Effect of Acupuncture and Pain Medication on Radicular Pain Using QST

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Principal Investigator: Lucy Chen, M.D.

I. BACKGROUND

a. Historical background

Acupuncture is an ancient healing art. Like other modalities of alternative medicine, acupuncture has recently gained popularity as well as scrutiny in Western nations (Eisenberg et al., 1998; Wearn and Greenfield, 1998; Bracha, 2005; Kozak et al., 2008). Due to a dramatic increase in the use of acupuncture, the National Institutes of Health (NIH) convened a Consensus Development Conference on Acupuncture more than a decade ago, which found that acupuncture has been practiced by thousands of physicians, dentists, acupuncturists, and other practitioners for relief of pain and other health conditions (NIH Consensus, 1997). In 2002, the World Health Organization (WHO) published a review of all clinical trials through 1999 in which acupuncture was used (WHO, Acupuncture: Review and Analysis of Reports on Controlled Clinical Trials. 2002. www.who.int). The WHO summary categorizes the clinical data into four groups based on the data quality. A recent meta-analysis indicates that significant methodological differences exist with regard to the quality of clinical trials evaluating non-pharmacological (e.g., acupuncture) versus pharmacological treatments, showing a lower quality score for reports of non-pharmacological treatments than those for reports of pharmacological treatments (Boutron et al 2003). A subsequent study found that the reporting quality for acupuncture trials was significantly improved after introduction of STRICTA and CONSORT recommendations for the standard reporting of acupuncture trials (Prady et al., 2008), although these reports do not specifically address the issue of developing comparative and translational research tools. To date, there still lacks a standard clinical assessment paradigm to comparatively evaluate the efficacy of acupuncture therapy. Thus, a pressing issue is how to evaluate the clinical efficacy of acupuncture therapy, given the current trend towards evidence-based medicine using high-quality, randomized, controlled trials for clinical outcome measures. This issue is further complicated by the fact that pain is historically considered as a subjective experience that has individual variations. As such, evaluating the effectiveness of acupuncture in pain management presents an even more daunting challenge.

b. Previous pre-clinical or clinical studies

Acupuncture has been used for clinical pain management, particularly for chronic pain (Carlsson et al., 2001; Leibing et al., 2002; Molsberger et al., 2002; Manhermer et al., 2005, 2006; Cherkin et al., 2009), although its clinical outcome remains uncertain. For example, in a randomized, blinded, and placebo controlled trial of 131 back pain patients treated with acupuncture or physical therapy, acupuncture was found to be superior to controls on pain reduction and improvement in disability and psychological distress. When compared to the sham acupuncture group, however, acupuncture was only superior in reducing psychological distress (Leibing et al., 2002). In another prospective randomized controlled trial, acupuncture treatment was significantly better in pain reduction than sham controls at a 3-month follow up (Molsberger et al., 2002), whereas other studies demonstrate a long-term beneficial effect (up to 6 months) after a 20-session acupuncture therapy in patients with fibromyalgia or neck and shoulder pain (He et al., 2004; Targino et al. 2008). Of interest to

note is that there are only few head-to-head comparison studies comparing the effect of a medication with acupuncture on chronic pain treatment. For example, a randomized controlled clinical trial compared pain medication, needle acupuncture, and chiropractic spine manipulation on chronic (>13 weeks duration) spine pain. Patients were assessed before and after a treatment using Oswestry Back Pain Disability Index (Oswestry), Neck Disability Index (NDI), Short-Form-36 Health Survey questionnaire (SF-36), visual analog scale (VAS) of pain intensity and the range of movement. The highest percentage of recovery was found in patients receiving spine manipulation (27.3%), followed by acupuncture (9.4%) and medication (5%), suggesting that acupuncture does show a clinical effect comparable to spine manipulation or medication alone (Giles and Muller, 2003). These data indicate that acupuncture therapy may be beneficial in pain management, although the outcome measure varies from study to study.

c. Rationale

We chose gabapentin as the pain medication to be used in this study because: **a)** gabapentin has been used to treat neuropathic pain including radicular pain, **b)** gabapentin is a non-opioid pain medication, which will be easy to titrate and monitor, and **c)** gabapentin attenuates hyperalgesia (exacerbated painful response to noxious stimulation) and allodynia (painful response to innocuous stimulation) that can be evaluated by Quantitative Sensory Testing (QST) (Mao and Chen, 2000).

