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Received: January 25, 2021 Revised: April 27, 2021 Accepted: April 28, 2021

(onlinelibrary.wiley.com) DOI: 10.1111/ner.13463

Higher Pain Sensitivity Predicts Efficacy of a Wearable Transcutaneous Electrical Nerve Stimulation Device for Persons With Fibromyalgia: A Randomized Double-Blind Sham-Controlled Trial

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ABSTRACT

Objectives: This study investigated the efficacy of a transcutaneous electrical nerve stimulation (TENS) device (Quell®) for persons with symptoms due to fibromyalgia (FM).

Materials and Methods: One hundred nineteen ($N = 119$) subjects were randomly assigned to use an active ($N = 62$) or sham ($N = 57$) TENS for three months. All subjects completed baseline questionnaires and were administered quantitative sensory testing (QST). Subjects completed the Patients' Global Impression of Change (PGIC, primary outcome measure) and other mailed questionnaires (secondary outcome measures) at six weeks and three months.

Results: The subjects averaged 50.4 ± 13.5 years of age, 93.3% were female, and 79.8% were Caucasian. Most showed benefit from using the TENS, but no differences between groups were found on the primary outcome measure after three months (active 3.87 ± 1.85, sham 3.73 ± 1.80, 95% confidence interval [CI] [−0.60, 0.88], $p = 0.707$). Those with more hypersensitivity showed most improvement on the PGIC at six weeks (0.22, 95% CI [0.01, 0.43], $p = 0.042$) and three months (0.20, 95% CI [0.00, 0.41], $p = 0.049$) and among those with higher sensitivity based on QST, the active TENS group showed the most benefit with TENS compared with the sham treatment (1.20, 95% CI [0.22, 2.18], $p = 0.017$). No TENS-related serious adverse events were reported. Subjects in the sham group correctly identified their treatment 87.5% of the time, while, surprisingly, subjects in the active group correctly identified their treatment only 17.4% of the time.

Conclusion: This study found no differences between those who were exposed to maximal-frequency active stimulation or minimal-frequency sham stimulation from a wearable TENS in reducing FM-related symptoms. However, those with greater hypersensitivity showed most benefit from TENS. Additional studies to help determine the role individual differences play in the use of TENS in managing FM-related symptoms are needed.

Keywords: Controlled trial, fibromyalgia, helpfulness, quantitative sensory testing, sham, transcutaneous electrical nerve stimulation

Conflict of Interest: The authors reported no conflict of interest.

INTRODUCTION

Fibromyalgia (FM) is a medical diagnosis that is characterized as wide-spread pain, sleep disturbances, and fatigue that is estimated to affect 2–8% of the population (1–3). Neuropathic pain and major depressive disorder often co-occur with FM (1,2,4). The evidence suggests that the pain in FM results primarily from pain processing pathways functioning abnormally. Some neurochemical abnormalities that occur in FM also regulate mood, sleep, and energy, thus explaining why mood, sleep, and fatigue problems are commonly comorbid with FM (1,3,5).

In psychophysical studies, individuals reporting persistent FM pain are characterized by enhanced pain sensitivity on quantitative sensory testing (QST) (6–8), which refers to a set of psychophysical methods used to quantify somatosensory function in patients with neuropathic pain (9) as well as chronic noncancer pain (10). Formal QST studies have shown that individuals with FM have greater sensitivity (compared to pain-free controls) to a broad variety of

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For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please go to http://www.wiley.com/WileyCDA/Section/id-301854.html

Source(s) of financial support: This project was supported in part by an investigator-initiated grant from Neurometrix.

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standardized noxious stimuli (11). Specifically, FM patients exhibit a tendency toward greater central sensitization-like processes, such as temporal summation of pain (TSP) (12,13), and a deficiency of endogenous pain-inhibitory systems such as conditioned pain modulation (CPM) (14,15).

It is well-known that cutaneous stimulation that activates large fibers in the peripheral nervous system (e.g., vibration, transcutaneous electrical nerve stimulation [TENS], massage) can decrease pain based on experimental studies among both healthy subjects and persons with neurogenic and musculoskeletal acute or chronic pain (16–20). Daily et al. (21), in a study of four weeks of active TENS use, showed significant improvement in movement-evoked pain among women with FM. Although the primary mechanism of pain relief from cutaneous stimulation has not been definitively established, proposed theories to explain this effect in pain from both animal and human clinical studies have included activation of endogenous inhibitory mechanisms to reduce central excitability and restore central pain modulation (22–26), diffuse noxious inhibitory controls (27), lateral inhibition within the spinal cord (28), stimulation of coinciding cortical coding areas involved with pain and touch in the brain (29–31), and selective attention, distraction (12,32) and placebo analgesia (33).

