Curriculum Vitae

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- 2003-2004 Internship, Internal Medicine
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Certifications

- 2006 Internal Medicine, American Board of Internal Medicine
- 2008 American Board of Medical Acupuncture
- 2008 Medical Oncology, American Board of Internal Medicine

Medical Licensures

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Professional Society Memberships

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- 2008-present American Board of Medical Acupuncture
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- 2010-present Society of Integrative Oncology

Honors and Awards

- 1998 Winner of the Agnes F. Perkins Prize for Prose, Wellesley College English Department, Wellesley College, MA
- 1999 The Charlotte Paul Reese '38 Memorial Prize for Creativity in Writing, Wellesley College, MA
- 1999 Lingos Prize in the Life Sciences, Wellesley College, MA
- 1999 Departmental Honors in Biological Chemistry and English, Wellesley College, MA

- 1999 *Magna Cum Laude*, Wellesley College, MA
- 2000 Sarah Perry Wood Medical Fellowship
- 2008 ASCO Foundation Young Investigator's Award
- 2008 Susan G. Komen Post-Doc Fellowship Award
- 2009 ASCO Merit Award
- 2013 Super Doctor 2013 Washington, DC-Baltimore-Northern Virginia Rising Star

Publications:

1. Bao, T, "The Doctor" *Pharos*, 2004; 67: 37-38

2. **Bao, T**, Smith, B.D., Karp, J.E. "New Agents in the Treatment of Acute Myeloid Leukemia: A Snapshot of signal Transduction Modulation" *Clinical Advances in Hematology & Oncology,* 2005 Apr; 3(4):287-302.
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ABSTRACT

Title of Thesis: A Pilot Study of Acupuncture in Treating Bortezomib-Induced Peripheral Neuropathy in Multiple Myeloma Patients

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Peripheral neuropathy is the main dose limiting toxicity of bortezomib, an effective multiple myeloma (MM) therapy. To examine the safety, feasibility and efficacy of acupuncture in reducing Bortezomib-Induced Peripheral Neuropathy (BIPN) symptoms. MM patients experiencing ≥ grade 2 BIPN after discontinuation of bortezomib were included. Patients received acupuncture twice weekly for 2 weeks, then weekly for 4 weeks, and finally biweekly for 4 weeks. Clinical Total Neuropathy Score (TNSc),

Functional Assessment of Cancer Therapy/ Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) questionnaire and Neuropathy Pain Scale (NPS) were used to assess patients' responses. Proinflammatory and neurotrophic cytokines at baseline, weeks 1, 2, 4, 8, 14 were measured in serum. Nerve conduction studies were performed at baseline and week 12. Twenty-seven MM patients were enrolled in the trial, 26 (96%) were evaluable, 25 (93%) completed at least 4 acupuncture sessions, 20 (77%) completed all 10 sessions. There were no adverse events associated with the acupuncture treatment. At the end of the treatment, eighteen patients (69%) had > 30% reduction in NPS scores. NPS and FACT/GOG-Ntx scores improved significantly at week 10 and 14 when compared to baseline ($p < 0.001$). The TNSc scores, an objective clinical assessment, did not significantly change. No significant changes were seen in serum cytokines. Of fifteen patients who had nerve conduction studies, five showed >10% increase in motor nerve amplitude. Acupuncture is safe, feasible and induces subjective improvements in patients' symptoms. Further studies of Acupuncture are warranted.

A Pilot Study of Acupuncture in Treating Bortezomib-Induced Peripheral Neuropathy in Multiple Myeloma Patients

By

Ting Bao

Thesis submitted to the Faculty of the Graduate School of the
University of Maryland, Baltimore in partial fulfillment
of the requirements for the degree of
Master of Science
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Introduction

Bortezomib is an effective therapy for relapsed and newly diagnosed multiple myeloma (MM) patients. Peripheral neuropathy is a common and debilitating side effect of bortezomib therapy, affecting 37-44% of patients [1]. BIPN usually occurs within the first 5 cycles of bortezomib, requires dose modification and interruption of therapy; negatively affecting the benefit of therapy. BINP is reversible with improvements of symptoms at a median of 1.5 to 3 months (range 0.8-2.7 months) after the discontinuation of bortezomib [2-4]. Painful BIPN accounts for 5%-10% of BIPN, and usually occurs suddenly within the first 3 cycles of bortezomib. It tends to be more severe than non-painful PN and has not been well characterized by the NCI/CTC toxicity criteria. Additionally, it usually takes a longer time to resolve after discontinuation of bortezomib [3, 5]. In few patients, BIPN persist for years after discontinuation of bortezomib and cause significant deterioration of patients' quality of life. [6].

BIPN affects mostly sensory nerves causing spontaneous pain, parenthesia (tingling, numbness), hyperalgesia (increased sensitivity to painful stimuli), allodynia (hypersensitivity to non-painful stimuli), and decreased physical activity [6, 7]. Nerve conduction study suggests that BIPN is a length-dependent, sensory, axonal, large-fiber polyneuropathy [8]. Motor and autonomic dysfunction have also been reported [6].

The treatment for BIPN has been limited to symptomatic management with narcotics, antidepressants, anticonvulsants, and vitamins although data supporting their efficacy is limited [1]. Studies suggest that such analgesic regimens usually only provide modest pain relief and are associated with side effects such as dizziness, sedation, dry mouth and constipation [1, 5, 9]. Several observational and pilot studies have suggested that acupuncture could alleviate peripheral neuropathy symptoms associated with diabetes, HIV and chemotherapy [10-14]. We have previously reported a case report and case series of five MM patients with BIPN who improved significantly after acupuncture treatment [15, 16]. Here we report a single arm prospective clinical trial of MM patients suffering from BIPN treated with a standard acupuncture protocol to assess the safety, feasibility and efficacy of acupuncture in reducing BIPN symptoms.

