



# Acupuncture for Bortezomib-Induced Peripheral Neuropathy: Not Just for Pain

Integrative Cancer Therapies  
2018, Vol. 17(4) 1079–1086  
© The Author(s) 2018  
Article reuse guidelines:  
sagepub.com/journals-permissions  
DOI: 10.1177/1534735418788667  
journals.sagepub.com/home/ict  


W. Iris Zhi, MD, PhD<sup>1,\*</sup> , Evan Ingram, MS<sup>2,\*</sup> , Susan Qing Li, MS<sup>1</sup>,  
Patricia Chen, BA<sup>1</sup>, Lauren Piulson, BS<sup>1</sup>, and Ting Bao, MD, DABMA, MS<sup>1</sup>

## Abstract

**Background:** Bortezomib-induced peripheral neuropathy (BIPN) is a common and debilitating side effect. Our pilot study demonstrated that acupuncture is safe and can decrease total neuropathic symptoms. However, there is lack of knowledge in which individual BIPN symptoms benefited from acupuncture. **Purpose:** To characterize individual symptoms reduced by acupuncture in patients with BIPN. **Methods:** Patients with multiple myeloma treated with bortezomib who developed BIPN grade 2 or above, based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), were enrolled and received 10 acupuncture treatments over 10 weeks. Self-reported BIPN-associated symptoms assessments were collected weekly at baseline, during, and after acupuncture treatment using the Neuropathy Pain Scale (NPS) and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity (FACT/GOG-Ntx) questionnaires. Changes in individual symptoms were analyzed based on FACT/GOG-Ntx and NPS scores. **Results:** There were statistically significant reductions in individual symptoms in both NPS and FACT/GOG-Ntx. The FACT/GOG-Ntx reductions were most pronounced in hand/feet numbness/tingling, discomfort, and trouble walking. The sensory symptoms, such as tingling and numbness, especially in the feet, reduced the most ( $P < .0001$ ), and motor dysfunction also reduced significantly ( $P = .0001$ ). Both hearing and dysfunction scores were also statistically significantly increased, indicating improved symptoms. The NPS scores showed significant symptom relief in all 10 items from the NPS assessment, particularly in cold sensitivity and an unpleasant feeling. **Conclusions:** Acupuncture can improve multiple symptoms associated with BIPN, particularly numbness and tingling in hands and feet, cold sensitivity, and an unpleasant feeling. Further randomized control trials are warranted to confirm our findings.

## Keywords

acupuncture, bortezomib, multiple myeloma, peripheral neuropathy

Submitted February 24, 2018; revised May 27, 2018; accepted June 18, 2018

## Introduction

Bortezomib is an effective therapy for patients with multiple myeloma (MM). However, more than one third of patients develop bortezomib-induced peripheral neuropathy (BIPN), requiring dose reduction or treatment interruptions, leading to adverse patient outcomes.<sup>1-4</sup> In addition, BIPN can last for years after bortezomib discontinuation and have a significant negative impact on quality of life.<sup>3</sup> BIPN usually presents as both sensory and motor neuropathies, such as paresthesia (tingling, burning sensation), hyperalgesia (increased sensitivity to noxious stimulation) or allodynia (pain that results from a normally innocuous stimulation), distal sensory loss, and reduced deep tendon reflexes.<sup>5</sup> The treatment for BIPN is mainly limited to pharmacological

interventions such as opioids, gabapentin, and duloxetine. However, these medications often have limited effectiveness and undesirable adverse effects,<sup>6-8</sup> creating the unmet need to explore complementary treatment options.

Acupuncture, a traditional Chinese medical technique in which needles are inserted into certain points on the body,

<sup>1</sup>Memorial Sloan Kettering Cancer Center, New York, NY, USA

<sup>2</sup>University of Toledo, Toledo, OH, USA

\*Co-first authors, equal contribution.

### Corresponding Author:

Ting Bao, Integrative Medicine Service, Memorial Sloan Kettering Cancer Center, 1429 First Avenue, New York, NY 10021, USA.  
Email: baot@mskcc.org



has demonstrated benefits to neuropathic pain in patients with diabetes,<sup>9</sup> cancer,<sup>10</sup> and other conditions. Different acupuncture techniques, for example, auricular acupuncture, have been shown to decrease pain intensity, while more standard reference points for needle insertion have also demonstrated neuropathic symptom improvement in cancer patients.<sup>9,11-16</sup> Reviews of integrative oncology services at our institution found that approximately one third of the patients receiving acupuncture are treated for peripheral neuropathy,<sup>17</sup> suggesting the need for continued research of its effectiveness.

Our prior single-arm pilot study showed that acupuncture was safe and potentially effective in reducing BIPN-associated pain and improving function, supporting the need for further research. The study focused on the feasibility and safety of acupuncture and reported the overall assessment results as the secondary objective.<sup>11</sup> In this report, through validated Neuropathy Pain Scale (NPS) and Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity (FACT/GOG-Ntx) questionnaires, we investigated the effect of acupuncture on individual self-reported BIPN symptoms.