A fixed-site high-frequency TENS wearable device was developed for persons with chronic pain and joint discomfort (www.quellrelief.com) and was cleared by the FDA (K152954) for symptomatic relief and management of chronic intractable pain. The primary aim of the study was to determine the effect of an active TENS to manage FM pain compared with a sham TENS device. We employed objective QST measures to assess pain sensitivity and tracked each of the subjects using the TENS app. A secondary goal was to help understand individual differences in response to using the TENS device and to identify specific demographic factors that may contribute the most to benefit from this intervention for painful symptoms among individuals diagnosed with FM. We hypothesized that those randomly assigned to using the active TENS would report greater improvement and reduced pain compared with those in the sham TENS. We also hypothesized that the TENS device would be safe to use, with minimal significant adverse effects. Finally, we planned to investigate whether certain individual characteristics, such as greater pain sensitivity, disability, and negative affect, would predict greater benefit from using the TENS.

MATERIALS AND METHODS

This study was approved by the Internal Review Board of the hospital and was registered in ClinicalTrials.gov (# NCT03714425). It was a prospective, double-blind, randomized, sham-controlled trial. We recruited 119 patients with a primary complaint of FM and randomized each of the subjects to one of two treatment conditions: 1) an active TENS device and 2) a sham TENS device. All participants were adults age 21 or older and diagnosed with FM. Patients were included if they 1) had chronic wide-spread pain related to FM for longer than three months, 2) averaged 4 or greater on a pain intensity scale of 0–10, and 3) were able to speak and understand English. All participants needed to meet the criteria set out by Wolfe et al. (34) for FM in order to be considered for inclusion in this trial: 1) wide spread pain at multiple pain sites (as identified on a body map), 2) pain present at a similar level for three months or longer, and 3) pain that is not accounted for by any other medical condition. We also required that the participants had a ''physician diagnosis'' of FM, meaning that they had been told that they had FM and the diagnosis was entered somewhere in their medical record.

Patients were excluded from participation if they met any of the following criteria: 1) diagnosis of cancer or any other malignant disease; 2) acute osteomyelitis or acute bone disease; 3) present or past DSM-5 diagnosis of schizophrenia, delusional disorder, psychotic disorder, or dissociative disorder that would be judged to interfere with study participation; 4) pregnancy; 5) any clinically unstable systemic illness judged to interfere with treatment; 6) a pain condition requiring urgent surgery; 7) an active substance use disorder, such as cocaine or IV heroin use (positive on the Mini International Neuropsychiatric Interview; M.I.N.I. v.5.0), that would interfere with study participation; and 8) an implanted cardiac pacemaker, defibrillator, or other implanted device. All subjects were asked to not change their treatment during the study period.

Patients were randomized to one of two experimental groups: a commercially available active TENS and a sham TENS. The active TENS utilizes mild stimulation for 60-min periods with modulated pulse frequency (60–100 Hz), maximum average current of 5.6 mA, and pulse duration of 380 μsec (for specifications, see https://www.quellrelief.com/the-quell-system/tech-specs-2-0/). This TENS is applied to the calf region of one leg and cutaneous disposable electrodes are attached to a Velcro band that is wrapped around the calf (Fig. 1). The sham TENS looked exactly like the active TENS but was programmed to only give 2 min of stimulation three times during a one-hour therapy session (at 0, 30, and 60 min). The manufacturer of the TENS device was responsible for randomizing the devices using a randomization table (www.graphpad.com/quickcalcs/randomize) and sent the devices unmarked to the study center. After each participant was consented, the research assistant (RA) randomly assigned a device to each subject. The RA could not determine whether a device was an active or sham device based on any markings or physical characteristics. All subjects were given a demonstration of the TENS at the time of the initial evaluation. In both the active and sham devices, the intensity was initially set to a strong but comfortable level through an automated calibration procedure and could subsequently be manually adjusted by subjects. Subjects were told that they would receive either a low intensity or high intensity TENS device as part of the randomized trial. The study coordinators and investigators did not discuss stimulation characteristics with the subjects. All subjects completed baseline assessment measures and were followed for three months. All participants were also given a battery of QST testing at baseline.

All subjects (active TENS and sham TENS) were encouraged to use their device for at least two therapy sessions (two hours of stimulation) every day, and to wear the device as often as possible, even at night. Tracking of use of the device was available electronically through a TENS app. All subjects were asked to complete a packet of mailed questionnaires six weeks and three months after the start of the study and to return the completed assessments in preaddressed stamped envelopes. Each subject was compensated $50 at baseline and $50 at study completion upon receipt of their completed questionnaires. All subjects returned their study TENS device at the end of the trial and were given a new active TENS device.

Blinding

Neither the principal investigator, the coinvestigators, the study RA, or the subjects knew if they are given a sham or active TENS

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Figure 1. The TENS. [Color figure can be viewed at wileyonlinelibrary.com]

device. The numbered devices were randomly assigned to subjects. At the end of the study, all subjects were asked if they thought they had the sham or active TENS device. The RA was also asked to identify which subjects she thought had the active versus sham TENS prior to analysis of the data. Both the active and sham TENS communicated via Bluetooth with the same mobile application. This application provided the subjects with a dashboard of device information, trending data on device usage, and the ability to track daily pain and sleep quality. This same information was synced to the cloud so that investigators involved in the study could collect this data remotely, as well as monitor adherence with the device.

