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ORIGINAL ARTICLE

Wireless transcutaneous electrical nerve stimulation device for chemotherapy-induced peripheral neuropathy: an open-label feasibility study

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Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) occurs in approximately 68% of patients who receive neurotoxic chemotherapy and lasts at least 6 months post-chemotherapy in approximately 30% of individuals. CIPN is associated with decreased quality of life and functional impairments. Evidence suggests that CIPN symptoms are caused, in part, by enhanced excitability and impaired inhibition in the central nervous system. Transcutaneous electrical nerve stimulation (TENS) decreases pain by counteracting both of these mechanisms and is efficacious in other conditions associated with neuropathic pain. This single-arm study ($n = 29$) assessed the feasibility of investigating TENS for CIPN after chemotherapy completion using a wireless, home-based TENS device. Eighty-one percent of eligible patients who were approached enrolled, and 85% of participants who received the TENS device completed the primary (6-week) study term. Qualitative interview data suggest that use of the device on the continuous setting that automatically alternates between 1-h stimulation and rest periods for 5 h/day would be acceptable to most participants. Significant (i.e., $p < 0.05$) improvements were observed with the EORTC-CIPN20 (percent change from baseline: 13%), SF-MPQ-2 (52%), numeric rating scale of pain (38%), tingling (30%), numbness (20%), and cramping (53%), and UENS large fiber sensation subscore (48%). Preliminary data that support the reliability and construct validity of the UENS for CIPN in cancer survivors are also provided. Together these data suggest that it is feasible to evaluate TENS for CIPN using a wireless, home-based device and that further evaluation of TENS for CIPN in a randomized clinical trial is warranted.

Keywords Chemotherapy-induced peripheral neuropathy · Transcutaneous electrical nerve stimulation · Cancer survivors · Feasibility trial

Introduction

CIPN occurs in approximately 68% of patients who receive neurotoxic chemotherapeutic agents (e.g., platinums, taxanes, and vinca alkaloids) and lasts at least 6 months after termination of chemotherapy in approximately 30% of individuals [1]. Neurotoxic agents are used to treat a wide variety of common cancers including breast, gastrointestinal, lung, ovarian cancers, and multiple myeloma, which together were estimated to make up ~40% of new US cancer cases in 2017 [2]. CIPN presents as a variable combination of neuropathic symptoms, commonly including burning/shooting pain, tingling, cramping, and numbness. CIPN is associated with functional limitations such as impaired balance [3], increased falls [4–6], interference with walking [7], limitations in activities of daily living [4], impaired sleep quality [8], and decreased quality of life [9]. No gold-standard treatments are available

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for CIPN. While duloxetine improved painful CIPN in one randomized clinical trial (RCT) [10], this drug contributes to the adverse effects of polypharmacy and is only modestly effective.

Evidence suggests that CIPN symptoms are caused, in part, by enhanced excitability and impaired inhibition in the central nervous system [11–14]. Central excitatory pathways in the spinal cord amplify signals to the brain from the ascending sensory neurons (i.e., nociceptive neurons). In contrast, central inhibitory signals from the brain stem and spinal cord inhibit signals from nociceptive neurons (Fig. 1a) [15–17]. In animal models of CIPN, dorsal horn neurons that transmit noxious sensory signals show enhanced responsiveness to noxious stimuli, suggesting enhanced central excitability [11–13]. In addition, reduced central inhibition (measured via conditioned pain modulation test) is associated with more severe CIPN symptoms in humans [14]. Thus, interventions that reduce central excitability and enhance central inhibition may improve CIPN symptoms.

Transcutaneous electrical stimulation (TENS) is a safe, non-pharmacologic, and inexpensive therapy commonly used for pain control [18]. In animal models, TENS reduces the enhanced central excitability of nociceptive neurons induced by inflammation and nerve injury [19] and decreases release of the excitatory neurotransmitter glutamate in the dorsal horn of the spinal cord [20]. TENS also produces analgesia in animal models by activating central inhibitory pathways in the brain stem and spinal cord through activation of endogenous opioid receptors [21, 22]. Human studies confirm opioid receptor activation by TENS during pain inhibition [23] and show that TENS restores central inhibition in individuals with fibromyalgia [24]. The analgesic efficacy of TENS for pain is supported by its widespread clinical use as well as positive results from multiple RCTs in various chronic pain conditions including diabetic peripheral neuropathy [25, 26], fibromyalgia [24, 27], and migraine [28].