## Methods

### Patients

Patients with MM who received bortezomib and developed persistent BIPN of grade 2 or higher were eligible for the study; no acupuncture was allowed within 1 month prior to enrollment. The grading system is based on National Cancer Institute Common Toxicity Criteria Adverse Event and defined 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 interfere with daily living activities. A detailed recruitment plan and exclusion criteria were described in our previous publication.<sup>11</sup> Written consent was provided by each of the 27 patients before enrollment into the clinical trial. The trial was approved by the institutional review board at the University of Maryland and registered at clinicaltrials.gov (NCT01541644).

### Interventions

All patients received 10 acupuncture treatments: twice weekly for the first 2 weeks, weekly for 4 weeks, and then biweekly for 4 weeks. The acupuncture treatments were performed by a licensed acupuncturist with 8 years of experience. All acupuncture points were selected for their analgesic characteristics and effectiveness in treating pain, swelling, and numbness (Yin Yang House, 2013). Points

included bilateral ear points (Shen men, point zero, and 2 additional auricular acupuncture points where electrodermal signal was detected), bilateral body acupuncture points (LI4, TE5, LI11, ST40), and Ba Feng located in upper and lower extremities were selected, and procedures were described in detail in our previous publication.<sup>11</sup> The de qi, a sense of aching pain, soreness, and heaviness, was achieved in certain acupuncture points (LI4, LI11, and ST40). All patients continued their previously prescribed peripheral neuropathy medications and were encouraged to avoid any changes for the duration of the study.

### Peripheral Neuropathy Assessments

Patients were assessed for self-reported signs and symptoms of neuropathy using FACT/GOG-Ntx and NPS. The FACT/GOG-Ntx is an 11-item neurotoxicity subscale to assess patients' symptoms from neuropathy. The score includes sensory neuropathy, motor neuropathy, hearing neuropathy, and dysfunction associated with neuropathy. The FACT/GOG-Ntx symptoms include numbness and tingling in the hands (Ntx 1) and feet (Ntx 2), discomfort in the hands (Ntx 3) and feet (Ntx 4), joint pain/muscle cramps (Ntx 5), feeling weak all over (HI 12), trouble hearing (Ntx 6), ringing/buzzing in the ears (Ntx 7), trouble buttoning buttons (Ntx 8), trouble feeling the shape of small objects (Ntx 9), and trouble walking (AN 6).<sup>18,19</sup> The sensory subscale includes Ntx 1 to 4; the hearing subscale includes Ntx 6 to 7; the motor subscale includes Ntx 5, HI 12, and AN 6; and the dysfunction subscale consists of Ntx 8 to 9. The FACT/GOG-Ntx has been demonstrated as valid, reliable, and sensitive to meaningful clinical distinctions over time.<sup>20</sup> The scores were standardized, the resulting cumulative scores range from 0 to 44, with higher scores indicating less neuropathy.

The NPS is a multidimensional tool with self-reported visual analogue to define pain intensities and associated characteristics. The 10 items of NPS consist of 2 global pain domains (pain intensity and unpleasantness), 6 specific pain qualities (sharp, dull, sensitive, hot, cold, and itchy pain), and 2 spatial qualities (deep and surface pain).<sup>15</sup> With each item scored from 0 to 10, NPS has a cumulative score ranging from 0 to 100. The higher NPS scores indicate worse neuropathic pain symptoms and lower NPS scores indicate less neuropathic pain symptoms.

Both FACT/GOG-Ntx and NPS assessments were administered before the first acupuncture treatment (baseline/week 0), during weeks of 1, 2, 3, 4, 5, 6, 8, and 10 (end of treatment), as well as at 4-week follow-up (week 14).

### Data Analysis

Mean FACT/GOG-Ntx and NPS individual item scores were calculated for each week. We used 1-way repeated

**Table 1.** Baseline Characteristics of the 27 Enrolled Patients (Bao et al<sup>11</sup>).

Median age	63 years (range = 49-77)
Race, n (%)	
Caucasian	17 (63%)
African-American	9 (33%)
Median BMI	32 (range = 24-49)
Peripheral neuropathy grade, n (%)	
2	12 (44%)
3	14 (52%)
4	1 (4%)
Acute painful peripheral neuropathy, n (%)	8 (9%)
Median months after drug discontinuation	19 (range = 1-83)
Multiple myeloma status at enrollment, n (%)	
Remission	19 (70%)
Progression	8 (30%)

Abbreviation: BMI, body mass index.

measures analysis of variance to determine if there were differences in FACT/GOG-Ntx and NPS individual item and domain scores among enrolled subjects over the 14 weeks due to acupuncture treatment. Statistical analyses were conducted using STATA 12 (STATA Corp, College Station, TX). All analyses were 2-sided, with  $P < .05$  indicating significance.