Methods

Patients

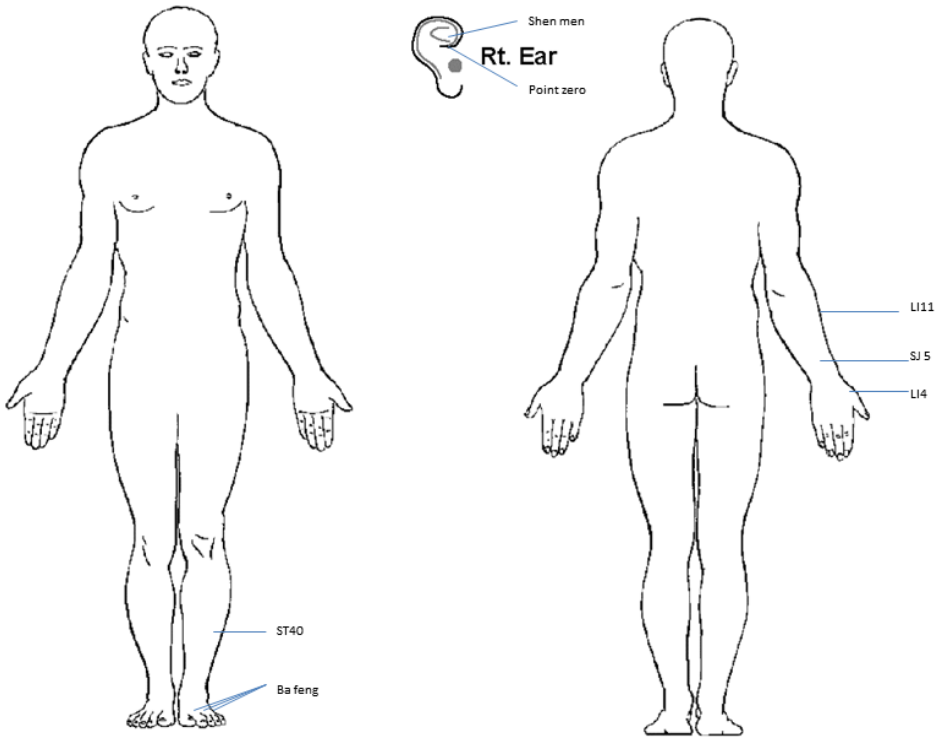
MM patients with persistent, greater than or equal to grade 2 BIPN were eligible. PN was defined by the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) 4.0 despite discontinuation of bortezomib. The grading system is as follows: grade 1: paresthesias or areflexia without pain or loss of function; grade 2: symptomatic, interferes with function but not daily living activities; grade 3: symptomatic, interferes with daily living activities and grade 4: sensorimotor neuropathy that significantly interferes with daily living activities. All patients were treated at the University of Maryland Greenebaum Cancer Center (UMGCC). Patients were excluded from the study if they had acupuncture treatment within the previous month. All patients provided a written informed consent prior to enrollment. This clinical trial was approved by the Institutional Review Board of UMGCC and registered at clinicaltrials.gov (NCT01541644).

Interventions

Patients had acupuncture treatment twice weekly for 2 weeks, weekly for 4 weeks, and then biweekly for 4 weeks (10 sessions). All patients continued their prescribed peripheral neuropathy medications and were encouraged not to change the type or dosage of such medications during the study. Acupuncture treatment was provided by an experienced acupuncturist (T.B.) and used a standard protocol, which includes acupoints that were selected based on our clinical experience and prior research. These included bilateral ear points (shen men, point zero, and two additional auricular acupuncture points where electro-dermal signal was detected), bilateral body acupuncture points LI4, SJ5,

LI11, ST40, and Ba Feng located in upper and lower extremities (Fig.1). For auricular points, the electro-dermal signal was detected through a hand held auricular acupoint finder (the Pointer-Excell II™) through which an alert sounded when the electro-dermal signal was detected. The procedure was performed in a quiet room, using a comfortable bed or massage table. The patient was placed in supine position. The skin at the site of acupoint was disinfected with an alcohol swab. Disposable sterilized Seirin® acupuncture needles were used, filiform 0.16mm x15mm for the ear points and 0.25mm x 40mm for the body points. The acupuncture needles were inserted 0.5 inch into the skin and remained in the skin for 20 minutes after *de qi* sensation, which is a feeling of soreness, numbness and distention was achieved. Acupuncture needles were manufactured by Seirin Co., Japan.

Figure 1. Acupuncture Point Location Map



NOTE: Acupuncture needles were inserted 0.5 to 2 inch into the skin to reach De Qi sensation and remained in the skin for 20 minutes.

Outcome Measures

Clinical Total Neuropathy Score (TNSc, Appendix A), Functional Assessment of Cancer Therapy/ Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx, Appendix B) questionnaire and Neuropathy Pain Scale (NPS, Appendix C) were used to assess objective and patient self-report of BIPN severity at baseline (before the 1st acupuncture

session), after the 1st acupuncture session (week 1) and before the 3rd (week 2), 5th (week 3), 6th (week 4), 7th (week 5), 8th (week 6), 9th (week 8), 10th (week 10) acupuncture sessions and at week 14 follow up. Research nurse (J.P.) conducted TNSc testing, and the patients filled out the FACT/GOG-Ntx and NPS questionnaires before being collected by the research nurse (J.P.) Blood was drawn from the subjects at baseline (before the 1st acupuncture session), right after first acupuncture session (week 1), before the 3rd (week 2), 6th (week 4), 9th (week 8) acupuncture session and at week 14 follow up to measure changes in proinflammatory cytokines: Interleukin 6 (IL6), IL8, IL10, Tumor Necrosis Factor-α (TNF-α), Vascular Endothelial Growth Factor (VEGF), Insulin-like Growth Factor 1 (IGF-1); neurotrophic factors: Nerve Growth Factor (NGF), Brain-Derived Neurotrophic Factor (BDNF), Neurotrophin 3 (NT-3); and beta endorphins (β-EP) concentrations. Lastly, at baseline and at week 12, a board-certified neurologist (N.P.) conducted nerve conduction studies on the subjects who consented to electrodiagnostic testing.