This single-arm, learning phase study examined the feasibility and preliminary efficacy of a wireless, home-based TENS device for CIPN. The purpose of this study was to inform a future randomized phase 2 study and determine if TENS has the potential to improve CIPN.

Methods

Study design

This was a single-arm, single-site feasibility study of 6 weeks of therapy with a wireless TENS device (Quell, Neurometrix) for CIPN in patients who completed chemotherapy at least 3 months prior. Participants were consented and completed baseline symptom diaries for 1 week prior to receiving the TENS device. They completed daily symptom diaries during the primary study period (i.e., 6 weeks) and completed patient reported outcome measures (PROs) and physical exams at the baseline and 6-week visits. After completing the primary study period, participants were given the option to continue participation up to 6 months with no obligation (Fig. 1b). Participants were recruited from the University of Rochester Wilmot Cancer Center between March 2016 and September 2017. Clinician co-investigators screened potentially eligible patients in their clinics for CIPN of a minimum severity (see eligibility criteria). If the patients were potentially eligible and interested in participating, a member of the research staff completed the eligibility screening and executed the informed consent process. The study was approved by the University of Rochester Research Subjects Review Board, and all participants provided informed consent.

Intervention

The device emits a 60–100-Hz stimulation with a 200–400-μs pulse duration and uses a biphasic waveform with an alternating leading phase. It is secured below the knee using an elastic band. In this study, the intensity was set to 2 times the participant's sensation threshold using the device's calibration process. If the stimulation did not feel strong, the participants were asked to manually increase the intensity until it felt strong but comfortable. During the first 3 weeks of the study, participants were asked to use the device for two individual 1-h sessions, once in the morning and once in the evening. During the second 3 weeks of the study, participants were permitted to continue using the device for two individual sessions per day or to wear the device between 3 and 12 h per day on the continuous setting that automatically alternates between 1-h treatment and 1-h rest periods (i.e., between 2 and 6 h of stimulation) (Fig. 1b). This dosing paradigm was chosen in order to evaluate the feasibility of prescribing a specific duration of treatment versus allowing participants to choose their desired duration of TENS usage.

Patient population

Eligible patients had completed chemotherapy with a neurotoxic agent (e.g., taxane, platinum, vinca alkaloid) at least 3 months prior to trial enrollment. Participants had a clinical diagnosis of CIPN from one of the three clinician-investigators (two neuro-oncologists (NM, JB), one gastrointestinal oncologist (MT)). They also reported at least one of the following symptoms as ≥ 4 out of 10 on a 0–10 numeric rating scale (NRS) that asked participants to rate their worst symptoms in their lower limbs over the past week: pain, tingling, numbness, or cramping. Participants had a life expectancy of at least 6 months and were willing to not start or increase dosages of any analgesics for the 6-week primary study period. Patients were not eligible if they met any of