## Results

Forty-six MM patients were screened between May 2011 and February 2012. Of 27 eligible patients, all 27 were consented and enrolled in the study (Table 1). The previously published pilot study detailed both patient enrollment and completion.<sup>11</sup> The pharmacological interventions for neuropathy included narcotics (n = 13), gabapentin (n = 12), amitriptyline (n = 3), pregabalin (n = 2), and duloxetine (n = 2). During the study, 22 of the 27 patients remained on the same dose of medication, while 3 patients increased narcotic dosage and 2 decreased.

The analysis of all 11 items of the FACT/GOG-Ntx demonstrated increasing scores from baseline (week 0) through the end of treatment (week 10) that continued to increase after completion of treatment (week 14; Table 2). The higher FACT/GOG-Ntx scores reported at the 4-week posttreatment follow-up (Week 14) indicate a reduction in peripheral neuropathy-associated symptoms as well as an improvement in function. All 4 FACT/GOG-Ntx subscale domains (sensory, motor, hearing, and dysfunction) increased from baseline, during acupuncture treatment, and through posttreatment follow-up at week 14 (Figure 1). The sensory score increased more than 4 points over 14 weeks (5.48 to 9.88,  $P < .0001$ ), and the motor score also increased from 6.89 to 8.38 ( $P = .0001$ ). Hearing and dysfunction scores also increased with statistical significance, indicating improved symptoms. After breaking down each

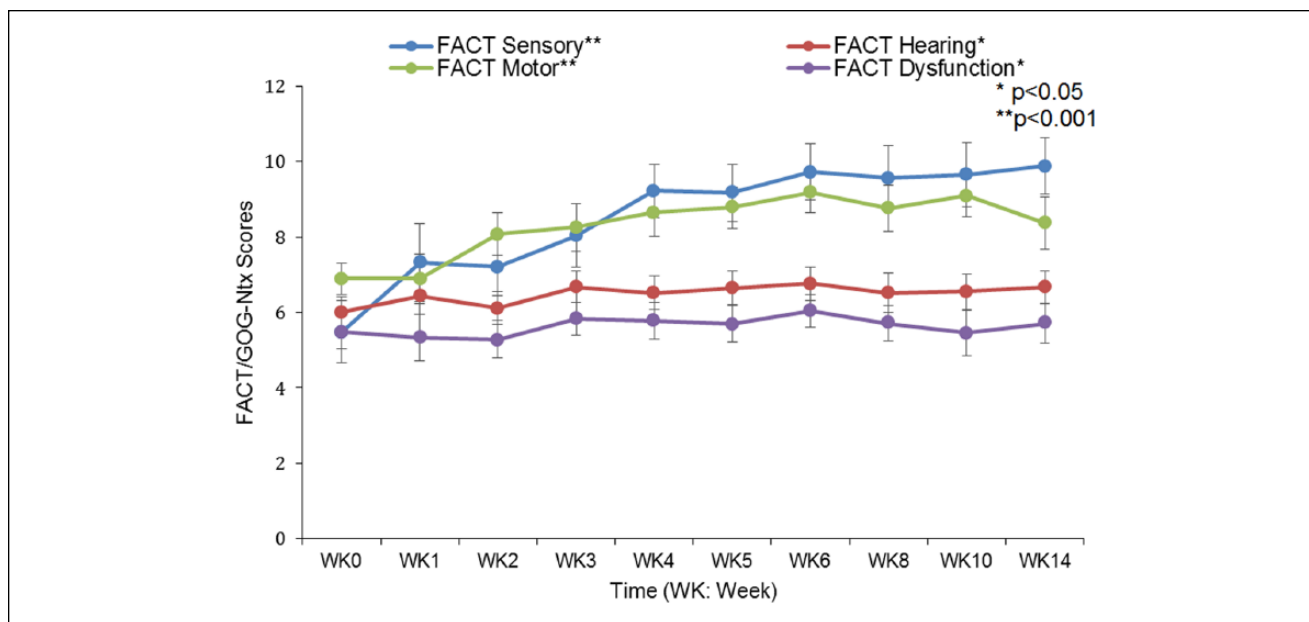
individual symptoms, the mean score of numbness and tingling in hands increased from 1.85 to 2.67 ( $P < .0001$ ), and the mean score of numbness and tingling in feet increased from 0.7 at baseline to 2.13 at week 14 ( $P < .0001$ ). The discomfort in both hands and feet were lessened with statistical significance. This was more noticeable in foot discomfort, as the mean score increased from 0.81 to 2.25 ( $P < .0001$ ). The motor symptoms, including joint pain/muscle cramps and feeling “weak all over,” also increased over time but were not statistically significant ( $P = .41$  and  $.26$ , respectively). A similar trend was observed among the hearing-related symptoms, with higher reported scores for trouble hearing and ringing/buzzing in ears during 10 weeks of acupuncture that remained elevated at week 14, although these were not statistically different from week 0 ( $P = .058$  and  $.36$ , respectively). Dysfunction associated with BIPN, such as trouble with buttons, difficulty with sensing the shape of small objects, and trouble walking all scored higher at week 14, which indicated significant improvement in walking (mean score from 1.67 to 2.5,  $P < .0001$ ) and buttoning buttons ( $P = .0016$ ). These results suggested that acupuncture significantly improved debilitating symptoms associated with BIPN.