The TNSc is a shorter version of TNS that combines information from symptoms and signs of neuropathy and generates a single score to quantify neuropathy (Appendix A). TNS has demonstrated reliability and validity, with inter- and intra- reliability being 0.97 and 0.99 respectively [17, 18]. TNSc has been shown to be sensitive and accurate in assessing the severity and change in patients' CIPN [19]. It results in a cumulative score ranging from 0 to 28, with the higher TNSc scores reflecting worsening neuropathy symptoms and signs [18]. When compared to FACT/GOG-Ntx and NPS, TNSc is a slightly more objective measure of peripheral neuropathy as the TNSc requires a trained

examiner (J.P.) to conduct neurological testing to assesss pin and vibration sensibility, muscle strength and deep tendon reflexes.

The FACT/GOG-Ntx is an 11-item neurotoxcity subscale covering sensory neuropathy, motor neuropathy, hearing neuropathy, and dysfunction associated with neuropathy to assess the details of neurotoxicity symptoms in the patient (Appendix B). It correlates with meaningful clinical changes in neuropathy. The FACT/GOG-Ntx has demonstrated reliability and validity, with a Cronbach's alpha of 0.81 for the neurotoxicity subscale and an overall Cronbach's alpha of 0.84 [20]. Further, the FACT/GOG-Ntx has demonstrated sensitivity to meaningful clinical distinctions and change over time [20]. The FACT/GOG-Ntx has been validated for self, interviewer, and computer administration [20]. It results in a cumulative score ranging from 0 to 44, with the higher scores reflecting worse neuropathy symptoms.

The Neuropathic Pain Scale (NPS) is a multidimensional tool that uses self-report visual analogue scales to quantify on a scale of 0-10, global pain intensity and unpleasantness and eight other descriptive qualities of neuropathic pain (Appendix C). The NPS also includes one semi-structured question about temporal sequence [21, 22]. The NPS is capable of distinguishing neuropathic pain from non-neuropathic pain [23]. The 10 items demonstrate weak correlations with one another, supporting their discriminate validity [21]. It results in a cumulative score ranging from 0 to 100, with increasing scores reflecting worsening symptoms of neuropathic pain.

Nerve Conduction Studies

After enrollment, but prior to receiving the intervention and at week 12, the subjects who consented to electrodiagnostic testing underwent nerve conduction studies. Motor nerve conduction studies were performed on both peroneal and tibial nerves. Motor amplitudes, motor conduction velocities, distal latencies, and F-wave latencies were recorded from each nerve in standard fashion. Similarly, sensory nerve conduction studies were performed on both sural nerves. Sensory amplitudes and conduction velocities were recorded on each nerve.

Biomarkers collection and testing

The blood samples were collected into BD Vacutainer® SST™ serum tube at the baseline and before each acupuncture treatment on week 1, 2, 4, 8, and 14. The serum was isolated according to the manufacturer's protocol, aliquoted and stored at -80˚C until analysis. The level of seven cytokines: IL6, IL8, IL10, TNF-α, VEGF, nerve growth factor and IGF was detected in the serum samples using a Multiplex system (Millipore, Billerica, MA) at the Cytokine Core Laboratory at the University of Maryland, School of Medicine. The level of β-endorphin (β-EP), BDNF and neurotrophic factor in patients' sera was detected using the specific quantitative ELISA kit form Wuhan EIAab Science Co., (China) at the Cytokine Core Laboratory as well.

Statistical consideration

The objective of this one-arm clinical trial study was to assess the feasibility and safety of acupuncture in treatment of multiple myeloma patients with moderate to severe BIPN. The acupuncture administered to MM patients was considered a feasible intervention if at least 80% patients completed 4 or more acupuncture sessions. One of the end-points used to evaluate the efficacy of this intervention was the reduction in patients' TNSc from baseline level. An average reduction in subjects' TNSc over 10 weeks of treatment of at least 10% would be considered sufficient. We assumed that correlation between observations (TNSc) on the same patient under two different conditions (visit number) is within a range from 0.5 to 0.8, and is constant between each pair of measurements. Using the range of TNSc as 0-28, we calculated summary statistics and used simulations to get the required design parameters. The sample size calculations were done under assumption that each subject would have at least 8 measurements of TNSc. When the sample size is 25, a single-group repeated measures analysis of variance with a 0.05 significance level would have about 90% power to detect a difference in means across the 8 levels of the repeated measures factor characterized by an effect size as small as 0.075. Effect size is a combined measure of variance of the means of individual levels, correlation between observations and standard deviation (SD), variability between subjects, constant at each level. With 25 patients on the study, there will be adequate 80% power to estimate changes in FACT/GOG-Nts and NPS using analogous to TNSc repeated measures approach.

Data on 27 patients treated on GCC 1068 trial were analyzed using the intention-to treat analysis to solve problems with noncompliance and missing outcomes. TNSc, FACT/GOG-Ntx, and NPS were estimated and compared between the baseline and preselected time-points during treatment. Plausible changes in multiple cytokines over time were estimated and compared using the doubly repeated measures approach (multiple markers and repeated time points). Fisher's exact test and logistic regression were used to estimate whether there were any differences in demographic and clinical characteristics between responders and non-responders to acupuncture. The statistical tests were 2-sided and done at the 0.05 level of significance. The feasibility of acupuncture was estimated and reported with the corresponding 95% exact Casella binomial interval Statistical analyses were conducted using S-plus (TIBCO, v. 8.0).

Results:

From May 17, 2011 to February 28, 2012, 46 MM patients were screened and 27 patients who met the eligibility criteria and agreed to participate were enrolled in the study. Patients' baseline characteristics are summarized in Table 1.