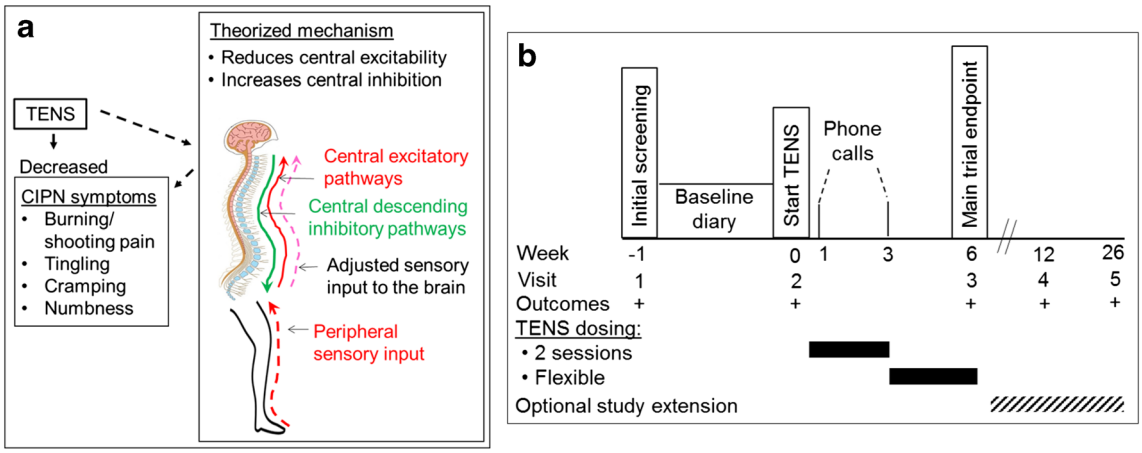

Fig. 1 **a** Conceptual framework. **b** Study schema

the following criteria: (1) had a diagnosis of pre-existing neuropathy prior to starting chemotherapy as reported in the medical record or by the patient; (2) had unilateral peripheral neuropathy symptoms; (3) were taking any medications that the neuro-oncologist co-principal investigator (Co-PI) (NM) deemed to potentially cause neuropathy; (4) were using a TENS device for CIPN or other condition; (5) had lower extremity wounds, ulcers, or edema that would interfere with wearing the device on the lower limb; or (6) had a pacemaker, heart dysrhythmia, or epilepsy. Initially, participants who had diabetes, defined as HbA1C ≥ 7, were excluded. After 15 participants were enrolled, eligibility criteria were modified to allow participants with diabetes in an effort to speed enrollment.

Outcome measures

Feasibility measures included (1) the percentage of eligible patients who enrolled in the study and received the device and (2) the percentage of participants who received the device that completed (a) the outcome measures and (b) the 6-week study visit. Data from the qualitative interviews were used to assess the acceptance of the device and the duration of TENS prescription. Multiple measures were used to assess preliminary efficacy. The European Organization for Research and Treatment of Cancer-CIPN20 (EORTC-CIPN20) [29] is a composite measure of CIPN symptoms and functional impairments. Multiple studies support its content and construct validity [30–32], and it was identified as the best available PRO for CIPN at the NCI CIPN planning meeting [33]. The Short-Form McGill Pain Questionnaire-2 (SF-MPQ-2) is a validated measure to assess different qualities of pain [34]. Participants also completed a daily diary of 0–10 NRS (*0 = none, 10 = worst possible*) for the following CIPN symptoms: pain, tingling, numbness, and cramping. They were asked to rate the worst symptoms in the legs and feet that they felt over the past 24 h. They were asked to perform the ratings around bedtime and not while they were using the TENS device. The Utah Early Neuropathy Score (UENS) and a forced choice monofilament test developed at the Mayo Clinic were used to assess clinical signs of neuropathy. The UENS is a clinician-rated sign measure for peripheral neuropathy. It includes assessments that evaluate the following domains, motor neuropathy, large and small fiber sensory neuropathies, and reflexes. It has been validated in patients with diabetic peripheral neuropathy [35]. The UENS was performed independently by two raters, one neurologist, and one non-clinician researcher. In the monofilament test, the participant is asked to close their eyes while each monofilament is applied (or not) in random order 10 times (i.e., trials). With each trial, the participant is asked to state whether they felt the filament touch their skin. For each set of 10 trials with a single monofilament, if the participant guesses correctly ≥ 9 times, the next weaker monofilament is used. If the participant guesses correctly seven or eight times, this filament is documented as the participant's sensation threshold. If the participant guesses correctly ≤ 6 times, the next stronger filament is trialed. The participant's sensation threshold is the outcome of the test. The monofilament set is supplied by WR Medical Electronics, Inc. The clinical exam results were only available for 73% ($n = 16$) of evaluable subjects because the equipment was purchased with a grant that was received after the study was started.

Qualitative interview

Qualitative interviews were performed by the co-PI (JG) using a structured interview format that included open-ended questions to elicit participants' feedback regarding the utility of the device and their perceptions of its efficacy. The co-PI took notes during the interview and identified the most favorable and unfavorable reported opinion regarding any aspect of the device for each participant.

Safety assessment

Adverse events (AE) were assessed by asking participants if they had experienced any new symptoms since starting the TENS therapy including any problems with the skin where the electrodes were attached. The following information was recorded for all AEs: start date, stop date, severity (mild, moderate, severe, serious), any action taken in response to AE (including stopping or decreasing TENS dosage), the relationship with the study device as determined by the clinician co-PI of the study (e.g., possible related) whether it was continuing or resolved at the end of the study, and any treatment provided for the AE. AEs were assessed for all participants who received the TENS device.