II. SPECIFIC AIMS

a. Objectives and hypotheses

In this aim, we propose to conduct a double blind, placebo-controlled, and randomized clinical trial to compare the clinical effectiveness of radicular pain relief by either acupuncture therapy or a course of pain medication (gabapentin) using QST. The QST results will allow us to compare between the two treatments, thereby verifying the potential for alternative treatments for those with chronic neck and back pain.

III. SUBJECT SELECTION

a. Inclusion/exclusion criteria

We propose to recruit subjects with cervical or lumbar radicular pain. The rationale for selecting subjects with cervical or lumbar radicular pain is two-fold: 1) there is a large pool of patients with such pain conditions and 2) a QST plate can be placed along the mirror distribution areas to compare the effect of acupuncture between the two sides. Every effort will be made to make demographic matches (age, gender, duration of pain, etc.) among study groups in order to minimize study bias.

Inclusion criteria:

(1) Subject will be between ages 18 to 75 years. Both male and female subjects will be recruited.
(2) Subject should have had cervical or lumbar radicular pain for at least two months. This requirement is to avoid the uncertainty of an unstable pain condition and to minimize the study variation.
(3) Subject has a pain score of 4 or above (visual analog scale, VAS: 0 – 10 from no pain to worst pain).

(4) Cervical or lumbar radicular pain will include, but is not limited to, such clinical conditions as disk herniation, spinal stenosis, and post-laminectomy syndrome.

Exclusion criteria:

(1) Subject has detectable sensory deficits at the site of QST. Sensory deficits refer to such conditions resulting from neurological diseases or medical conditions causing peripheral polyneuropathy and sensory changes, which include but are not limited to diabetic neuropathy, alcoholic neuropathy, AIDS neuropathy, severe thyroid disease, and severe liver or kidney disorders.
(2) Subject has scar tissue, infection, or acute injury at the site of QST.
(3) Subject is pregnant or nursing.
(4) Subject tests positive for illicit drugs, marijuana, or drugs not prescribed to him/her.
(5) Subject has a pacemaker.
(6) Subject is currently taking gabapentin.
(7) Subject is hypersensitive to diphenhydramine and/or gabapentin.

b. Source of subjects and recruitment methods

Study subjects will be recruited from 1) pools of pain patients under treatment at the MGH Center for Pain Medicine and 2) local community through advertisements and referrals. The MGH Center for Pain Medicine is a multidisciplinary unit including an acupuncture clinic. There are over 14,000 annual visits at the Center with hundreds of acupuncture visits.

IV. SUBJECT ENROLLMENT

a. Methods of enrollment, including procedures for a patient registration or randomization

1. Study subjects will be recruited through advertisements, U.S. post, or in person initially by a non-study clinical caregiver at the MGH Center for Pain Medicine. Study subjects can contact the MGH Center for Translational Pain Research for information about the study.
2. The study investigator will obtain verbal approval through colleagues from patients before contacting them. The patient's attending will introduce the study, and if the patient is interested, study details will be explained to potential subjects by a study staff member. If the subject is still interested, an initial evaluation will be conducted with a prepared phone-screening questionnaire.
3. If a subject passes the initial evaluation, Visit #1 will be scheduled. At Visit #1, the study protocol will be explained and all questions and concerns will be fully answered.

Four groups (n=25) of subjects with cervical or lumbar radicular pain will be recruited. Study subjects will be assigned to one of four groups using a computer-generated randomization protocol (Randomization.com).

b. Procedures for obtaining informed consent

At Visit #1, the subject will meet with a study investigator (licensed as a physician and acupuncturist) to review and sign the consent form.

c. Treatment assignment, and randomization

One hundred subjects with cervical or lumbar radicular pain will be recruited. Potential study subjects will first be selected based on the general inclusion and exclusion criteria described above. These subjects will be randomly assigned into one of four groups (n=25): ***Group 1***) subjects will receive a course of gabapentin treatment; ***Group 2***) subjects will receive a course of sham drug, diphenhydramine; ***Group 3***) subjects will receive acupuncture therapy; and ***Group 4***) subjects will receive sham acupuncture. A sham acupuncture group is included in the acupuncture arm in order to match the design in the pain medication arm that includes a sham drug group as well. Study subjects will be assigned to one of four groups using a computer-generated randomization protocol (Randomization.com). The subjects and investigators will be blinded within the medication groups (drugs vs. sham drug)/acupuncture groups (acupuncture vs. sham) but not between these groups.