Research Objectives

This study was conducted between February 2019 and June 2020. The primary outcome was improvement on global impression of change. Secondary outcomes on the effective use of the active TENS (vs. sham TENS) were assessed on self-reported pain intensity, activity interference, pain catastrophizing, emotional distress, neuropathic pain symptoms, prescription pain medication use, and overall impact of FM. We hypothesized that 1) those assigned to using the active TENS device would report reduced pain compared with those in the sham TENS condition; with those using the active device also showing improvement in sleep, mood, and level of activity; 2) frequency of using the TENS (increased tolerability and adherence) would be correlated with greater reduction in pain.

Quantitative Sensory Testing

Mechanical Pain

Responses to punctate mechanical stimuli were measured using a standard set of weighted probes (pinprick stimulators) that exert forces between 8 and 512 mN; subjects provided estimates of pain intensity ratings and mechanical temporal summation. Singular taps were performed on the metacarpophalangeal joint of the middle finger of the nondominant hand using these probes developed by the German Research Network (35). The lowest-force stimulator that produced a sensation of discomfort at the level 10 out of a 100 point scale were then used to assess the TSP that occurred with rapid administration of identical stimuli for a series of ten pinpricks (with 1-sec interstimulus intervals). Participants rated the painfulness of the first, fifth, and tenth stimulus; as in our prior studies, mechanical temporal summation was defined as the increase in pain from the first to the final stimulus (36–38). A Somedic pressure algometer was utilized to assess responses to pressure stimulation at several anatomical sites. Pain pressure thresholds (PPTs) were determined twice on the right and left sides of the body: the trapezius and thumb joint. Mechanical pressure was applied using a 0.5-cm^2 probe covered with 1 mm polypropylene pressure-transducing material; pressure was increased at a steady rate of 30 kPA/sec until the subject indicated that the pressure became painful. Finally, we used cuff algometry to assess responses to sustained mechanical pressure. A Hokanson rapid cuff inflator was used to inflate a standard blood pressure cuff around the gastrocnemius muscle of the dominant leg until the subject indicated the pain level was 40 out of a 100-point scale. This pressure was used in the next test and was not changed. Over the course of 2 min, at 30 sec intervals, the subject was asked to rate her or his current pain level on a scale 0–100. As with each of these psychophysical testing procedures, participants were informed that they could terminate the procedure at any time.

Cold Pain Assessment

Responses to noxious cold were evaluated using a repeated cold pressor task (CPT), which involved immersion of the right hand in a circulating water bath (Neslab RTE17) maintained at a temperature of 4°C. Participants underwent a series of several CPTs, with the first two consisting of serial immersions of the dominant hand for approximately 30 sec, with 2 min between immersions. Once the subject removed their hand, pain ratings were asked at 0, 15, 30, and 60 sec. CPM (which refers to the phenomenon of one noxious stimulus inhibiting the pain of a second noxious stimulus) was measured during these cold pressor trials by assessing PPT during the immersion. The final CPT involved an immersion of the dominant hand lasting until a participant

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reached maximum pain tolerance (or a 3 min maximum). Their pain level was asked in 15 sec intervals while submerged and as soon as they removed the hand from the water. The participants rated the intensity of the cold pain on a 0–100 scale (''no pain'' to ''most intense pain imaginable''). These procedures are similar to those we have utilized in prior studies of patients with osteoarthritis and other chronic pain conditions (6,7,19,20).

Patient Measures

A packet of study measures was completed at the time of recruitment and follow-up questionnaires at six weeks and three months were mailed to the subjects with a self-addressed stamped envelope so that they could be completed and returned. We targeted the *Patients' Global Impression of Change (PGIC)* (39) at three months as the primary outcome measure. This self-report measure reflects a patient's belief about the efficacy of treatment and assesses change in activity limitations, symptoms, emotions, and overall quality of life (40). The following secondary outcome measures were administered to all study participants at baseline, six-week midpoint, and three-month follow-up time points: 1) *The Brief Pain Inventory (BPI)* (41) is a well-known measure of clinical pain and has shown sufficient reliability and validity. 2) *Pain Disability Inventory (PDI)* (42) is a 7-item questionnaire rated from 0 to 10 on level of disability of seven areas of activity interference including family/home responsibilities, recreation, social activity, occupation, sexual behavior, self-care, and life-supporting behaviors. 3) *Pain Catastrophizing Scale (PCS)* (43,44) is a 13-item instrument that examines three components of catastrophizing: rumination, magnification, and helplessness. 4) *Hospital Anxiety and Depression Scale (HADS)* (45,46) is a 14-item scale designed to assess the presence and severity of anxious and depressive symptoms over the past week. 5) *Revised Fibromyalgia Impact Questionnaire (FIQR)* (47) is a commonly used instrument in the evaluation of FM patients and has the same three domains as the original FIQ (function, overall impact, and symptoms). 6) *Pain Detect Neuropathic Pain Questionnaire (painDETECT*) (48) is a reliable screening tool with high sensitivity, specificity, and positive predictive accuracy with higher scores indicating more of a neuropathic component of pain.