Sample size calculation

Since this was an early learning phase, feasibility study, a formal sample size calculation was not performed. We aimed to recruit 30 patients as that was the sample size that we estimated would be feasible with limited resources to support the study and that would provide sufficient information to assess acceptance of the device and optimal daily therapy duration.

Statistical analyses

Descriptive statistics were used to summarize feasibility and preliminary efficacy outcomes. Percent changes from baseline were calculated using the following formula: [(baseline median score – endpoint median score)/baseline median score]. Changes from baseline in continuous efficacy outcomes were assessed using the paired Wilcoxon signed rank test based on evaluable data. The percentage of participants who reported an improvement of at least 30 or 50% in at least one CIPN-related symptom was calculated to estimate the percentage of participants who experienced a clinically meaningful improvement. Although no perfect consensus exists regarding a minimal clinically meaningful improvement in pain, 30 and 50% are often cited as reasonable cutoffs for clinically meaningful improvements in chronic pain. The clinical meaningfulness of the 30% cutoff is supported by data demonstrating an association of 30% improvement in pain ratings with "much improved" or "very much improved" on a patient global rating of change scale in a large study of neuropathic pain patients [36]. The percentage of participants whose sensation threshold from the monofilament test improved was reported together with the 95% Fisher exact confidence interval and tested against the null hypothesis of no improvement. Because of the exploratory nature of the study and because preliminary efficacy was a secondary objective of the study, a primary efficacy outcome measure was not pre-specified, efficacy analyses were based on evaluable data without methods to accommodate missing data, and a p value of < 0.05 was considered significant without adjusting for multiplicity. The final objective of the study was to assess the interrater reliability and construct validity of the UENS in CIPN. The 6-week data were used for these analyses. The interrater reliability was determined by calculating the intraclass correlation coefficient (ICC). The ICC was calculated using the "irr" package in R [37]. This model treats the raters and participants as random effects and uses the absolute agreement criterion. The following ICC classifications were used to interpret the reliability based on the ICC (1) moderate: 0.5 to 0.75, (2) good: 0.75–0.9, and (3) excellent: greater than 0.9 [38]. The construct validity of the UENS was evaluated using a Spearman's correlation between the UENS and the EORTC-CIPN20. All statistical analyses other than ICCs were performed using JMP Pro version 13.

Results

Participant flow/feasibility

Sixty-four patients were screened for the study; 28 were not eligible and 7 declined the invitation to participate. Thus, 29 (81%) participants enrolled in the study. Three participants were lost to follow-up during the baseline week, leaving 26 participants who received the TENS device. Four (15%) participants withdrew during the main 6-week study period, leaving 22 evaluable participants for the 6-week efficacy analyses. Nineteen participants chose to continue using the device after the initial 6 weeks and 15 completed the 6-month study period, 13 of whom stated that they planned to continue using the device (Fig. 2).

In the qualitative interviews, 100% of the participants reported that the length of the study was not too burdensome and that they would recommend the study to others. Seventeen (77%) of the participants reported that they preferred to use the device on the continuous setting throughout the day more than using it for one session in the morning and one session in the evening.

Participant characteristics

The majority of the enrolled participants were female (58%) and Caucasian (90%). Many participants had tried gabapentin (57%), duloxetine (31%), or opioids (24%) previously to treat their CIPN symptoms. The median time since completion of chemotherapy was 13 months (interquartile range 6, 34). The most common classes of neurotoxic chemotherapy agents were platinum agents (45%) and taxanes (31%) (Table 1).