Table 1. Patients Baseline Characteristics

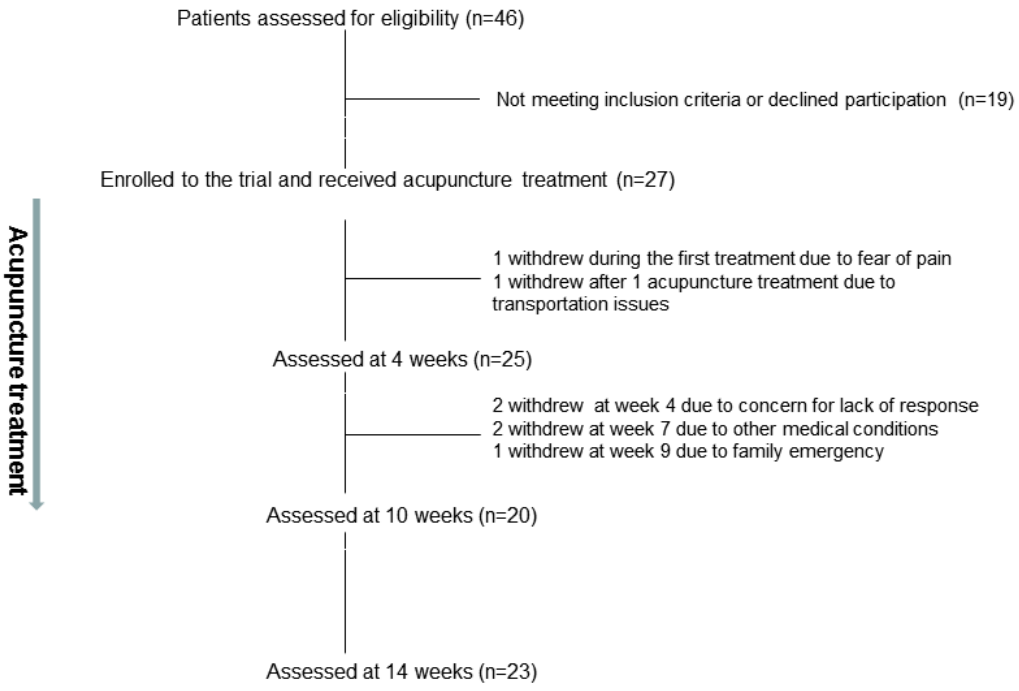
Characteristics	No. of Patients (N=27)
Age, years	
Median (range)	63 (49-77)
Race	
Caucasian	17 (63%)
African American	9 (33%)
BMI	
Median (range)	32 (24-49)
Grade of BIPN	
II	12 (44%)
III	14 (52%)
IV	1 (4%)
Acute Painful PN	8 (29%)

Median (range) time after discontinuing Bortezomib months	19 (1-83)
Disease status	
Remission	19 (70%)
Progression	8 (30%)

All patients had persistent PN after discontinuation of bortezomib for a median of 19 months (range: 1-83). Eight patients were enrolled within 6 months of stopping bortezomib; all of them had grade 3-4 painful PN. Median time from diagnosis of MM to study entry was 30 months (range: 5-178). Nineteen patients were in remission, with 12 on maintenance revlimid, and seven not on any therapy. Eight patients had progressive disease and were receiving salvage therapy such as carfilzomib (n=2). Therapy of PN included narcotics (n=13), gabapentin (12), amitriptyline (n=3), pregabalin (n=2), and duloxetine (n=2). Eight patients had diabetes (a known risk of PN in bortezomib treated patients).

There were no significant adverse events associated with the acupuncture treatment. One patient withdrew her consent after three ear needles were placed due to fear of pain and was deemed not evaluable. One patient discontinued the study after 1 acupuncture treatment due to transportation issues. Twenty five patients (93%) completed 4 acupuncture sessions. Trial schema is summarized in Figure 2. All but five patients maintained the same dose of pain medications throughout the study; 3 patients increased their pain medication and 2 decreased the use of pain medication.

Figure 2. Trial Schema



Objective assessment with TNSc scores did not significantly change over the course of intervention (Fig 3A). On the other hand subjective improvements in patients reported symptoms as measured by NPS and FACT/GOG-Ntx were impressive and statistically significant. Mean NPS score significantly decreased from 41 at baseline to 29 after the first acupuncture treatment, and to 17 after 10 weeks of treatment ($p= 0.0003$); the low score was maintained at 18 at week 14 ($p<0.0001$), 4 weeks after the last acupuncture treatment (Fig. 3B). Mean FACT/GOG-Ntx scores also significantly decreased from baseline (20.2) to week 6 (12), week 10 (13.8, $p=0.0008$), and remained low at week 14 (12.4, $p<0.0001$), (Fig. 3C).