Perceived Helpfulness

At the end of the three-month trial, the subjects were asked to complete 11 questions to assess the helpfulness of and satisfaction with the TENS. Similar helpfulness questions had been developed and used in a previous study (49). On a 0–10 scale, the participants rated 1) how helpful the TENS was for their FM, 2) how helpful the TENS was for other pain sites, 3) how bothersome the TENS device was to use, 4) how easy was it to recharge the TENS, 5) how willing was the user to use the TENS in the future, 6) how helpful the TENS app was, 7) how often was the TENS used to treat their pain (0 = only as needed; 10 = daily routine), 8) how many days per week did they use the TENS, 9) in general, how many minutes did they wear the TENS each time they used it, 10) which group they thought they were assigned to (low intensity or high intensity), and 11) were there any things about the TENS that they felt were particularly helpful or harmful.

Statistical Analysis

This study was designed to gather data on the feasibility, tolerability, safety, and efficacy of the TENS among persons with FM. Differences between groups at baseline were assessed and univariate and multivariate descriptive analyses were performed on all the dependent variables. The primary research objective to measure perceived improvement in pain at three months was assessed using a two-sample *t*-test of PGIC scores between the active and sham treatment groups using a type I error rate of 0.05 (two-sided). For this analysis, missing PGIC scores were imputed using an intention-to-treat analysis. Power analyses, as outlined by Cohen (50), determined that a sample size of 100 subjects (50 per treatment group) gave the study a >80% probability of detecting a 10-point group difference on a 0–100 rating scale (assuming a standard deviation [SD] of 16). Collectively, this sample size ($N = 100$), together with previously observed high retention rates and the expected efficacy of the device (20), provided adequate power to detect moderate-size effects. It was expected that 15% of the participants would withdraw before completing the study and therefore the target recruitment was 115 subjects. Most of the analyses involved delta scores reflecting changes within subjects, though in the primary analysis we compared PGIC raw scores rather than change scores (as the PGIC variable is a patient-reported rating of change). We classified patients with higher and lower sensitivity using two-step cluster analyses. Statistical analyses were conducted using SPSS (v.21; IBM, Chicago, IL, USA).

RESULTS

One hundred seventy ($N = 170$) individuals responded to the research flyers and/or online information about the study and were screened for participation in the trial. One hundred nineteen ($N = 119$) individuals with a diagnosis of primary FM were recruited. Of those who were screened but were not consented ($N = 51$), 38 (74.5%) failed to show up for the initial visit, 6 (11.8%) did not meet the inclusion criteria (e.g., no FM diagnosis, not ≥4/10 pain), 6 (11.8%) were undecided about the study and worried that it might take too much time, and one (2.0%) subject reported being too far away to travel to the clinic. Three individuals did not have a compatible mobile phone and instead were offered a tablet to borrow to monitor their daily TENS use. None of the potential subjects decided not to participate because they disliked the sensation of using the TENS after an initial trial. Three subjects discontinued the trial early but agreed to complete the follow-up questionnaires. These three subjects had all been assigned to the active TENS condition.

Participant Characteristics

Of the 119 participants who were consented, the average age was 50.4 years (SD = 13.5), almost all were female (93.3%), and 79.8% were Caucasian (Table 1). All the subjects reported experiencing wide-spread pain and had been given a diagnosis of FM from a provider. Their pain duration averaged almost 18 years. Fifty subjects (42.0%) fell within the healthy normal range on body mass index (BMI), while 69 (58.0%) were considered overweight (≥25.0 BMI), and of these 39 (56.5%) were classified as obese (≥30.0 BMI) (51). At baseline, 56 (47.1%) participants were taking over-the-counter pain medication (e.g., ibuprofen) and 26 ($N = 26$; 21.8%) subjects were taking prescription opioids, including tramadol.

Over the course of the study, 19 ($N = 19$; 16.0%) subjects withdrew from the trial (Fig. 2). Sixteen (7 active, 9 sham) were lost to follow-up. Three of the subjects in the active TENS group who requested to discontinue the trial early agreed to complete the

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Table 1. Patient Demographic Characteristics and Mean Baseline Quantitative Sensory Testing Scores ($N = 119$).