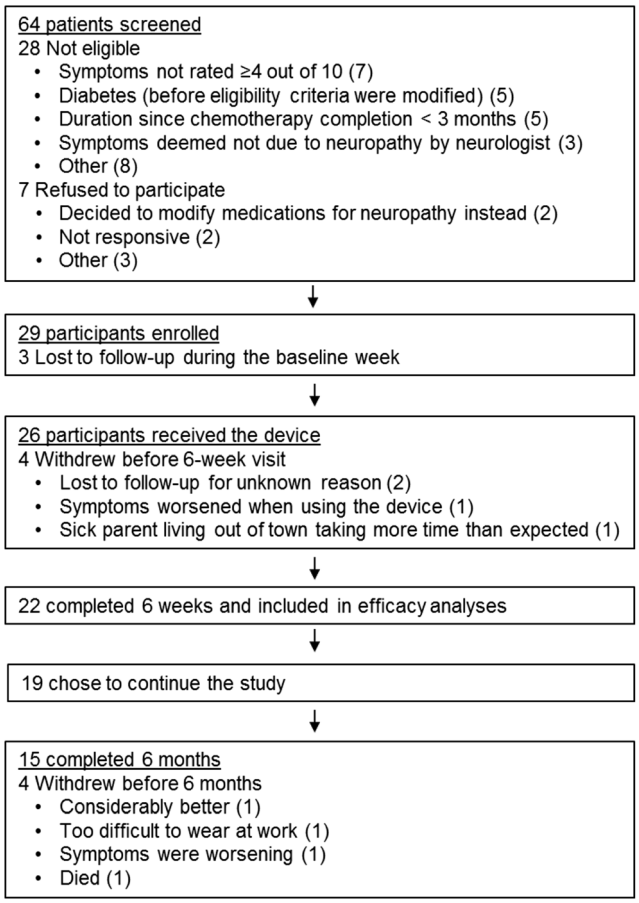

Fig. 2 CONSORT diagram of participant disposition

Preliminary efficacy

The EORTC-CIPN20 improved by 13% ($p = 0.004$) from baseline after 6 weeks of treatment with TENS. The SFMPQ-2 improved by 52% ($p = 0.002$), with the largest improvements in the neuropathic, intermittent, and continuous pain subscales (Fig. 3a). Improvements were also observed with the 0–10 NRS daily diary scores for individual symptoms: pain (38%, $p = 0.0001$), tingling (30%, $p = 0.002$), numbness (20%, $p < 0.0001$), and cramping (53%, $p = 0.005$) (Fig. 3a). Seventeen (81%) participants reported an improvement from baseline of at least 30% in at least one of the symptoms (i.e., pain, numbness, tingling, or cramping). Seven (33%) reported at least a 50% improvement in at least one symptom.

The UENS score did not demonstrate a significant improvement from baseline after 6 weeks of treatment with TENS; however, the large fiber sensation subscore improved by 48% ($p = 0.04$) (Fig. 3a). The sensation threshold improved in 10 of 16 (63%; 95% CI [35–85%], $p < 0.0001$) participants who performed the monofilament test (Fig. 3b).

Qualitative feedback regarding the utility of the wireless device

Table 2 includes select quotes from the qualitative interview that represent each participant's most enthusiastic and most critical feedback regarding the device and its efficacy.

UENS interrater reliability and construct validity

The ICCs were as follows: (1) total UENS score: 0.93 (95% CI [0.78–0.98]), (2) large fiber sensation subscore: 0.85 (95% CI [0.63–0.94]), and (3) pinprick subscore 0.87 (95% CI [0.66–0.95]). The total UENS scores were well correlated with the EORTC-CIPN20 self-report measure of CIPN ($\rho = 0.81$, $p = 0.004$).

Adverse events

Three serious AEs occurred during the study that were not related to use of the device. Two participants were hospitalized for gastrointestinal symptoms and one participant died from respiratory failure. One participant developed mild contact dermatitis that was related to the TENS device. Four participants reported worsening or new paresthesias and pain or cramping in their lower limbs. One participant reported tightness in the lower limbs. These AEs were deemed mild and possibly related to the device by the clinician co-PI (NM). All mild AEs resolved after discontinuation or lowering of the TENS duration. The tightness in the lower limb was not resolved at study completion, but the participant declined to reduce the TENS dosage due to the perceived CIPN-related benefits and continued to use the device after study completion.

Discussion

This study supports the feasibility of evaluating TENS for symptoms and signs of CIPN using a wireless, patient-controlled TENS device. Our high rate of enrollment of eligible patients suggests that cancer patients no longer receiving chemotherapy will be eager to enroll in studies that evaluate TENS for CIPN. Data from our qualitative interviews suggest that the device is easy to use and convenient for most individuals and that asking participants to wear the device on the continuous setting for at least 5 h (delivers 3 h of TENS stimulation) will be acceptable.