Figure 3. Change in TNSc, NPS and FACT/GOG-Ntx over 14 weeks

Fig. 3A. Change TNSc scores over 14 weeks

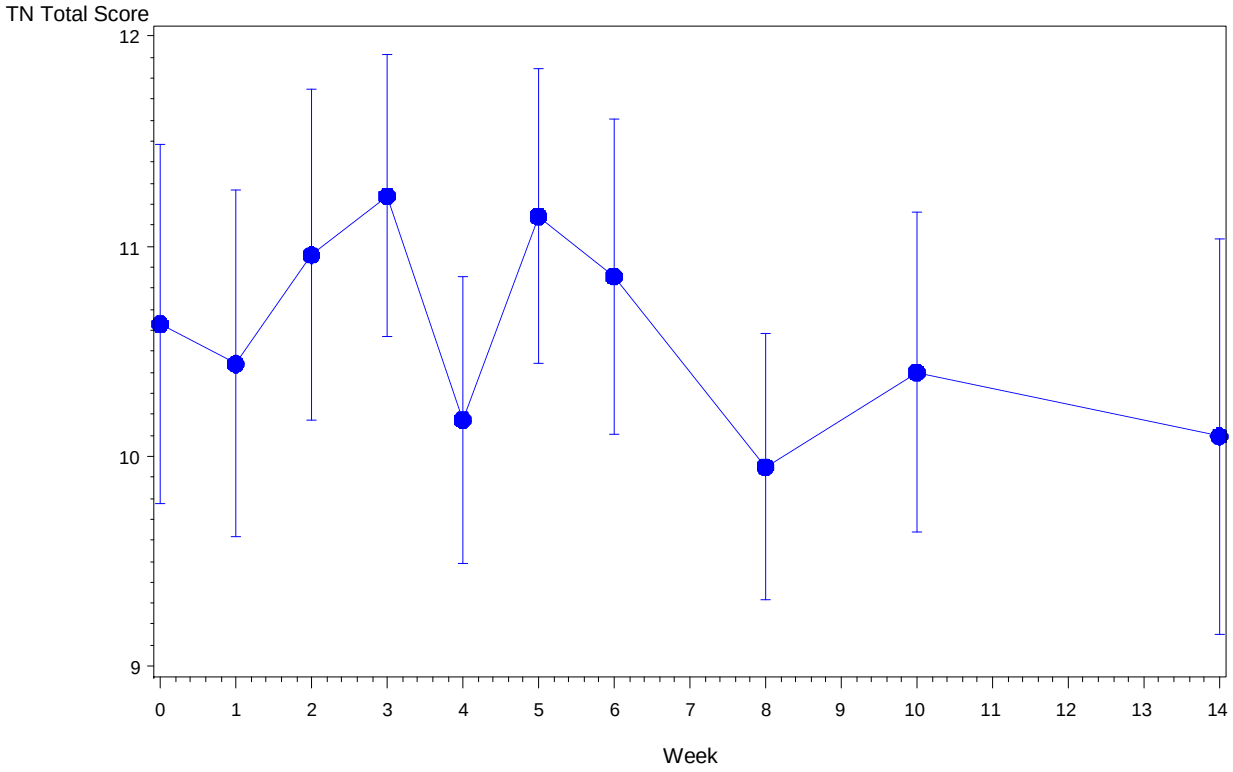


Fig. 3A. TNSc scores at each time point (means and standard deviations).

Fig. 3B. Change in NPS scores over 14 weeks

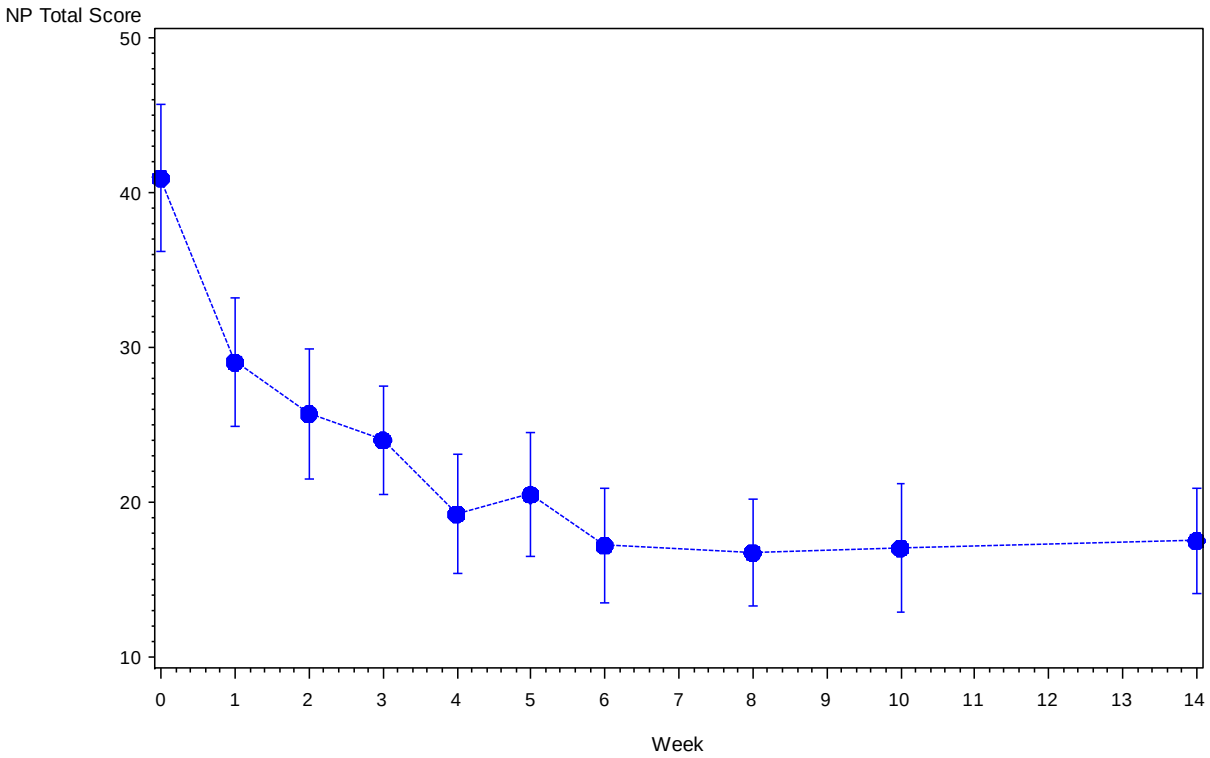


Fig. 3B. NPS scores at each time point (means and standard deviations).