Data collected from the NPS assessment showed consistent, statistically significant score reductions across all 10 items, which indicates reduction in neuropathic pain symptoms after acupuncture treatment. In 6 out of 10 items, the mean NPS score reductions before treatment (week 0) and at posttreatment follow-up (week 14) were greater than 2 points, which is considered a clinically significant change.<sup>15</sup> In particular, the pain intensity score had a mean score reduction of 2.42 points ( $P < .0001$ ), from 4.96 at baseline down to 2.54 at week 14. The unpleasant scores also significantly decreased over time from 5.63 to 2.96, with mean score reduction of 2.67 points ( $P < .0001$ ). Both score reductions suggested less pain and less

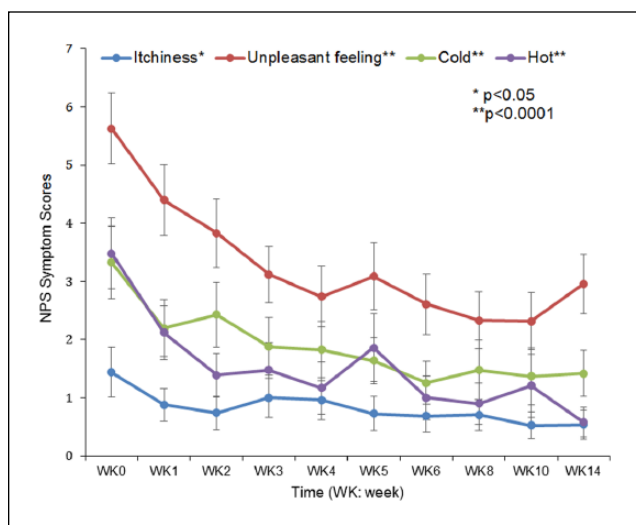
**Table 2.** Weekly FACT/GOG-Ntx Individual and Subscale Item Averages With Standard Deviations (SD).