The improvements in a composite measure of CIPN and individual CIPN-related symptoms in this single-arm, open-label study suggest that a RCT evaluating the efficacy of TENS for CIPN is warranted. Improvements in pain and cramping with CIPN were particularly promising, with mean improvements of greater than 40%. Additionally, although the

Table 1 Characteristics of 29 enrolled participants

	N (%) or median [IQR]
Age	56 [53–63]
Sex	
Female	17 (59%)
Male	12 (41%)
Race	
Caucasian	26 (90%)
Black	2 (7%)
Asian	1 (3%)
Ethnicity	
Non-Hispanic	27 (93%)
Hispanic	2 (7%)
Medications previously tried for CIPN	
Gabapentin	17 (59%)
Duloxetine	9 (31%)
Opioids	7 (24%)
NSAIDs	4 (14%)
Steroids	3 (10%)
Time since neurotoxic chemotherapy completion (in months)	13 [6, 34]
Type of chemotherapy	
Platinum	13 (45%)
Taxane	9 (31%)
Taxane and platinum	2 (7%)
Other[a]	5 (17%)
Diabetes	
No	28 (97%)
Yes	1 (3%)

[a] Examples of other include combination of classes other than platinum and taxane, bortezomib, brentuximab, and vinca alkaloid

improvement in numbness was smaller (i.e., 20%), such an improvement could be particularly beneficial to patients because pharmacologic treatments generally do not improve numbness [39]. The fact that 58% of the participants who received the TENS device reported that they planned to continue using it after the end of the 6-month study period is also promising. It is important to note that the median time since chemotherapy termination was 13 months, suggesting that these results are not likely solely due to natural improvements that often occur within the first 3–6 months after chemotherapy termination. Additionally, improvements in clinical exam scores (i.e., UENS large fiber sensation scores) and sensation as measured by the monofilament test further support the potential of TENS for CIPN.

Five of 26 participants reported new or worsening sensory symptoms while using the device, suggesting that TENS therapy might not be useful for everyone. However, these symptoms all reversed after discontinuation or decrease of TENS usage. Thus, TENS is not likely to irreversibly harm CIPN patients. It is difficult to compare these results to previous studies of TENS because a recent Cochrane review of RCTs of TENS for neuropathic pain [43] found that only 40% of studies reported AEs. These studies reported either no AEs or minor skin irritation [40].

The improvements in CIPN after TENS therapy observed in this study are consistent with two previous single-arm studies that evaluated two TENS-like therapies for CIPN symptoms. One showed that TENS delivered at acupuncture points reduced CIPN-related numbness [41]. Two studies showed that scrambler therapy, another electro-cutaneous treatment approach that delivers 16 different waveforms of stimulation, improved pain, numbness, and tingling [42, 43]. According to clinicaltrials.gov, the scrambler therapy is currently being evaluated in a RCT, which could provide a new therapeutic option for CIPN patients if proven efficacious. However, the scrambler technology requires travel to the clinic and is only available in

a

	Baseline median [IQR]	6-Weeks median [IQR]	P-value	% change from baseline
EORTC-CIPN20	39.5 [31 – 47.3]	34.5 [28.8 – 41.8]	0.004	13%
McGill Pain Questionnaire (Total)	60.5 [21.8 – 88.5]	29.0 [8.8 – 63.8]	0.0002	52%
Neuropathic Subscale	19 [7.8 – 30.5]	10.5 [5.8 – 20]	0.0003	45%
Affective Subscale	3.5 [0.8 – 9.3]	3.5 [0 – 7.3]	0.21	0%
Intermittent Subscale	12 [3.5 – 25.8]	7.5 [2.8 – 14.5]	0.02	38%
Continuous Subscale	18 [5.3 – 28.3]	10 [3 – 17.8]	0.0004	44%
0-10 NRS diary scores				
Pain	6 [1.8 – 6.3]	3.7 [0.42 – 5.5]	0.0001	38%
Tingling	5.7 [4.1 – 7.1]	4 [1.8 – 5.1]	0.002	30%
Numbness	5.5 [4.7 – 6.6]	4.4 [3.0 – 5.2]	<0.0001	20%
Cramping	3.0 [0.3 – 5.8]	1.4 [0.0 – 3.1]	0.0005	53%
UENS (Total)	12 [8.3 – 19.8]	9.5 [7 – 11.8]	0.051	21%
Large fiber sensation	3.8 [2 – 5.4]	2 [0.3 – 4.8]	0.04	48%
Pin sensation	1.5 [0.3 – 7.5]	1 [0 – 4.75]	0.62	33%