V. STUDY PROCEDURES

a. Study visits and parameters to be measured

The following are the highlights of the study protocol.

(1) Informed consent will be obtained by a licensed physician who is also licensed in acupuncture.
(2) Subjects will be randomly assigned to one of the four groups (n=25).
(3) An initial physical examination will be performed, including Traditional Chinese Medicine (TCM) measurements (tongue, pulse, mood, and sleep). A urine toxicology screen to test for illicit drugs, marijuana, and drugs not prescribed to the subject, and a pregnancy test, if female subject is of reproductive potential, will be performed.
(4) Each subject will be asked to complete a pain questionnaire, Beck Depression Inventory II (BDI-II), a modified McGill Pain Questionnaire and SF-36 form at three different time points: baseline (before any intervention), after session 3 for acupuncture or within treatment week 2 (e.g. day 11) for the medication group, and after session 6 for acupuncture or within treatment week 3 (e.g. day 18) for the medication group. Subjects in the acupuncture group will be asked to fill out the Massachusetts General Hospital Acupuncture Sensation Scale (MASS) at visits 2-7.
(5) All subjects will be measured by the TCM at every office visit. All subjects will complete the daily pain log throughout the treatment period of the study.
(6) For the acupuncture group, acupuncture or sham acupuncture will be performed twice weekly for at least three consecutive weeks to complete a total of 6 sessions in order to match the total experimental period for the medication group.
(7) For the medication group, the dosing/taper schedule will be followed as listed in the table below. Subjects in the medication group will receive a phone call during the titration phase and at the end of the taper phase.
(8) Quantitative pain assessment (thermal QST). The assessment will be made at three different time points: baseline (before any intervention), after session 3 for acupuncture or within treatment week 2 (e.g. day 11) for the medication group, and after session 6 for acupuncture or within treatment week 3 (e.g. day 18) for the medication group.
(9) Subjects will receive up to $180 for completing the study and transportation costs will be covered with a $10 travel stipend for each office visit. A parking sticker for the MGH garages will be available upon request at each visit. The parking sticker will replace the travel stipend for that visit.

The following guidelines have been created for cases concerning pro-rated remuneration:

1. Subjects testing positive for illicit drugs, marijuana, or undisclosed prescriptions will receive zero payment.
2. Subjects who do not complete the study through their own decision will receive only the travel stipend for the visits attended.
3. Subjects who are withdrawn by an investigator by no fault of their own will receive full payment for the visits attended.

All prorated remuneration will be documented via progress notes and kept with the subject's research folder.

b. Drugs used

Gabapentin or diphenhydramine (sham drug) will be used as two independent treatments in the medication arm. The titration schedule for each medication is shown in the following table. Both medications will be taken orally, and will be prepared, dispensed, and coded by our central pharmacy. The assignment will not be disclosed to the study subject or investigator.

(1) Gabapentin 100 mg capsules will be used, which is easy to titrate. Since the recommended dosing interval for gabapentin is every 8 hours, a three time daily dose (TID) regimen will be used. Tentatively, the target daily gabapentin dose will be 900 mg at the end of the dose titration period.

(2) Diphenhydramine (Benadryl; 25 mg) will be ordered as sham drug. Diphenhydramine could mimic some of the most common side effects of gabapentin such as sedation, drowsiness, and lightheadedness. Diphenhydramine has been successfully used as sham drug in double blind clinical trials of pain medications (e.g., Atkinson et al., 1999; Wallace et al., 2000). However, some uncommon side effects of gabapentin (e.g., mood swing) are unlikely to be mimicked by diphenhydramine. If a subject experiences mood swings after taking the study drug, that subject will be taken off the study medication accordingly.

(3) For both gabapentin and diphenhydramine, we will use a slow titration schedule as listed below based on our clinical experience with both medications. When a slow titration schedule is used, the vast majority of patients are able to continue with these medications (particularly gabapentin), which will help decrease the dropout rate. (4) Because most pain patients are on more than one pain medication, it will be impractical to find subjects who are not on other pain medications (e.g., NSAIDs). Thus, other pain medications will be allowed but their dose should be kept unchanged during the entire experimental period for all subjects in both study groups.