	Week 0 Mean (SD) (n = 27)	Week 1 Mean (SD) (n = 18)	Week 2 Mean (SD) (n = 24)	Week 3 Mean (SD) (n = 24)	Week 4 Mean (SD) (n = 23)	Week 5 Mean (SD) (n = 23)	Week 6 Mean (SD) (n = 22)	Week 8 Mean (SD) (n = 21)	Week 10 Mean (SD) (n = 20)	Week 14 Mean (SD) (n = 24)	P
Ntx 1: Hands numbness/tingling	1.85 (1.46)	2.06 (0.21)	2.29 (1.16)	2.38 (1.21)	2.57 (1.08)	2.57 (0.99)	2.68 (1.04)	2.52 (1.17)	2.7 (1.03)	2.67 (1)	<.0001
Ntx 2: Feet numbness/tingling	0.7 (1.27)	1.44 (1.54)	1.33 (1.24)	1.58 (1.28)	1.83 (1.23)	1.78 (1.2)	2 (1.27)	2 (1.05)	2.05 (1.15)	2.13 (1.156)	<.0001
Ntx 3: Hands discomfort	2.11 (1.37)	2.33 (1.08)	2.46 (1.14)	2.38 (1.38)	2.83 (1.07)	2.87 (1.06)	2.86 (1.08)	2.9 (1.18)	2.8 (1.06)	2.83 (1.01)	.0001
Ntx 4: Feet discomfort	0.81 (1.36)	1.5 (1.58)	1.13 (1.12)	1.71 (1.27)	2 (1.21)	1.96 (1.15)	2.18 (1.05)	2.14 (1.24)	2.1 (1.21)	2.25 (1.29)	<.0001
Ntx 5: Joint pain/ muscle cramps	2.44 (1.15)	2.67 (1.37)	2.83 (1.31)	2.79 (1.35)	2.91 (1.2)	3 (1.17)	3.18 (1.09)	3.14 (1.01)	3.1 (1.29)	2.79 (1.56)	.414
HI 12: Feel weak all over	2.78 (0.93)	2.72 (1.02)	3 (0.88)	2.13 (0.99)	3.22 (1.09)	3.26 (0.92)	3.41 (0.73)	3.19 (1.08)	3.45 (0.76)	3.08 (1.35)	.2611
Ntx 6: Trouble hearing	2.96 (1.34)	3.11 (1.23)	3 (1.35)	3.41 (1.06)	3.26 (1.05)	3.26 (1.18)	3.5 (0.96)	3.29 (1.19)	3.3 (1.13)	3.38 (1.01)	.0582
Ntx 7: Ringing/ buzzing ears	3.04 (1.37)	3.33 (1.33)	3.13 (1.51)	3.25 (1.26)	3.26 (1.36)	3.39 (1.31)	3.27 (1.42)	3.24 (1.45)	3.25 (1.37)	3.29 (1.27)	.363
Ntx 8: Trouble with buttons	2.59 (1.34)	2.33 (1.49)	2.63 (1.17)	2.88 (1.15)	2.78 (1.24)	2.78 (1.24)	2.95 (1.09)	2.76 (1.22)	2.75 (1.33)	2.79 (1.32)	.0016
Ntx 9: Trouble with small shapes	2.89 (1.37)	3 (1.14)	2.67 (1.43)	2.96 (1.12)	3 (1.21)	2.91 (1.2)	3.09 (1.02)	2.95 (1.02)	2.7 (1.34)	2.92 (1.28)	.3858
AN 6: Trouble walking	1.67 (1.24)	1.5 (1.09)	2.25 (1.07)	2.33 (1.31)	2.52 (1.24)	2.52 (1.12)	2.59 (1.09)	2.43 (1.16)	2.55 (1.05)	2.5 (1.22)	<.0001
FACT Sensory	5.48 (4.27)	7.33 (4.39)	7.21 (3.79)	8.04 (4.11)	9.21 (3.41)	9.17 (3.62)	9.73 (3.55)	9.57 (3.94)	9.65 (3.84)	9.88 (3.66)	<.0001
FACT Motor	6.89 (2.19)	6.89 (2.74)	8.08 (2.72)	8.25 (3.07)	8.65 (3.02)	8.78 (2.63)	9.18 (2.58)	8.76 (2.79)	9.1 (2.55)	8.38 (3.36)	.0001
FACT Hearing	6 (2.17)	6.44 (2.15)	6.13 (2.13)	6.67 (2.06)	6.52 (2.17)	6.65 (2.12)	6.77 (2.09)	6.52 (2.36)	6.55 (2.09)	6.67 (2.09)	.014
FACT Dysfunction	5.48 (2.38)	5.33 (2.63)	5.29 (2.46)	5.83 (2.12)	5.78 (2.29)	5.69 (2.3)	6.04 (1.99)	5.71 (2.12)	5.45 (2.67)	5.71 (2.54)	.0378

Abbreviation: FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity. Boldface indicate values ( $P < 0.01$ ), suggesting statistically significant with substantial evidence against the null hypothesis.



**Figure 1.** FACT/GOG-Ntx domain scores (mean and 95% confidence intervals) change over time. (The higher score, the lesser BIPN; \* $P < .05$  and \*\* $P < .001$ .)



**Figure 2.** Selected NPS symptoms (unpleasant feeling, hot, cold, and itchiness) scores change over time. (The lower score, the lesser BIPN; \* $P < .05$  and \*\* $P < .0001$ .)

unpleasant feeling associated with pain after acupuncture therapy (Figure 2). Among 6 specific pain qualities, hot, cold, sharp, and dull pain were all significantly reduced ( $P < .001$ ), with the most significant score reductions observed in hot and sharp sensations (Figure 2). Sensitivity to light touch and itchy pain scores also significantly decreased over time ( $P = .001$  and  $.021$ , respectively). Table 3 displays the NPS individual item scores at each time point during the study.

## Discussion

In this study, we report that acupuncture reduced multiple symptoms associated with BIPN. The self-reported, well-validated FACT/GOG-Ntx and NPS scores were analyzed to delineate which individual BIPN symptoms benefitted the most from acupuncture. The FACT/GOG-Ntx sensory subscale had the lowest score at baseline (indicating the most severe neuropathy symptoms) and the highest score at post-treatment week 14 (indicating the least neuropathy symptoms) with a mean score increase of 4.4 points ( $P < .0001$ ). This suggests sensory subscale symptoms may benefit the most from acupuncture. Of the individual symptoms within the sensory subscale, numbness and tingling sensations in both hands and feet and discomfort in feet benefitted the most from acupuncture (all 3 symptoms have  $P < .0001$ ). With improvement of feet symptoms, the individual symptom score for difficulty walking also significantly increased and improved ( $P < .0001$ ). The NPS scores decreased across all 10 evaluated items, indicating acupuncture treatment comprehensively alleviates neuropathic pain symptoms. The most significant reductions were observed in pain intensity, sharp pain, hot pain, unpleasantness of pain, and surface pain.