Fig. 3C. Change in FACT/GOG-Ntx scores over 14 weeks

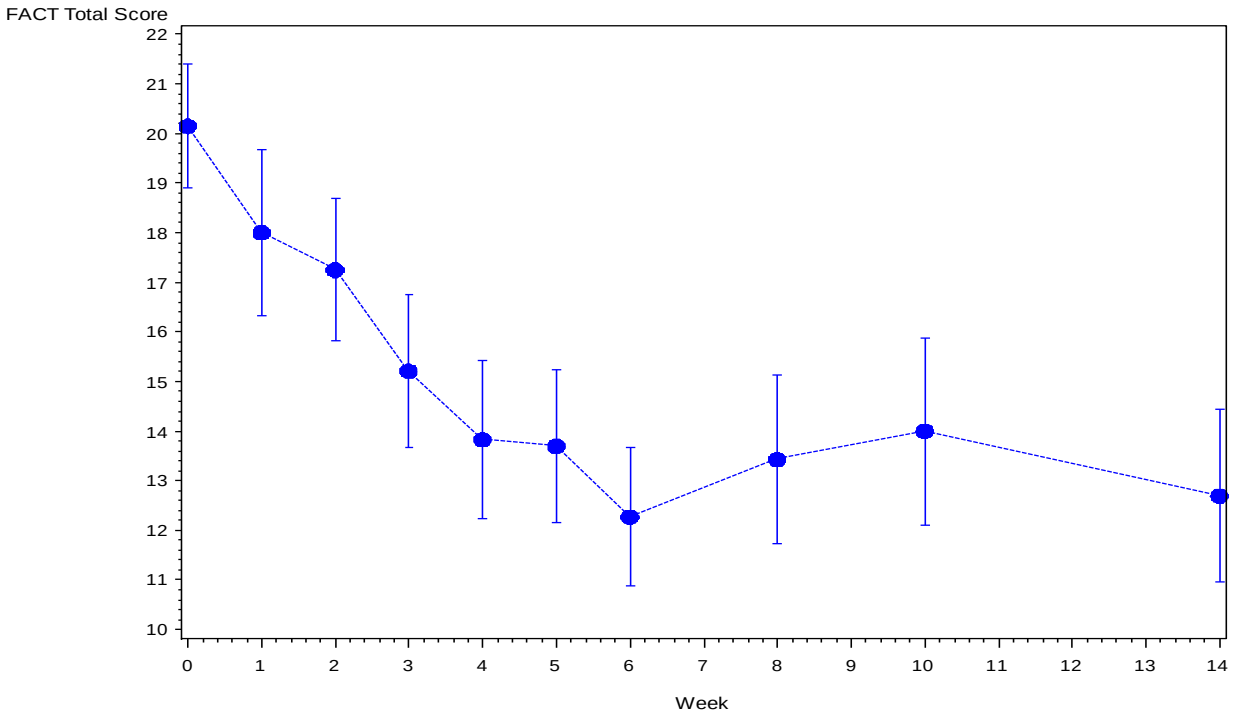


Fig. 3C. FACT/GOG-Ntx scores at each time point (means and standard deviations).

Among the 25 patients who has completed at least 4 acupuncture treatments, at the end of their acupuncture treatment, fourteen (56%) reported improved daily functions (e.g. walking and coordination); 10 (40%) reported > 50% decrease in average NPS, and 7 (28% reported > 50% reduction in FACT/GOG-Ntx total scores. Improvements in the FACT/GOG-Ntx scores during the study were reported in parenthesis, walking, hand function (buttoning buttons, trouble feeling objects), and ear functions (ears ringing or buzzing, trouble hearing); However overall function (joint pain or muscle cramps, and weakness) did not improve (Table 2).

Table 2. Estimated Summary Statistics for FACT/GOG-Ntx Item Scores Over Time

FACT Item	Baseline N=27 Median (Range)	Week10 N=21 Median (Range)	Week14 N=23 Median (Range)
Hands numbness or tingling	3 (0-4)	1 (0-4)	1 (0-3)
Feet numbness or tingling	4 (0-4)	2 (0-4)	2 (0-4)
Hands discomfort	2 (0-4)	1 (0-4)	1 (0-4)
Feet discomfort	4 (0-4)	2 (0-4)	1 (0-4)
Joint pain or muscle cramps	1 (0-4)	0 (0-4)	0 (0-4)
Weak all over	1 (0-3)	0 (0-4)	0 (0-4)
Trouble hearing	1 (0-4)	0 (0-4)	0 (0-4)
Ears ringing or buzzing	0 (0-4)	0 (0-4)	0 (0-4)
Trouble buttoning buttons	1 (0-4)	1 (0-4)	1 (0-4)
Trouble feeling objects	0 (0-4)	1 (0-4)	1 (0-4)
Trouble walking	2 (0-4)	1 (0-4)	1 (0-4)

Improvements of multiple components of neuropathic pain were reported during the study (table 3). It is interesting to note that acupuncture also reduced the unpleasant hot, cold sensation, which was usually not alleviated by opioid [22].

Table 3. Estimated Summary Statistics for NPS Item Scores Over Time

NPS Item	Baseline N=27 Median (Range)	Week 1 N=25 Median (Range)	Week10 N=20 Median (Range)	Week14 N=23 Median (Range)
Intensity	5 (0-10)	4 (0-10)	1 (0-8)	1 (0-8)
Sharpness	5 (0-10)	4 (0-10)	0.5 (0-8)	1 (0-8)
Hotness	3 (0-10)	2 (0-8)	0 (0-8)	0 (0-5)
Dullness	5 (0-10)	3 (0-10)	1 (0-7)	1 (0-8)
Coldness	3 (0-10)	1 (0-7)	0 (0-7)	1 (0-6)
Skin Sensitivity	1 (0-10)	1 (0-9)	0 (0-7)	0 (0-10)
Skin Itchy	0 (0-8)	0 (0-5)	0 (0-3)	0 (0-5)
Pain Unpleasant	6 (0-10)	5 (0-10)	1 (0-8)	2 (0-8)
Deep Pain	6 (0-10)	3 (0-10)	1 (0-10)	2 (0-9)
Surface Pain	5 (0-10)	3 (0-9)	1 (0-8)	1 (0-7)

Six patients refused nerve conduction study, and four patients had baseline measurement only. Of the fifteen patients who had nerve conduction studies before and after acupuncture treatments, five patients (33%) showed >10% increase in motor nerve amplitude, eight (53%) showed no significant changes and two (13%) showed >10% decrease in motor nerve amplitude. At baseline, the majority of patients (87%) had severe sensory nerve deficits, with no measurable sural nerve sensory responses. Two patients (13%) had >10% increase in sensory nerve amplitude, 12 (80%) showed no changes and 1 (7%) showed >10% decrease in sensory nerve amplitude. There was no significant correlation observed between symptoms/functional improvements and the nerve conduction studies.