(5) With regard to subject compliance with the study medication, there is a lack of a practical method to check whether a subject has been taking the medication as instructed, particularly for the medications used in this study. However, we will provide study subjects with a log sheet to record their daily medication intake (date and time). Study subjects will also be asked to bring the medication bottle to each scheduled study visit (see below). Capsules will be counted to make sure it matches the balance between total capsules given and capsules taken based on the log sheet. Study medications will be dispensed at the initial visit and the follow-up visit in week 2 (e.g. day 11).

GABAPENTIN/ SHAM DRUG DOSING SCHEDULE						
Day	**Gabapentin AM (mg)**	**Gabapentin Noon (mg)**	**Gabapentin Bedtime (mg)**	**Diphen. AM (mg)**	**Diphen. Noon (mg)**	**Diphen. Bedtime (mg)**
D1	0	0	100	0	0	3
D2	100	0	100	3	0	3
D3	100	100	100	3	3	3
D4	100	100	200	3	3	6
D5	200	100	200	6	3	6
D6	200	200	200	6	6	6
D7	200	200	300	6	6	9
D8	300	200	300	9	6	9
D9	300	300	300	9	9	9
D10	300	300	300	9	9	9
D11	300	300	300	9	9	9
D12	300	300	300	9	9	9
D13	300	300	300	9	9	9
D14	300	300	300	9	9	9
D15	300	300	300	9	9	9
D16	300	300	300	9	9	9
D17	300	300	300	9	9	9
D18	300	300	300	9	9	9
GABAPENTIN/ SHAM DRUG TAPER SCHEDULE						
Day	**Gabapentin AM (mg)**	**Gabapentin Noon (mg)**	**Gabapentin Bedtime (mg)**	**Diphen. AM (mg)**	**Diphen. Noon (mg)**	**Diphen. Bedtime (mg)**
D19	200	200	200	6	6	6
D20	200	200	200	6	6	6
D21	200	200	200	6	6	6
D22	200	200	200	6	6	6
D23	100	100	100	3	3	3
D24	100	100	100	3	3	3
D25	100	100	100	3	3	3
D26	100	100	100	3	3	3
D27	100	0	100	3	0	3
D28	100	0	100	3	0	3
D29	100	0	100	3	0	3
D30	100	0	100	3	0	3
D31	0	0	100	0	0	3

c. Devices used

Quantitative pain assessment:

(1) Quantitative pain assessment will test responses to mechanical andthermal stimulation. We will follow the QST protocols described in previous reports (Price et al., 1994; Yarnitski 1997; Doverty et al., 2001; Angst et al., 2003; Koppert et al., 2003a; Reznikov et al., 2005; Chen et al., 2009). We chose to examine three stimulation modalities in order to compare and contrast the specificity of using QST to examine changes of each sensory modality. All sensory and QST testing will be done on either both arms or both legs depending on cervical or lumbar radicular pain respectively. To evaluate the response to mechanical stimulation, mechanical allodynia will be examined.

a. *For mechanical allodynia*, von Frey filaments will be used at the initial visit. A set of von Frey filaments consists of calibrated synthetic fibers. Each filament delivers a calibrated force when it is bent against the tested site. A series of von Frey filaments will be used in an ascending order to determine the threshold force of stimulation perceived as painful. Each filament will be used five times.

(2) To examine the response to thermal stimulation (thermal QST), Medoc Thermal Sensory Analyzer will be used. Heat/cold threshold, heat/cold pain threshold, pain tolerance, and windup will be examined, as these parameters are reproducible and specific based on our experience with QST (Price et al., 1994; Chen et al., 2009).

a. *To detect heat/cold sensation,* a contact thermode will be placed to the designated body part. The thermode-skin interface temperature will change at 1 ºC/sec from a baseline 32 ºC to maximum 53 ºC or a minimum of 0 ºC. Subject will stop the stimulation by pushing a button when the temperature change is first felt. This test will be repeated three times and the average value from these tests will be used as the heat/cold sensation (in degree Celsius).

b. *To detect heat/cold pain threshold*, a contact thermode will be placed on the designated body part. The thermode-skin interface temperature will change at 1 ºC/sec from a baseline 32 ºC to maximum 53 ºC or a minimum of 0 ºC. Subject will stop the stimulation by pushing a button when the pain is first felt. This test will be repeated three times and the average value from these tests will be used as the heat/cold pain threshold (in degree Celsius).