b

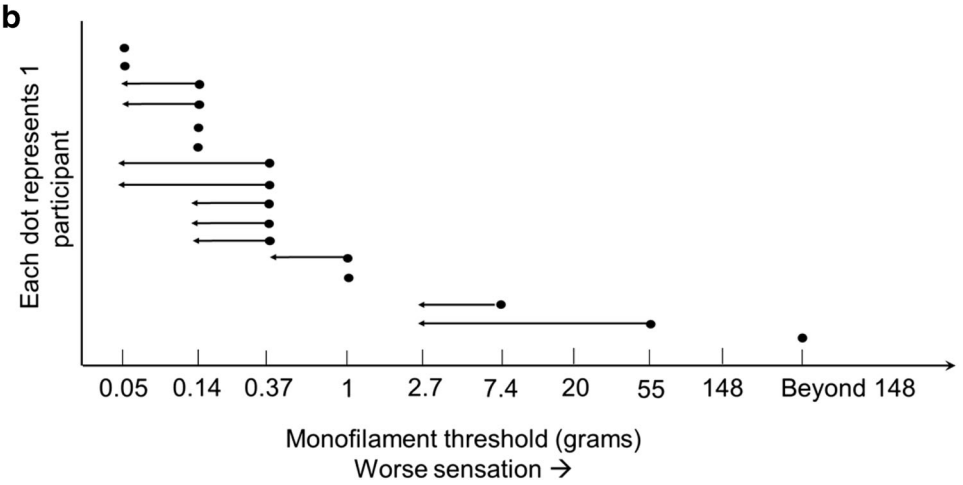

Fig. 3 Preliminary efficacy based on patient-reported outcome and physical exam measures. **a** The large fiber sensation subscore of the UENS is comprised of the vibration and joint position exam items. The diary scores are the mean of the baseline and 6-week diary entries. **b** The baseline sensation threshold from the monofilament test is represented by the circle. The endpoint sensation threshold is represented by the arrowhead. In the case where there is only a circle, the sensation threshold was the same at the baseline and endpoint visits. IQR interquartile range

certain geographic locations. Thus, usage of this technology is limited and costly. A home-based, wireless TENS device that can be worn during activity can be easily disseminated, and according to our qualitative data, may encourage compliance.

Our results also support the use of the UENS in cancer survivors with CIPN. A previous study demonstrated good interrater reliability for the UENS between two physician raters when implemented in a population of patients with diabetic peripheral neuropathy [35]; however, to our knowledge, our study is the first to demonstrate good to excellent interrater reliability between a neurologist and a non-clinician researcher when considering the 95% CI of the ICC for the total UENS score. Our study also suggests that the UENS is a useful instrument to detect changes in established CIPN over a relatively short duration, suggesting that it may be a sufficiently sensitive outcome measure for RCTs of CIPN. In addition, we found a high correlation between the UENS score and the EORTC-CIPN20, which provides the first evidence of which we are aware to support the construct validity of the UENS for CIPN after discontinuation of chemotherapy. Considering that neuropathy induced by most chemotherapies is predominantly sensory [44], the UENS also has face validity for use in CIPN because it heavily weights sensory signs over motor or autonomic neuropathy signs.