Variable	Total sample ($N = 119$)
Age (years, SD)	50.4 ± 13.5
Ethnicity (% Caucasian)	79.8
Gender (% female)	93.3
Married (% yes)	44.8
Employed (% yes, full-time or part-time)	49.5
Years of education (mean, SD)	15.7 ± 2.9
Pain-related surgeries (mean, SD)	1.4 ± 2.8
Pain duration (years)	17.6 ± 13.1
Weight (mean, SD, lbs)	163.8 ± 41.4
BMI (mean, SD)	27.5 ± 6.2
Pain intensity (0–10):	
Current*	5.7 ± 2.0
Average*	5.6 ± 1.5
Worst*	7.2 ± 1.6
Least*	4.0 ± 2.2
% take pain medication (% yes)	78.6
% take opioid medication (% yes)†	21.8
QST average thumb (in kPa)‡	213.3 ± 1.4
QST average shoulders (in kPa)‡	253.0 ± 151.2
256 mN probe average pain	29.7 ± 22.0
Stim1 average pain rating	11.9 ± 13.1
Stim 10 average pain rating	26.0 ± 19.4
QST temporal summation§	14.1 ± 15.5
Cuff pressure (in mmHg)	131.6 ± 66.5
Pressure pain numerator	394.1 ± 226.2
Pressure pain denominator	272.2 ± 169.6
CPM score (× 100)	161.3 ± 91.5
Time hand withdrawal (in sec)	38.0 ± 48.5

*1 = least; 10 = most.
†Including 11 patients taking tramadol.
‡Average mean scores of 8 measures from the pressure algometer: 4 left and 4 right × 100.
§Average left and right change scores of 60 sec minus 1 sec ratings.

three-month post-treatment questionnaires. No significant differences were found between those who dropped out of the study and those who completed the trial, except that those who dropped out reported having a shorter duration of pain versus those who completed the trial (11.4 vs. 18.6 years; $t = 2.1$; $p = 0.035$).

Baseline differences between subjects assigned to the active TENS and the sham TENS are presented in Table 2. Those assigned to the active TENS condition showed higher scores on the Fibromyalgia Impact Questionnaire (FIQR Total 61.4 vs. 52.8; 95% confidence interval [CI] [1.93–15.16], $p = 0.012$). All other comparisons were nonsignificant.

The participants used the TENS an average of 74.9 (SD = 22.4) days and for a total average of 357.4 (SD = 231.0) sessions (one hour each session) according to the TENS app (range 3–103 days; 9–1290 sessions). No differences were found in the number of days the TENS was used between the active and sham groups (71.7 ± 23.7 vs. 65.9 ± 30.3, CI [−4.13, 15.75], $p = 0.249$) or in the number of sessions the TENS was used between groups (335.3 ± 217.4 vs. 315.1 ± 251.7, CI [−64.96, 105.42], $p = 0.639$). The sensation threshold determined by calibration of the TENS averaged 8.1 mA (SD = 5.0; range 3.0–35.5) and the actual median intensity used during the therapy sessions over the entire study was 14.9 mA (SD = 9.7; range 1.0–74.5). No difference were found between active and sham groups (baseline intensity active 7.9 ± 4.9 vs. sham 8.2 ± 5.1, CI [−2.11, 1.54], $p = -0.304$; final intensity active 15.5 ± 10.4 vs. sham 14.3 ± 8.9, CI [−2.36, 4.77], $p = 0.671$).The median stimulation ratio (defined in decibels as 20 * log10) between the final stimulation and the initial threshold intensity averaged 5.2 (SD = 3.4; range −16.9 to 18.2). No differences were found between groups (active 5.5 ± 4.8, sham 4.9 ± 0.6, CI [−0.63, 1.84], $p = 0.332$).

Of the 103 subjects who finished the trial, 89 (86.4%; active = 45; sham = 44) completed and mailed back the mid-study questionnaires after six weeks, and 99 of the 103 subjects (96.1%; active = 54; sham = 45) completed and mailed back the post-study questionnaires after three months. There were no differences between groups based on age, ethnicity, race, BMI, marital status, years of education, work and compensation status, and smoking cigarettes.

Primary Outcome Measure

There were no significant differences on the PGIC found between those assigned to the active TENS group and the sham group at six weeks (active 3.8 ± 1.9 vs. sham 3.8 ± 1.7, CI [−0.78, 0.75], $p = 0.964$) and three months (active 3.9 ± 1.9 vs. sham 3.7 ± 1.8, CI [−0.60, 0.88], $p = 0.707$). We grouped all of the subjects on the PGIC among those who rated 5, 6, or 7 on the 1–7 scale (noticeable improvement at six weeks, $N = 36$; noticeable improvement at three months, $N = 46$) and compared them with those subjects who rated 1–4 on the PGIC (no noticeable improvement at six weeks, $N = 51$; no noticeable improvement at three months, $N = 58$). Again, no differences were found between treatment groups at six weeks ($p = 0.435$) and at three months ($p = 0.754$).

Secondary Outcomes

Overall, improvements were noted among the subjects on the self-report outcome variables from baseline to six weeks and from baseline to three months, including improvements in pain intensity (BPI), pain relief (BPI), activity interference (BPI), disability (PDI), mood (HADS), catastrophizing (PCS), impact of FM (FIQR), and neuropathic pain symptoms (PainDETECT; Table 3). Those assigned to the active TENS group showed a significant improvement difference in "least pain" ratings at six weeks ($p = 0.037$) and total FIQR scores at three months ($p = 0.049$). Among all of the study subjects, the number of sessions using the TENS registered on the TENS app was found to be positively related to duration of pain (those with longer pain duration used the TENS more often, $r = 0.28$, $p = 0.002$).

