense magnetic field will relieve pain in the low back. The United States Food and Drug Administration (FDA) has approved a similar device for treatment of migraine, but this type of device has not been studied for the treatment of low back pain. No significant adverse reactions or side effects have been reported from the use of magnetic stimulation for headache treatment. Some patients who have migraine headaches have excellent pain relief with the magnetic treatment even if they did not get pain relief with medications.

We do not know whether magnetic treatment will relieve low back pain, so we will test this by applying a powerful electromagnet to the painful area of the low back. In some subjects, the magnet will be turned on, but in other patients the magnet will not be turned on. Neither subjects nor subjects' treating doctor will know whether the magnet was turned on or not, although the study team will know which subjects received treatment with magnetic pulses. The effect on pain will be recorded periodically for 2 days. If the subjects' reported pain is reduced as a result of the magnetic treatment compared with subjects who did not have the magnet turned on, then the magnet might have reduced the pain. Additional studies will be needed to further investigate whether this therapy reduces low back pain.

Keywords: low back pain, TCMS (Transcutaneous Magnetic Stimulation)**, TENS** (Transcutaneous Electrical Nerve Stimulation)

RATIONALE AND BACKGROUND

Approximately one third of the population suffers from acute and chronic pain at any given time, and the lifetime incidence of low back pain is 80%. Pain has been called a silent epidemic. Treatment of pain with medication incurs significant risks and side effects; even over-the-counter medication causes occasional fatalities (e.g., acetaminophen or Tylenol can cause liver toxicity; and nonsteroidal anti-inflammatory drugs, such as aspirin and ibuprofen, can cause bleeding). Opioid medications have a significant potential for abuse, addiction, and adverse reactions, such as respiratory depression and death.

Electrical stimulation for the relief of pain has been used since antiquity, and with the development of compact power sources and solid state electronics in the last century, it has become commonplace. Electrical stimulation has been applied to the peripheral (e.g., in the limbs) as well as the central (brain and spinal cord) nervous system, using implanted as well as external noninvasive devices.

Electrical stimulation specifically for low back pain, the condition addressed in this protocol, is supported by high quality clinical trial evidence for spinal cord stimulation (SCS), using surgically implanted electrodes and pulse generators. Randomized controlled trials have shown that SCS is superior to optimal medical management and to repeated low back surgery in patients with persistent or recurrent low back and leg

pain following spinal surgery (North et al., 2005). High frequency SCS has been effective for low back pain in particular. SCS has been in use for nearly 50 years. Medtronic, Inc.; St. Jude Medical, Inc.; and Boston Scientific Corporation all have FDA-approved devices, which require surgical implantation and maintenance for the production of electrical pulses to relieve pain.

Subcutaneous peripheral nerve field stimulation targets low back pain via electrodes implanted directly over the painful area and is less invasive than SCS even though it uses the same implanted pulse generators as SCS (Barolat et al., 2009).

Transcutaneous electrical nerve stimulation (TENS), a noninvasive technique, has been used for several decades to treat low back pain. TENS passes current through intact skin via surface electrodes with conductive gels and adhesives. TENS is available without a prescription but is not free from side effects, notably skin pain caused by recruitment of small nerve fibers immediately beneath the surface of the skin [Barker 85], which limits the usage amplitude of the electrical current and thus makes it difficult to stimulate deep structures.