Our study had a few important limitations. We recruited patients from a single academic cancer center and largely from a neuro-oncology clinic within that center. Therefore, the patients who were screened for the study may have had more severe neuropathy than those treated by community oncologists. This could have increased the rate of eligible patients who were willing to join the study. In addition, the percentage of eligible patients who are willing to enroll in a future randomized study may be lower than in this open-label study in which all participants receive the active device. However, a potential decrease in enthusiasm could be countered by providing an active device at the end of the study to participants who are randomized to the placebo group, a recruitment strategy that is currently being used successfully in the Fibromyalgia Activity Study with TENS clinical trial [45]. These results do not provide evidence of efficacy of TENS for CIPN due to the lack of a control group and multiple statistical tests without identification of a primary analysis. Furthermore, the preliminary

Table 2 Qualitative feedback regarding the efficacy and acceptability of the TENS device

PT	Most enthusiastic feedback	Most critical feedback	Disposition	Time since chemo
1	Severe cramps stopped when using the device	Difficult to use and uncomfortable, unusual sensations in the feet	Stopped after 6 weeks	2.5 years
2	Most improvement in tingling, even minor improvements are worth it	None	Completed 6 months	4.9 years
3	It helps pain, swelling, everything (noted marked difference when started continuous setting for 12 h/day)	Two weeks in (i.e., when using for two independent sessions/day), I would not have known it was working	Completed 6 months	4 months
4	Pain changed enough that it is noticeable	Overall pain has come down, but still taking pain killers	Completed 6 months	2.25 years
7	Felt like band was slipping down the leg	Not really helping at all	Stopped after 6 weeks	8 months
9	Was not bad and easy to use	No improvement (Note that patient only has numbness)	Stopped after 6 weeks	1.1 year
10	Cured leg cramps, helped with numbness and tingling	None	Stopped after 10 weeks—better	5 months
11	Felt like it did not burn as much at night	Decreased burning (certain days better than others)	Stopped after 3 months	1.2 years
12	I would wear 2 if I had them. It is easy. You can use it at home, work, or on vacation.	I like the feeling in my foot, but it does not help the numbness	Complete 6 months	4 months
14	Feel a little more movement in my feet and a little less numbness and tingling	Would not recommend the device because did not help him that much	Died before 3-month visit	3 months
15	Cramps (in hands and feet) are gone	Electrodes snap off when I bump things	Completed 6 months	18 months
16	Nice to not feel like I am walking on sponges	Getting more stinging pains, maybe because I can feel more. Getting a little more pain is worth getting more feeling	Completed 6 months	4 months
17	Really is helping shin cramps; I have got feeling that I did not have before	None	Completed 6 months	4.2 years
18	None	Certain positions for the electrodes cause sharp pain or cramp	Stopped after 3 months (symptoms worsening)	3 months
19	Easier to walk barefoot	Not miraculous, but glad I am doing it so something must be helpful	Completed 6 months	2.75 years
20	Do not think [feet] are as numb, easy to use and not uncomfortable	Sometimes I do not think [the device] comes back on the way it should when I am sleeping	Completed 6 months	11 months
21	Could not feel toes during a pedicure before band and now can feel something in all toes; cramping has subsided	None	Completed 6 months	2.8 years
22	Tingling went away after a few days, numbness is still going away	The device did not feel secure in the band	Completed 6 months	1.1 years
23	Took some of the edge off, easy to take on and off	Felt like it did not always come back on by itself	Completed 6 months	3.5 years
24	Can take less opioids; the band is small and easy to hide under pants	Took at little while to figure out the best way to wear the band	Completed 6 months	5 years
27	Took a 12-h trip when I would usually have cramping and had a lot less than usual	Did not help as much as I would have hoped	Completed 6 months	3 years
28	Improvements in numbness and tingling during high impact exercise; it is simple to operate	None	Completed 6 months	2 years

efficacy results only reflect potential short-term improvements, although 68% of participants who decided to continue with the study past the primary 6-week trial period reported that they planned to continue using the device after completion of the final 6-month trial period.

In conclusion, TENS is a safe, non-pharmacologic, patient-controlled therapy that if demonstrated to be efficacious would provide CIPN patients with an important therapeutic option, especially for many patients who prefer to not take more medications after chemotherapy. This study demonstrates that it is feasible to evaluate TENS using a wireless, convenient TENS device. Preliminary efficacy results suggest that further evaluation of TENS for CIPN in a RCT is warranted.

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Compliance with ethical standards

Conflicts of interest Neurometrix provided the devices and electrodes for this investigator-initiated study and funds to support the conduct of the trial. The authors had complete control over the development of the protocol, conduct of the study, and publication of the results. Neurometrix was provided a copy of the manuscript prior to submission for publication, but did not provide any input on the manuscript.

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