Pain Sensitivity Analyses

We analyzed the QST data by dividing the subjects into two groups based on a two-step cluster analysis of 1) the average pressure pain threshold at the trapezius, 2) mean ratings of the probe stimuli (average of first, fifth, and tenth), 3) temporal summation with the probes (rating of the tenth minus rating of the first stimulus), 4) inflation (in mmHg) of the cuff at which a pain level of 40/100 was experienced, 5) cold pain tolerance (in seconds) and cold pain aftersensations at 30 sec (after hand removal), and 6) CPM, calculated as mean pressure pain threshold during cold water divided by baseline pressure pain threshold and then multiplied by 100. The cluster analyses, using distance measure, log-likelihood, standardized variable, and Schwarz Bayesian Criterion (52,53), resulted in two groups identified as lower pain sensitivity ($N = 68$) and higher pain sensitivity ($N = 51$). No demographic differences were found between groups. PGIC was significantly improved among subjects

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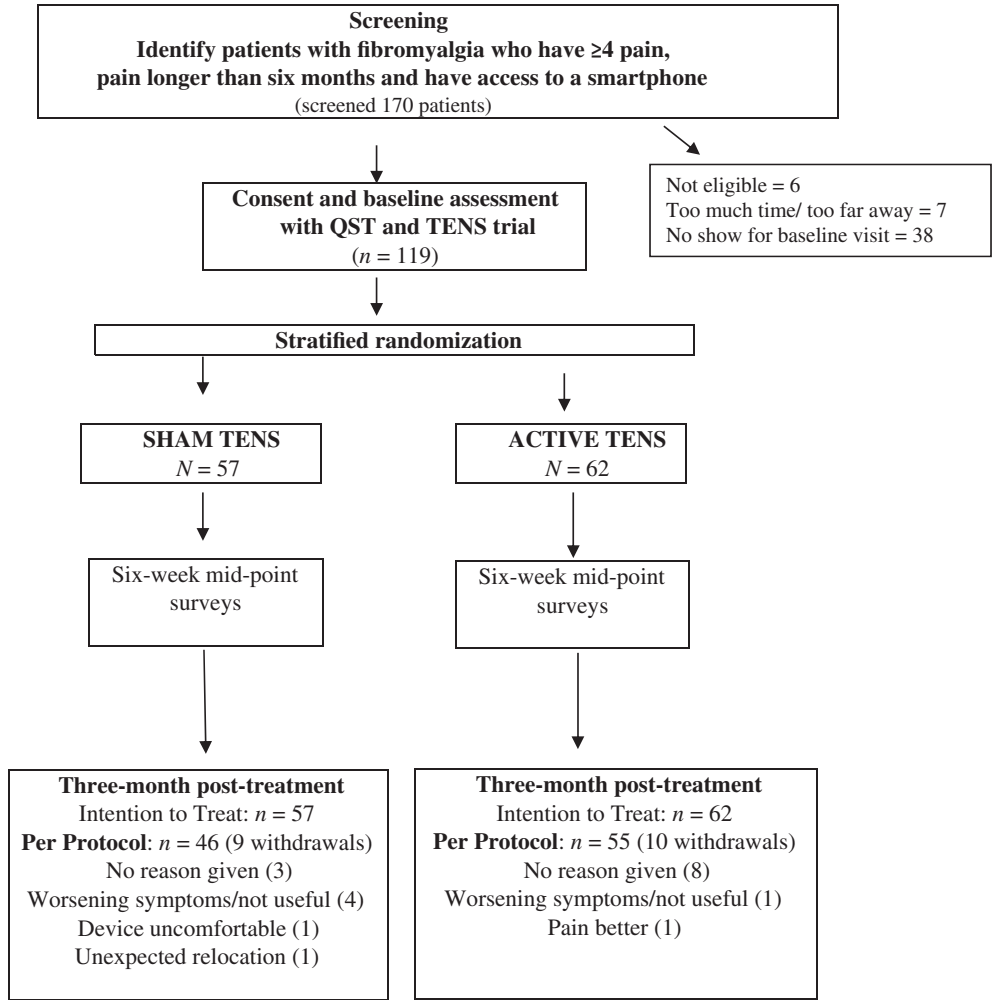

Figure 2. Study design and Consolidated Standards of Reporting Trials (CONSORT) diagram.

with higher pain sensitivity at six weeks (0.22, 95% CI [0.01, 0.43], $p = 0.042$) and at three months (0.20, 95% CI [0.00, 0.41], $p = 0.049$). This finding is consistent with the hypothesis that TENS is most effective in sensitized pain pathways (54). We also examined differences among those with active or sham TENS and higher and lower sensitivity on the PGIC (% improved, Table 4). Those in the active group with higher pain sensitivity showed more benefit with TENS at six weeks and three months (60.9% and 63.0%) compared with the active treatment among subjects with lower pain sensitivity (28.6% and 30.0%; 1.20, 95% CI [0.22, 2.18], $p = 0.017$).