c. *To detect heat/cold pain tolerance*, the same contact thermode will be placed on the designated body site as described above. Two types of heat pain tolerance will be measured. In one protocol, subject will be asked to tolerate the rising temperature above the pain threshold until he/she can no longer tolerate (the cutoff will be at 53 ºC). (This process will be repeated using cold sensations and the cutoff will be at 0 ºC.) In another protocol, the temperature will be preset at 47 ºC and the subject will be instructed to tolerate the stimulation as long as he/she can (cutoff at 60 sec). The latency between the beginning of heat stimulation and the subject's withdrawal from the stimulation will be recorded. In each case, the subject can withdraw from the stimulation at any time. Each test will be repeated three times and the values from three tests will be averaged.

d. *To examine windup (temporal summation of second pain),* a train of four identical stimuli at 47 ºC (supra-threshold heat stimulation), separated by a 2.2-second interval between each stimulus, will be applied. Subject will be asked to rate pain intensity by VAS following each of the four stimuli. The test will also be repeated three times.

(3) The Medoc QST devices are FDA approved. The MGH Bioengineering Department annually tests the devices for calibration and safety.

(4) The testing will be performed according to the following sequence: mechanical allodynia (von Frey filaments), heat/cold sensation, heat/cold pain threshold, heat/cold pain tolerance, and windup, in order to minimize the confounding effect from one test to the next. Because subjects from all groups will be tested in this same sequence, testing bias will be minimized.

(5) All tests will be performed with the examiner unaware of a treatment condition within the groups (true vs. sham acupuncture, gabapentin vs. sham drug), but the examiner will be not be blinded between the acupuncture and study medication groups. The duration for each QST session including all tests (mechanical, and heat/cold) will run about one hour. Our previous experience suggests that a subject is less likely to become distracted and the results are more reliable when a QST session is kept within approximately one hour.

d. Procedures/surgical interventions, etc.

(1) *Acupuncture mode* -- Different acupuncture modes have been used in clinical practice including electrical acupuncture (electroacupuncture) and manual acupuncture (e.g., Qu and Zhou, 2007; Kong et al., 2009). Apparently, manual acupuncture represents a more traditional mode of acupuncture and may be preferred in many clinical settings (particularly in Southeast Asian countries). In comparison with manual acupuncture, electroacupuncture is easy to perform and can be standardized with regard to its parameters and performance. This is preferred in clinical studies aimed at examining the validity of QST as a tool for the acupuncture outcome assessment. Since examining which acupuncture mode would be more effective in clinical acupuncture therapy is *not* the primary goal of this project, we will use an effective electroacupuncture mode in our experiments.

(2) *Electroacupuncture parameters* -- Different electroacupuncture parameters may produce distinct endogenous biological changes (e.g., opioid versus non-opioid-mediated responses) (Taguchi and Taguchi, 2007; Qu and Zhou, 2007). By the same reasoning that this study is not to examine the differential effect of various electroacupuncture parameters on clinical pain, we opt to use a modified set of electroacupuncture parameters that are familiar to us and have been successfully used in our practice including the treatment for radicular pain from disk herniation and spinal stenosis. Briefly, we will use the following parameters: 3 Hz (frequency), intensity tolerable to subject, 70 microseconds (pulse width), continuous mode, biphasic square wave, and 30-min duration (Electroacupuncture Model ITO IC-1107). The needle size (e.g., 0.2 x 30 mm or 0.25 x 40 mm) will be based on the choice of acupoints. For cervical radicular pain, we will use acupoints Fengchi (GB 20), JianLiao (SJ 14), Quchi (LI 11), Hegu (LI 4), ShouShanLi (LI 10), WaiGuan (SJ 5). For lumbar radicular pain, we will use ShenShu (BL 23), QiHaiShu (BL 24), DaChangShu (BL 25), ZhuShanLi (ST 36), YanLingChaun (GB 34), and HuanTiao (GB 30). These acupoints are chosen based on our clinical

experience. We are aware that there really is not a standard choice of acupoints for a given clinical condition, which may be the ultimate uncertainty and mystery of acupuncture as an ancient healing art. Nonetheless, for the purpose of conducting scientific studies, we will use this set of pre-chosen acupoints in order to minimize clinical variations. However, adjustments can be made during the study if the chosen set of electroacupuncture parameters and acupoints fail to yield a satisfactory therapeutic effect. If any adjustment is made, the change will be applied to all study groups to ensure valid comparisons.