Our study identified individual symptoms that were alleviated the most by acupuncture. The result confirmed that acupuncture might be beneficial for certain symptoms associated with BIPN. Numbness and tingling in hands and feet, typically debilitating, improved the most along with trouble walking. Other symptoms that significantly improved after acupuncture were pain intensity and both

**Table 3.** Weekly NPS Individual Items Averages With Standard Deviations (SD).

	Week 0 Mean (SD) (n = 27)	Week 1 Mean (SD) (n = 25)	Week 2 Mean (SD) (n = 23)	Week 3 Mean (SD) (n = 25)	Week 4 Mean (SD) (n = 23)	Week 5 Mean (SD) (n = 22)	Week 6 Mean (SD) (n = 23)	Week 8 Mean (SD) (n = 21)	Week 10 Mean (SD) (n = 19)	Week 14 Mean (SD) (n = 24)	P
Q1: Intensity	4.96 (3.19)	3.96 (3.26)	3.43 (2.92)	3.52 (2.57)	2.17 (2.29)	2.64 (2.65)	2.3 (2.42)	1.86 (1.85)	1.95 (2.32)	2.54 (2.84)	<.0001
Q2: Sharp	4.56 (3.38)	3.36 (3.09)	2.82 (2.98)	2.56 (2.48)	2.09 (2.35)	1.91 (2.37)	1.96 (2.2)	1.52 (1.89)	1.74 (2.56)	1.67 (2.37)	<.0001
Q3: Hot	3.48 (3.17)	2.12 (2.39)	1.39 (1.77)	1.48 (2.35)	1.17 (2.17)	1.86 (2.73)	1 (1.83)	0.9 (1.64)	1.21 (2.37)	0.58 (1.25)	<.0001
Q4: Dull	4.19 (2.89)	3.04 (2.85)	2.91 (2.45)	3.16 (2.76)	2.09 (1.98)	2.09 (2.49)	2.09 (2.15)	1.9 (1.84)	1.74 (2.05)	1.75 (2.19)	<.0001
Q5: Cold	3.33 (3.24)	2.2 (2.41)	2.43 (2.68)	1.88 (2.49)	1.83 (2.29)	1.64 (1.87)	1.26 (1.79)	1.48 (2.32)	1.38 (2.14)	1.42 (1.93)	<.0001
Q6: Sensitive	3.44 (3.8)	2.52 (3.07)	1.87 (2.65)	2.16 (2.81)	2.09 (3.04)	2.05 (2.77)	1.61 (2.31)	1.81 (2.46)	1.37 (2.19)	1.79 (2.86)	.0001
Q7: Itchy	1.44 (2.22)	0.88 (1.39)	0.74 (1.36)	1 (1.68)	0.96 (1.58)	0.73 (1.39)	0.69 (1.36)	0.71 (1.23)	0.53 (1.02)	0.54 (1.22)	.021
Q9: Unpleasant	5.63 (3.16)	4.4 (3.06)	3.83 (2.84)	3.12 (2.4)	2.74 (2.51)	3.09 (2.71)	2.61 (2.5)	2.33 (2.24)	2.32 (2.16)	2.96 (2.49)	<.0001
Q10a: Deep	4.96 (3.64)	3.56 (3.15)	3.26 (3.03)	2.96 (2.65)	2.26 (2.7)	2.81 (3.09)	2 (2.61)	2 (2.02)	1.68 (2.16)	3 (3.21)	.0001
Q10b: Surface	4.96 (3.32)	3.04 (2.75)	3.22 (2.61)	2.16 (1.84)	2.04 (2.31)	2.18 (2.3)	1.69 (1.84)	2.24 (2.12)	2.16 (2.25)	2.04 (2.14)	<.0001

Abbreviation: NPS, Neuropathy Pain Scale.

hot and sharp pain sensations. These results could help clinicians recommend acupuncture based on patients' individual BIPN symptoms.

Notably, our study has the following advantages: acupuncture was the only intervention allowed during the study, and the study did not permit initiating and/or adjusting pharmacological intervention or other interventions like reflexology. The literature suggests that acupuncture in combination with reflexology can reduce both sensory and motor neuropathy equally.<sup>13</sup> However, our study demonstrated that sensory symptoms were alleviated the most with improvement of gross motor symptoms, but not fine motor skills.

There are a few possible explanations to support our findings. Multiple studies have reported that acupuncture can stimulate both A $\delta$  and C fibers, which can be damaged from chemotherapy.<sup>21-24</sup> A $\delta$  and C fiber disruption from chemotherapy can cause peripheral neuropathy symptoms such as pain, burning, numbness, and tingling, as well as gait instabilities, weakness, hyperesthesia, allodynia, and dysregulation of temperature discrimination.<sup>23,24</sup> Itchiness and unpleasant sensations have been found to also be associated with dysfunction of the same fiber types.<sup>25</sup> Acupuncture can directly suppress diffuse noxious inhibitory controls and lead to activation of A $\delta$  and C fibers and transmission in neurons of the spinal dorsal horn or trigeminal caudalis.<sup>26</sup> Achievement of de qi sensation is a principal of acupuncture that served as the indicator for minimal stimulation level in our study. Studies have suggested that A $\delta$  and C fibers are involved during the de qi sensation and the signal integration into the central nervous system may contribute to the effectiveness of acupuncture for BIPN.<sup>27</sup>