Helpfulness Ratings With the TENS

The results of the end-of-study helpfulness questions are presented in Table 5. Helpfulness was scored from 0 = not at all helpful to 10 = very helpful. The results were grouped between those who rated the item as helpful (≥6/10) compared with those who rated the item as less or unhelpful (≤5/10). Even though pre-post questionnaire ratings demonstrated improvement in pain among most who were recruited for the study, less than half (40.6%) felt that the device that they used was very helpful in reducing their FM-related pain. Also, 38.5% of all the subjects felt that their device was helpful in relieving pain in other areas of the body; those in the sham TENS group rating this as higher (40.9%, ≥6/10) than those in the active TENS group (36.5%). Few (13.7%, ≥6/10) felt that their device was bothersome to use, although more in the active TENS group felt that the device was bothersome (17.3%) than in the sham TENS group (9.3%). Overall, 82.3% of all the subjects reported that they would be willing to use the TENS after the study was concluded (≥6/10), with those in the sham group indicating that they would be more willing to use the TENS in the future (sham = 86.4% vs. active = 78.8%). Those with baseline higher pain intensity (average BPI, $p = 0.017$), more activity interference (BPI, $p < 0.001$), greater disability (PDI, $p = 0.001$), more pain catastrophizing (PCS, $p = 0.047$), greater emotional distress (HADS total, $p = 0.008$), more impact from FM (FIQR total, $p = 0.002$), and higher sensitivity based on QST testing ($p = 0.004$) tended to reported more helpfulness from using either the active or sham device. By the end of the three-month study, 37.5% of the subjects in the active group discontinued using opioids compared with 11.1% in the sham group. Because of the low numbers in each group, the differences between groups were nonsignificant.

Blinding Assessment

Blinding was assessed as each subject completed the study by asking the RA and subjects to identify whether a low intensity or high intensity TENS was used. Overall, the study coordinator (RA) identified the correct treatment in 54.7% (95% CI [45.2–64.2])

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Table 2. Differences (Mean, SD) in Descriptive Characteristics at Baseline Between the Active and Sham TENS Groups.

Variable	Active TENS ($N = 62$)	Sham TENS ($N = 57$)	p value	95% confidence interval
Pain intensity (BDI, 0–10)*				
Worst	7.3 ± 1.6	7.1 ± 1.6	0.534	−0.40, −0.77
Least	4.2 ± 2.4	3.9 ± 2.1	0.546	−0.57, 1.06
Average	5.8 ± 1.6	5.3 ± 1.5	0.073	−0.05, 1.06
Now	5.9 ± 2.1	5.5 ± 1.8	0.277	−0.32, 1.11
Pain relief % (24 hours—0–100)†	31.2 ± 21.5	36.4 ± 26.0	0.255	−14.16, 3.79
Pain interference (BDI, 0–10)‡				
General activity	6.1 ± 2.6	5.8 ± 2.4	0.463	−0.58, 1.26
Mood	5.5 ± 2.5	5.5 ± 2.5	0.981	−0.96, 0.94
Walking ability	5.4 ± 2.8	5.1 ± 3.0	0.592	−0.74, 1.38
Normal work (wk/housewk)	6.6 ± 2.6	5.8 ± 2.9	0.132	−0.23, 1.75
Relations with others	4.9 ± 2.9	4.4 ± 2.9	0.368	−0.58, 1.54
Sleep	6.6 ± 2.9	5.8 ± 2.9	0.144	−0.27, 1.82
Enjoyment of life	6.5 ± 3.0	5.6 ± 2.9	0.108	−0.19, 1.94
Average interference (mean, SD)	5.9 ± 2.2	5.4 ± 2.2	0.212	−0.29, 1.30
Pain Disability Index (PDI)	39.4 ± 15.7	34.3 ± 15.8	0.089	−0.80, 11.16
HADS Anxiety	9.9 ± 4.6	8.6 ± 4.5	0.132	−0.39, 2.96
HADS Depression	8.5 ± 3.9	7.2 ± 4.0	0.095	−0.22, 2.72
HADS Total	18.5 ± 7.3	15.8 ± 7.6	0.059	−0.10, 5.39
Pain catastrophizing scale	21.5 ± 13.2	17.8 ± 12.4	0.122	−1.01, 8.46
FIQR Standard	16.3 ± 6.9	14.0 ± 6.5	0.080	−0.27, 4.79
FIQR Impact	13.4 ± 4.9	11.3 ± 5.5	0.034	0.16, 4.02
FIQR Symptom	31.4 ± 7.2	28.3 ± 7.9	0.030	0.31, 5.86
FIQR Total	61.4 ± 16.5	52.8 ± 17.3	0.012	1.93, 15.16
PainDETECT	18.4 ± 7.5	17.0 ± 6.7	0.326	−1.43, 4.27

*0 = no pain; 10 = pain as bad as you can imagine (past 24 hours).
†0 = no relief; 100 = complete relief.
‡0 = does not interfere; 10 = completely interferes.