(3) *"Sham" acupuncture* -- To use or not use a "sham" acupuncture control in a clinical trial is another controversial issue (Downs et al., 2005; McManus et al., 2007; Lundeberg, 2008; Lund, 2009). If a sham control is to be used, which one should be chosen? If "deqi" is a clinical indicator of effective acupuncture, how should "deqi" be evaluated using a standardized protocol? While we acknowledge that examining these issues is not the goal of this application, we feel that including at least one type of sham acupuncture control in this project will help make more informed data interpretation. Among several sham acupuncture controls (Manhermer et al., 2005, 2006; McManus et al., 2007), we will use the sham control reported by Streitberger and Kleinhenz (1998). The sham needle is designed so that it is not fixed inside the copper handle. Its tip is blunt, and when it touches the subject's skin a pricking sensation will be felt, simulating the puncturing of the skin. The needle moves inside the handle and appears to be shortened. The sham and true acupuncture procedure will be identical except that the sham acupuncture will use specially designed needles.

(4) In all experiments, QST sessions will be performed by a person who will be unaware of the subject group assignment (e.g., acupuncture versus sham acupuncture), but the examiner will not be blinded of the subject's treatment assignment (acupuncture or study drug).

e. Data collection

Data from descriptive assessments (e.g., McGill Pain Questionnaire, SF-36 form) will be collected throughout the study. Quantitative pain assessments (e.g., QST) will be made at three different time points: baseline (before any intervention), after session 3 for acupuncture or within treatment week 2 (e.g. day 11) for the medication group, and after session 6 for acupuncture or within treatment week 3 (e.g. day 18) for the medication group.

VI. BIOSTATISTICAL ANALYSES

a. Data variables collected for the study:

(1) Overall pain intensity and pain affect (VAS score);
(2) Pain characteristics (e.g., burning, shooting) before and after intervention;
(3) Mechanical allodynia (threshold force);
(4) Heat/cold sensation, heat/cold pain threshold (degree Celsius), and heat/cold pain tolerance (degree Celsius and withdrawal latency in seconds) – QST;
(5) Windup (temporal summation of second pain) – QST.

b. Study endpoints:

(1) Changes in one or more measures listed above among four groups of pain subjects – a between-group comparison;

(2) Differences, or lack thereof, in changes between pain subjects receiving different interventions (e.g., acupuncture or gabapentin) – a between-group comparison;
(3) Changes in one or more measures listed above across three time points within a given group (e.g., pain subjects receiving acupuncture therapy) – a within-group (chronological) comparison;
(4) Differences in altered QST parameters between the affected (with radicular pain) and non-affected (without radicular pain) side – a within-subject comparison;
(5) Differences, or lack thereof, in changes of QST parameters and other measures (e.g., overall pain intensity and pain affect by VAS score) within a given group – a within-group comparison.

c. Statistical methods:

Specifically, we will first identify **a)** QST responders, **b)** clinical responders, and **c)** combined QST and clinical responders.

a) QST responders refer to those subjects who show statistically significant differences in one or more QST parameters on the affected (with radicular pain) and/or non-affected (without radicular pain) side after an intervention (e.g., acupuncture or sham acupuncture).

b) Clinical responders refer to those subjects who show statistically significant improvement in overall VAS score and/or functional status after an intervention.

c) Combined QST/clinical responders refer to those subjects who show statistically significant differences in both QST (one or more QST parameters) and clinical status (VAS and/or functional status).

We will then evaluate the similarities and differences in the response to acupuncture or medication as detected by QST and clinical symptom relief. The goal is to determine whether the analytic approach proposed for the acupuncture outcome measure in *Specific Aim I & II* would be comparable for the outcome evaluation of a medication therapy as well. For example, the number of responders versus non-responders in each group as well as the ratio of responders over non-responders in each category will be used for such comparisons. If the outcomes are consistent and comparable between the acupuncture therapy and medication therapy, it would provide additional evidence for the validity of using QST in combination with other clinical tools as a standardized translational tool for acupuncture research and clinical evaluation.

d. Power analysis

While the response in each individual study may vary, we consider 1.2 degree Celsius in mean pain threshold temperature, 5 seconds in mean withdrawal latency (pain tolerance), and a 2-point change in VAS score to be meaningful differences between study groups (Chen et al., 2009). Thus, a minimal sample size of 20 subjects in each group will have 80% power to detect such differences assuming that the standard deviation is less than 2.0 with a significance level of $P< 0.05$. We anticipate a dropout rate of 10-20%. Accordingly, we will use a sample size of 25 subjects for each group in our study design. If time allows us to expand this group size, we will increase the group size to 30 subjects per group to enhance the statistical power for the analyses.