No significant changes in any of the 10 cytokines were observed at any time points (Table 4).

Table 4. Summary Statistics for Serum Concentrations of 10 Biomarkers over 14 weeks

Biomarker	Baseline N=27 Mean (SD)	Week 1 N=26 Mean (SD)	Week 2 N=24 Mean (SD)	Week 4 N=23 Mean (SD)	Week8 N=22 Mean (SD)	Week14 N=24 Mean (SD)
IL 6 (pg/ml)	4.04 (6.81)	3.54 (5.45)	2.58 (2.74)	2.58 (2.61)	7.21 (21.52)	3.16 (3.29)
IL 8 (pg/ml)	1.14 (0.13)	1.13 (0.10)	1.15 (0.13)	1.14 (0.12)	1.14 (0.13)	1.09 (0.20)
IL 10 (pg/ml)	3.81 (3.78)	3.73 (3.34)	3.76 (2.79)	3.62 (3.01)	11.35 (32.60)	6.71 (10.76)
TNF-α (pg/ml)	1.93 (1.12)	1.99 (1.31)	2.60 (2.80)	2.43 (2.97)	3.26 (3.44)	2.08 (1.33)
VEGF (pg/ml)	72.51 (43.91)	73.19 (43.63)	87.73 (75.73)	95.89 (86.48)	91.28 (59.30)	92.18 (81.98)
IGF 1 (pg/ml)	4839.67 (3241.82)	4811.01 (3423.22)	4928.70 (3517.36)	4822.97 (3138.45)	4763.74 (3219.96)	5565.86 (4338.65)
NGF (pg/ml)	1.08 (0.79)	1.13 (0.86)	1.54 (2.29)	1.98 (4.09)	1.18 (1.01)	0.98 (0.65)
BDNF (pg/ml)	952.60 (873.50)	756.90 (626.98)	926.83 (818.60)	1023.37 (947.13)	717.19 (513.33)	705.10 (579.02)
NT-3 (pg/ml)	30.85 (111.40)	31.58 (116.22)	29.37 (107.57)	30.22 (102.75)	36.42 (127.93)	24.77 (85.28)
β EP (ng/ml)	1.14 (0.13)	1.13 (0.10)	1.15 (0.13)	1.14 (0.12)	1.14 (0.13)	1.09 (0.20)

Patient was defined as responder if the reduction in NPS score from baseline to the end of acupuncture treatment was at least 30%, which is an end point used often in other pain research to define response [24]. Eighteen out of 26 patients (69%) responded to the treatment. Neither race, age, body mass index, diabetes status, grade of BIPN, duration of BIPN or the presence of painful PN were predictive of response or lack of to

acupuncture treatment Interestingly, NPS score improvement after the first acupuncture treatment positively correlated with continued improvement of the NPS score changes at week 10 (r^2=0.82, $p<0.0001$).

Discussion

To the best of our knowledge, this is the first prospective study on the use of acupuncture in treating multiple myeloma patients with moderate to severe BIPN. This is also the first study using TNSc, FACT/GOG-NTx and NPS to assess symptom severity and treatment response and explore the mechanism through cytokine testing. We established that acupuncture is a safe and feasible treatment option for patients experiencing BIPN, and significantly reduces neuropathic pain and improves function. However, despite symptomatic/subjective improvements there were no significant changes in the objective measurements performed including TNSc and nerve conduction studies. Similarly, there was no changes serum cytokines following acupuncture sessions and correlation between cytokines and overall observed responses.

The reason why acupuncture significantly improved the subjective endpoints such as patient reported pain, parenthesisa and hyperalgesia symptoms but not the objective end points such as nerve conduction studies may be due to the short duration of the treatment (10 weeks) and follow up period (14 weeks), which makes it easier to observe subjective symptoms changes rather than objective changes that requires reversal of the neuropathy process, such as nerve regeneration. It is imperative to note that at week 14 follow up, improvements in FACT/GOG-Ntx and NPS scores were maintained suggesting that acupuncture not only provide temporal short term relief with the sessions but rather a long-term benefit for BIPN.

Although studies have not been able to fully explain the mechanism of acupuncture, it has been proposed that acupuncture works through its effect on neurotransmitters and neurohormones. Animal research suggests that acupuncture accomplishes its analgesic effect by stimulating nerves in the muscle, which then relay the signal to the spinal cord, midbrain and hypothalamus-pituitary system, which then leads to the release of neurotransmitters and hormones such as β-endorphins [25-27]. Animal studies also suggest that acupuncture might stimulate nerve growth factors and accelerate nerve regeneration [28, 29]. Neurotrophins have been reported to promote axonal regeneration in central and peripheral nervous systems after axonal injury [30, 31]. Prior animal and human studies have suggested that acupuncture worked by improving brain NGF availability and utilization without eliciting the major side effects induced by NGF administration [32]. It has been reported that electro-acupuncture increased both NGF mRNA and protein levels in the spinal cord after dorsal rhizotomy [33] and dorsal root ganglion neurons after removal of adjacent ganglia [34]. It is possible that acupuncture stimulated nerve fibers such as A delta fibers, elicited the de qi sensation (dull, achiness sensation), which subsequently transmitted signal to the spinal cord, then brain to release neurohormones such as β-endorphin, NGF and BDNF, which achieved analgesic effect and stimulated nerve growth.

We did not observe any significant changes in any of the serum cytokines checked during the 10 weeks of acupuncture treatments. It is possible that in MM patients many of the

cytokines checked such as IL-6, TNF-α are affected by disease status and treatment making it is difficult to detect significant changes by acupuncture treatment. In addition, even though neurotrophic factors can be detected in the serum, the correlation between CSF/peripheral tissue level and blood has not been established.