Another possible mechanism is through the activation of neurotrophic factors. For example, neurotrophins are important regulators in the development of both the peripheral and central nervous system,<sup>28</sup> and bortezomib can interfere with neurotrophins and prevent nerve growth factor-mediated neuronal survival.<sup>29</sup> Another neurotrophic factor, brain-derived neurotrophic factor (BDNF), has been found to be inversely associated with neuropathic pain in animals.<sup>30</sup> There is evidence to suggest that acupuncture can upregulate BDNF expression and activate BDNF signaling pathways.<sup>31</sup> Further investigations in acupuncture and neuron regulatory factors are warranted to fully elucidate underlying mechanism(s).

The NPS scores have been utilized to analyze the effects of opioids on reducing diabetic neuropathy symptoms, and results showed that oxycodone did not change pain-related pruritus, cold, or sensitive symptoms.<sup>32</sup> In our study, NPS scores acupuncture significantly reduced NPS scores for sensitivity, cold pain, and other pain based on NPS scores. Similar studies also demonstrated the effectiveness of acupuncture but the exact mechanism of action remains unknown.<sup>33</sup> A future randomized control trial comparing opioids and acupuncture could compare the differences

between opioids and acupuncture in relieving neuropathic pain and related symptoms.

We would like to acknowledge the limitations of our study. The sample size ( $n = 27$ ) of the study was small; thus, a larger study is needed to truly understand the impact of acupuncture on peripheral neuropathy symptoms. Additionally, this is a single-arm trial rather than a randomized controlled study, and we could not rule out the placebo effect or regression to the mean effect.

In conclusion, our study provides interesting data suggesting that acupuncture could be particularly beneficial for patients who have BIPN-associated sensory and pain-related symptoms. Further randomized controlled studies are needed to determine the effectiveness of acupuncture to treat BIPN.

### Authors' Note

The funding sources had no involvement in the study design; collection, analysis, and interpretation of data; writing of the report; or decision to submit the article for publication.


### Declaration of Conflicting Interests


The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded in part by a Memorial Sloan Kettering Cancer Center P30 Grant (P30-CA008748). This study was also funded in part by a R21CA173263 (Ting Bao).

### ORCID iDs

W. Iris Zhi  <https://orcid.org/0000-0003-4263-7272>

Evan Ingram  <https://orcid.org/0000-0002-3019-8455>

### References

1. Farguhar-Smith P, Brown MRD. Persistent pain in cancer survivors: pathogenesis and treatment options. *Pain Clin Updates*. 2016;24:8.
2. Mateos MV, San Miguel JF. Bortezomib in multiple myeloma. *Best Pract Res Clin Haematol*. 2007;20:701-715.
3. Richardson PG, Briemberg H, Jagannath S, et al. Frequency, characteristics, and reversibility of peripheral neuropathy during treatment of advanced multiple myeloma with bortezomib. *J Clin Oncol*. 2006;24:3113-3120.
4. Seretny M, Currie GL, Sena ES, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. *Pain*. 2014;155:2461-2470.
5. Kerckhove N, Collin A, Conde S, Chateix C, Pezet D, Balayssac D. Long-term effects, pathophysiological mechanisms, and risk factors of chemotherapy-induced peripheral neuropathies: a comprehensive literature review. *Front Pharmacol*. 2017;8:86.