VII. RISKS AND DISCOMFORTS

a. Complications of surgical and non-surgical procedures, etc.

QST-related stimulation for pain threshold and pain tolerance, although transient, will elicit painful sensation in a study subject. Testing for pain tolerance and acupuncture may cause temporary skin sensitivity similar to mild sunburn. Subjects will be able to terminate a test at any time. If skin change persists, the subject will be withdrawn and proper treatment will be given or be referred to a dermatologist.

Acupuncture is well tolerated by most patients. Occasionally, vasovagal responses may occur and subjects will be attended to immediately by a Massachusetts licensed physician. Infection from acupuncture is rare and aseptic procedures will be followed during the study. Additionally, although rare, some mild skin redness may be noted at the acupuncture sites after treatment.

b. Drug side effects and toxicities

The most common side effects of gabapentin are diarrhea; dizziness; drowsiness; dry mouth; tiredness.

Uncommon but severe side effects that may occur when using gabapentin are rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue; unusual hoarseness; behavior changes; confusion; difficult or painful urination; fever; memory problems; new or worsening mental or mood changes (eg, depression, agitation, anxiety, panic attacks, aggressiveness, impulsiveness, irritability, hostility, exaggerated feeling of well-being, restlessness, inability to sit still); new or worsening trouble sleeping; red, swollen, blistered, or peeling skin; severe headache or dizziness; suicidal thoughts or actions; swelling of the hands, legs, or feet.

Diphenhydramine could mimic some of the most common side effects of gabapentin such as sedation, drowsiness, and lightheadedness.

c. Device complications/malfunctions

The QST device is FDA-approved and is inspected on a routine schedule established by the MGH Bioengineering Department.

d. Psychosocial (non-medical) risks

Uncommon but severe side effects that may occur when using gabapentin are: behavior changes; confusion; memory problems; new or worsening mental or mood changes (eg, depression, agitation, anxiety, panic attacks, aggressiveness, impulsiveness, irritability, hostility, exaggerated feeling of well-being, restlessness, inability to sit still); new or worsening trouble sleeping; severe headache or dizziness; and suicidal thoughts or actions.

e. Radiation risks

Not applicable.

VIII. POTENTIAL BENEFITS

a. Potential benefits to participating individuals

There may be benefits to participating individuals with pain as acupuncture may relieve pain. Gabapentin is often used to treat neuropathic pain and subjects may find some pain relief from taking it.

b. Potential benefits to society

This study will examine a new approach to evaluating the effectiveness of acupuncture therapy. This approach could be used to compare the therapeutic effects on clinical pain between acupuncture (other forms of alternative medicine as well) and conventional medicine and to advance the clinical research on alternative medicine.

IX. MONITORING AND QUALITY ASSURANCE

a. Independent monitoring of source data

The data will be monitored and kept confidential at the MGH Center for Translational Pain Research and the HIPPA procedure will be followed for the data handling. A department statistician will be monitoring the source data upon request.

b. Safety monitoring

A Data Monitoring Committee (DMC) will be formed to monitor the study progress. The DMC will consist of (3-5) members with experience in opioid therapy, pain management, regulatory oversight, and subject safety. The list of actual members will be provided as JIT information per the NIH requirement.

Adverse events will be reported to the PHRC in accordance to the PHRC unanticipated problems including adverse events guidelines.

<http://healthcare.partners.org/phsirb/adverse_events.htm>.

c. Outcomes monitoring

The PI will monitor study outcomes. A monthly study staff meeting will be held to review the study progress and discuss any adverse event.

d. Adverse event reporting guidelines

Adverse events will be reported to the PHRC in accordance with the PHRC unanticipated problems including adverse events guidelines.

<http://healthcare.partners.org/phsirb/adverse_events.htm>.

The Beck Depression Inventory (BDI) will be scored based on the user manual to monitor reports of mood changes, depression, and suicidal ideation. Study physicians will be notified immediately if a subject scores within the moderate to severe depression categories. Steps such as referring to the ED, Urgent Care Clinic, or PCP will be taken following this evaluation. MGH Acute Psychiatric Services (APS) will be informed about this study and the possibility that such subjects may be presented to the APS.

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