Despite the lack of a control group, to definitively establish the efficacy of acupuncture in reducing BIPN symptoms, the reported patients ' relief of symptoms is quite impressive in this group of patients who had persistent symptoms despite of discontinuation bortezomib at a median of 19 months, making spontaneous recovery unlikely explanation. A randomized controlled trial of acupuncture in MM experiencing BIPN symptoms is warranted.

APPENDIX A: Components of Clinical Total Neuropathy Score (TNSc)

Parameter	Score				
	0	1	2	3	4
Sensory symptoms	None	symptoms limited to fingers or toes	symptoms extend to ankle or wrist	symptoms extend to knee or elbow	symptoms above knees or elbow or functionally disabling
Motor symptoms	None	slight difficulty	moderate difficulty	require help/assistance	paralysis
Autonomic symptoms	None	1	2	3	4 or 5
Pin sensibility	Normal	reduced in fingers/toes	reduced up to wrist/ankle	reduced up to elbow/knee	reduced to above elbow/knee
Vibration sensibility	Normal	reduced in fingers/toes	reduced up to wrist/ankle	reduced up to elbow/knee	reduced to above elbow/knee
Strength	Normal	mild weakness	moderate weakness	severe weakness	paralysis
DTR	Normal	ankle reflex reduced	ankle reflex absent	ankle reflex absent, others reduced	all reflexes absent

APPENDIX B : FACT/GOG-Ntx Questionnaire

FACT/GOG-NTX (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4
NTX 5	I have joint pain or muscle cramps	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
NTX 6	I have trouble hearing	0	1	2	3	4
NTX 7	I get a ringing or buzzing in my ears	0	1	2	3	4
NTX 8	I have trouble buttoning buttons	0	1	2	3	4
NTX 9	I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4

APPENDIX C: Neuropathy Pain Scale

NEUROPATHY PAIN SCALE

Instructions: There are several different aspects of pain which we are interested in measuring: pain **sharpness, heat/cold, dullness, intensity,** overall **unpleasantness,** and **surface vs. deep** pain.

The distinction between these aspects of pain might be clearer if you think of taste. For example, people might agree on how *sweet* a piece of pie might be (the *intensity* of the sweetness), but some might enjoy it more if it were sweeter while others might prefer it to be less sweet. Similarly, people can judge the loudness of music and agree on what is more quiet and what is louder, but disagree on how it makes them feel. Some prefer quiet music and some prefer it more loud. In short, the *intensity* of a sensation is not the same as how it makes you feel. A sound might be unpleasant and still be quiet (think of someone grating their fingernails along a chalkboard). A sound can be quiet and "dull" or loud and "dull."

Pain is the same. Many people are able to tell the difference between many aspects of their pain: for example, *how much* it hurts and *how unpleasant* or annoying it is. Although often the intensity of pain has a strong influence on how unpleasant the experience of pain is, some people are able to experience more pain than others before they feel very bad about it.

There are scales for measuring different aspects of pain. For one patient, a pain might feel extremely hot, but not at all dull, while another patient may not experience any heat, but feel like their pain is very dull. We expect you to rate very high on some of the scales below and very low on others. We want you to use the measures that follow to tell us exactly what you experience.

1. Please use the scale below to tell us how **intense** your pain is. Place an "X" through the number that best describes the intensity of your pain.

No pain	0	1	2	3	4	5	6	7	8	9	10	The most **intense** pain sensation imaginable

2. Please use the scale below to tell us how **sharp** your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts."

Not sharp	0	1	2	3	4	5	6	7	8	9	10	The most **sharp** sensation imaginable ("like a knife")

3. Please use the scale below to tell us how **hot** your pain feels. Words used to describe very hot pain include "burning" and "on fire."

Not hot	0	1	2	3	4	5	6	7	8	9	10	The most **hot** sensation imaginable ("on fire")

4. Please use the scale below to tell us how **dull** your pain feels. Words used to describe very dull pain include "like a dull toothache," "dull pain," "aching" and "like a bruise."

Not dull	0	1	2	3	4	5	6	7	8	9	10	The most **dull** sensation imaginable

5. Please use the scale below to tell us how **cold** your pain feels. Words used to describe very cold pain include "like ice" and "freezing."

Not cold	0	1	2	3	4	5	6	7	8	9	10	The most **cold** sensation imaginable ("freezing")

6. Please use the scale below to tell us how **sensitive** your skin is to light touch or clothing. Words used to describe sensitive skin include "like sunburned skin" and "raw skin."

Not sensitive | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **sensitive** sensation imaginable ("raw skin")

7. Please use the scale below to tell us how **itchy** your pain feels. Words used to describe itchy pain include "like poison oak" and "like a mosquito bite."

Not itchy | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **itchy** sensation imaginable ("like poison oak")

8. Which of the following best describes the **time** quality of your pain? Please check only one answer.

( ) I feel a background pain all of the time **and** occasional flare-ups (break-through pain) some of the time.

Describe the background pain:_____

Describe the flare-up (break-through) pain:_____

( ) I feel a single type of pain all the time. Describe this pain:_____

( ) I feel a single type of pain only sometimes. Other times, I am pain free.

Describe this occasional pain:_____

9. Now that you have told us the different physical aspects of your pain, the different types of sensations, we want you to tell us overall how **unpleasant** your pain is to you. Words used to describe very unpleasant pain include "miserable" and "intolerable." Remember, pain can have a low intensity, but still feel extremely unpleasant, and some kinds of pain can have a high intensity but be very tolerable. With this scale, please tell us how **unpleasant** your pain feels.

Not unpleasant | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **unpleasant** sensation imaginable ("intolerable")

10. Lastly, we want you to give us an estimate of the severity of your deep versus surface pain. We want you to rate each location of pain separately. We realize that it can be difficult to make these estimates, and most likely it will be a "best guess," but please give us your best estimate.

HOW INTENSE IS YOUR *DEEP* PAIN?

No **deep** pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **intense deep** pain sensation imaginable

HOW INTENSE IS YOUR *SURFACE* PAIN?

No **surface** pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | The most **intense surface** pain sensation imaginable

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