6. Brown MR, Ramirez JD, Farquhar-Smith P. Pain in cancer survivors. *Br J Pain*. 2014;8:139-153.
7. Albers JW, Chaudhry V, Cavaletti G, Donehower RC. Interventions for preventing neuropathy caused by cisplatin and related compounds. *Cochrane Database Syst Rev*. 2014;(3):CD005228.
8. Piccolo J, Kolesar JM. Prevention and treatment of chemotherapy-induced peripheral neuropathy. *Am J Health Syst Pharm*. 2014;71:19-25.
9. Bailey A, Wingard D, Allison M, Summers P, Calac D. Acupuncture treatment of diabetic peripheral neuropathy in an American Indian community. *J Acupunct Meridian Stud*. 2017;10:90-95.
10. Lu W, Dean-Clower E, Doherty-Gilman A, Rosenthal DS. The value of acupuncture in cancer care. *Hematol Oncol Clin North Am*. 2008;22:631-648.
11. Bao T, Goloubeva O, Pelsler C, et al. A pilot study of acupuncture in treating bortezomib-induced peripheral neuropathy in patients with multiple myeloma. *Integr Cancer Ther*. 2014;13:396-404.
12. Abuaisa BB, Costanzi JB, Boulton AJ. Acupuncture for the treatment of chronic painful peripheral diabetic neuropathy: a long-term study. *Diabetes Res Clin Pract*. 1998;39:115-121.
13. Ben-Horin I, Kahan P, Ryvo L, Inbar M, Lev-Ari S, Geva R. Acupuncture and reflexology for chemotherapy-induced peripheral neuropathy in breast cancer. *Integr Cancer Ther*. 2017;16:258-262.
14. Garcia MK, Cohen L, Guo Y, et al. Electroacupuncture for thalidomide/bortezomib-induced peripheral neuropathy in multiple myeloma: a feasibility study. *J Hematol Oncol*. 2014;7:41.
15. Greenlee H, Crew KD, Capodice J, et al. Randomized sham-controlled pilot trial of weekly electro-acupuncture for the prevention of taxane-induced peripheral neuropathy in women with early stage breast cancer. *Breast Cancer Res Treat*. 2016;156:453-464.
16. Alimi D, Rubino C, Pichard-Leandri E, Fermand-Brule S, Dubreuil-Lemaire ML, Hill C. Analgesic effect of auricular acupuncture for cancer pain: a randomized, blinded, controlled trial. *J Clin Oncol*. 2003;21:4120-4126.
17. Lu Z, Moody J, Marx BL, Hammerstrom T. Treatment of chemotherapy-induced peripheral neuropathy in integrative oncology: a survey of acupuncture and oriental medicine practitioners. *J Altern Complement Med*. 2017;23:964-970.
18. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol*. 2006;24:3726-3734.
19. Huang HQ, Brady MF, Cella D, Fleming G. Validation and reduction of FACT/GOG-Ntx subscale for platinum/paclitaxel-induced neurologic symptoms: a gynecologic oncology group study. *Int J Gynecol Cancer*. 2007;17:387-393.
20. Calhoun EA, Welshman EE, Chang CH, et al. Psychometric evaluation of the functional assessment of cancer therapy/gynecologic oncology group-neurotoxicity (Fact/GOG-Ntx) questionnaire for patients receiving systemic chemotherapy. *Int J Gynecol Cancer*. 2003;13:741-748.
21. Gao X, Qin Q, Yu X, et al. Acupuncture at heterotopic acupoints facilitates distal colonic motility via activating M3 receptors and somatic afferent C-fibers in normal, constipated, or diarrhoeic rats. *Neurogastroenterol Motil*. 2015;27:1817-1830.
22. Zhang F, Wu L, Zhao J, et al. Neurobiological mechanism of acupuncture for relieving visceral pain of gastrointestinal origin. *Gastroenterol Res Pract*. 2017;2017:5687496.
23. Tavee J, Zhou L. Small fiber neuropathy: a burning problem. *Cleve Clin J Med*. 2009;76:297-305.
24. Voortman M, Fritz D, Vogels OJM, et al. Small fiber neuropathy: a disabling and underrecognized syndrome. *Curr Opin Pulm Med*. 2017;23:447-457.
25. Potenzieri C, Udem BJ. Basic mechanisms of itch. *Clin Exp Allergy*. 2012;42:8-19.
26. Kawakita K, Okada K. Acupuncture therapy: mechanism of action, efficacy, and safety: a potential intervention for psychogenic disorders? *Biopsychosocial Med*. 2014;8:4.
27. Zhou W, Benharash P. Significance of "Deqi" response in acupuncture treatment: myth or reality. *J Acupunct Meridian Stud*. 2014;7:186-189.
28. Siniscalco D, Giordano C, Rossi F, Maione S, de Novellis V. Role of neurotrophins in neuropathic pain. *Curr Neuropharmacol*. 2011;9:523-529.
29. Broyl A, Corthals SL, Jongen JL, et al. Mechanisms of peripheral neuropathy associated with bortezomib and vincristine in patients with newly diagnosed multiple myeloma: a prospective analysis of data from the HOVON-65/GMMG-HD4 trial. *Lancet Oncol*. 2010;11:1057-1065.
30. Geng SJ, Liao FF, Dang WH, et al. Contribution of the spinal cord BDNF to the development of neuropathic pain by activation of the NR2B-containing NMDA receptors in rats with spinal nerve ligation. *Exp Neurol*. 2010;222:256-266.
31. Lin D, De La Pena I, Lin L, Zhou SF, Borlongan CV, Cao C. The neuroprotective role of acupuncture and activation of the BDNF signaling pathway. *Int J Mol Sci*. 2014;15:3234-3252.
32. Jensen MP, Friedman M, Bonzo D, Richards P. The validity of the neuropathic pain scale for assessing diabetic neuropathic pain in a clinical trial. *Clin J Pain*. 2006;22:97-103.
33. Elmariah SB. Adjunctive management of itch in atopic dermatitis. *Dermatol Clin*. 2017;35:373-394.