Compared with electrical stimulation, magnetic stimulation has a much shorter history [Thomson 1910]. Magnetic stimulation is an application of Faraday's Law, whereby a high intensity magnetic pulse generates an electrical pulse within conductive media, including excitable tissue, viz., nerve and muscle. Magnetic stimulation has been used to stimulate peripheral nerves selectively [Oberg 73, Polson 82]. Compared with other forms of stimulation, transcutaneous magnetic stimulation (TCMS), which is administered through intact skin, can create larger electrical currents in nerves at greater depth with little, if any, skin pain [Barker 85]. In fact, magnetic stimulation can act through the skin and the skull to stimulate the brain, minimizing recruitment of overlying structures, such as pain fibers in the scalp. Such transcranial magnetic stimulation has been used extensively for the diagnosis and treatment of neurological disease (e.g., stroke) and treatment of psychiatric disease (e.g., depression). Repetitive transcranial magnetic stimulation [Wassermann 98] has been used to treat a number of pain conditions. A meta-analysis of repetitive transcranial magnetic stimulation, demonstrates effectiveness for craniofacial pain syndromes [Leung 09]. "Single pulse" transcranial magnetic stimulation (at a much lower power than used in repetitive TMS) has been effective for migraine using a device that can deliver pulses, each of duration less than 1 msec, as often as every 30 seconds [Lipton 10, Diener 10].

TCMS (of the periphery), unlike transcranial magnetic stimulation, has received little attention as a treatment for pain; it has been the subject of a single published case series, with reportedly positive results in 5 patients with painful peripheral nerve injury or neuroma [Leung 14]. Modification of peripheral nerve activity—even if it is distal or collateral—in the same segment as a pain generator can afford substantial relief (North et al., 1996). The development of an effective, minimal risk, non-invasive treatment of pain without medication would represent a significant advance in the field.

The first commercial magnetic TCMS stimulators were produced in Sheffield in 1985. These devices consist of a capacitor charge/discharge system with associated control and safety electronics. Using the charging circuitry, the capacitor stores energy to a pre-set level. When the device receives a trigger input signal, the stored energy, apart from that lost in the wiring and capacitor, is transferred to the stimulating coil and then returned to the instrument to reduce coil heating.

The most widely used description of the output of magnetic stimulators is “magnetic field strength,” although this refers to the density of magnetic flux rather than total magnetic flux and is a poor measure of output produced by the stimulating coil over its total area. In a small coil, where the magnetic flux is concentrated in a small area, the magnetic field intensity is higher than in a larger coil, but the field falls off much more rapidly with distance. Hence a small coil is somewhat more powerful in the stimulation of superficial nerves, and a large coil is more suitable for structures at depth. The amplitude, waveform, and spatial characteristics of the induced current all play a role in magnetic nerve stimulation.

A more accurate indicator of the stimulating power output is the induced charge density per phase defined as the integral of the induced current density during the rise time of the magnetic field. Unlike magnetic field strength, induced current density takes into account the effects of the amplitude and the duration of the induced stimulating current. Induced current density does not, however, consider the effects of the nodal time constant of the myelinated nerve fiber. Unfortunately, the actual value of the induced charge density per phase is difficult to calculate accurately due to the complexities of the structure being stimulated. Different areas, such as bone, fat, grey matter, and white matter, with differing conductivities all affect the induced current and its path.

The stimulating coil is the only part of a magnetic nerve stimulator that needs to come close to, or into contact with, the patient. During the discharge of the magnetic pulse, the coil winding is subjected to high voltages and currents. Although the pulse generally lasts for less than 1ms, the forces acting on the coil winding are substantial and depend on the coil size, peak energy, and construction. Careful coil design is, therefore, a very important aspect in the construction of a magnetic stimulator. Compared with a small coil, large coils contain more copper mass and generally have a lower electrical resistance; as a result, less heat is dissipated in the windings of large coils, and because of their higher heat capacity, they remain usable for much longer periods before becoming warm.

Since the magnetic field strength falls off with distance from the stimulating coil, the stimulus strength is at its highest close to the coil surface. The stimulation characteristics of the magnetic pulse, such as depth of penetration, strength, and accuracy, depend on the rise time, the peak magnetic energy transferred to the coil, and the spatial distribution of the field. The rise time and the peak coil energy are governed by the electrical characteristics of the magnetic stimulator and stimulating coil,

whereas the spatial distribution of the induced electric field depends on the coil geometry and the anatomy of the region of induced current flow.

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