Table 3. Pre-Minus Postdifferences (Mean, SD) Based on Baseline and Follow-Up Scores Between the Active TENS and Sham TENS Subjects on Pain, Activity Interference, Catastrophizing, and Mood at Six Weeks and Three Months.*

Variable	Six weeks			Three months		
	Active TENS ($N = 43$)	Sham TENS ($N = 40$)	p value	Active TENS ($N = 53$)	Sham TENS ($N = 45$)	p value
Pain intensity†						
Worst	1.1 ± 2.0	1.2 ± 1.8	0.848	1.4 ± 2.3	1.3 ± 2.0	0.880
Least	1.2 ± 2.3	0.2 ± 1.7	0.037	1.4 ± 2.4	0.8 ± 1.8	0.170
Average	0.9 ± 1.7	0.5 ± 1.6	0.277	1.0 ± 1.6	0.6 ± 1.5	0.167
Now	1.5 ± 2.2	0.6 ± 2.4	0.100	1.5 ± 2.3	0.8 ± 2.0	0.146
Pain relief %‡	7.0 ± 27.5	0.6 ± 24.1	0.373	5.7 ± 27.9	4.6 ± 24.9	0.859
Average interference	1.9 ± 2.0	1.0 ± 2.1	0.102	1.9 ± 2.1	1.1 ± 1.9	0.060
PDI	4.9 ± 10.6	2.3 ± 11.8	0.283	5.7 ± 11.1	4.2 ± 10.6	0.518
HADS Anxiety	1.0 ± 2.8	−0.1 ± 3.0	0.060	1.2 ± 3.0	0.4 ± 2.6	0.185
HADS Depression	0.7 ± 2.7	0.5 ± 2.5	0.699	0.7 ± 2.7	0.5 ± 2.5	0.699
HADS Total	1.7 ± 4.8	0.2 ± 4.7	0.086	1.9 ± 4.9	0.9 ± 3.8	0.305
PCS	2.1 ± 7.6	1.0 ± 5.7	0.446	3.8 ± 9.2	2.8 ± 8.0	0.581
FIQR Active	3.3 ± 4.4	1.9 ± 5.6	0.413	3.6 ± 5.9	1.5 ± 6.0	0.096
FIQR Impact	3.9 ± 4.5	2.9 ± 4.8	0.606	4.0 ± 4.6	2.1 ± 4.7	0.056
FIQR Symptom	5.3 ± 7.5	3.1 ± 8.8	0.239	6.0 ± 7.2	3.7 ± 7.3	0.128
FIQR Total	12.5 ± 13.9	8.8 ± 15.9	0.440	13.1 ± 15.8	5.9 ± 16.0	0.049
PainDETECT	1.6 ± 4.6	1.3 ± 5.7	0.784	2.1 ± 1.8	0.2 ± 5.0	0.157
PGIC (six weeks–three months)				0.22 ± 1.8	0.35 ± 1.9	0.617

*Positive scores indicate improvements, negative scores indicate worsening.
†Brief Pain Inventory 0 = no pain; 10 = pain as bad as you can imagine (past 24 hours).
‡0 = no relief; 100 = complete relief.

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Table 4. Percent Improvement in PGIC Scores (≥5) Among Those With Active or Sham TENS and Higher and Lower Sensitivity.

Week# (*N*)	Active TENS			Sham TENS		
	Lower sensitivity	Higher sensitivity	*p* value	Lower sensitivity	Higher sensitivity	*p* value
PGIC improved after six weeks (% yes)*	28.6	60.9	0.032	34.5	42.9	0.594
PGIC improved after 3 months (% yes)*	30.0	63.0	0.013	40.0	47.1	0.638

*Ratings of ≥5 on a 1–7 scale; 1 = no change; 7 = a great deal better.

of the subjects. Among all subjects, 84.9% (95% CI [77.3–92.5%]) believed they received a low intensity device. Subjects in the sham group correctly identified their treatment 87.5% (95% CI [77.3–97.7]) of the time, while subjects in the active group correctly identified their treatment only 17.4% (95% CI [6.4–28.3]) of the time.

DISCUSSION

This prospective randomized double-blind sham-controlled trial was designed to gather information about the efficacy of a wearable TENS device for persons with pain and symptoms related to FM. Contrary to the study hypothesis, no differences on the primary outcome measure of perceived change were found between those using the active TENS and those who received the sham TENS. Those with higher levels of sensitivity based on QST reported most benefit of TENS in treating their FM symptoms.

Although most subjects showed improvement by the end of the study, it is interesting that no differences on the primary outcome measure were found between those assigned to the active TENS and the sham TENS. Rampakakis et al. (55) found a weak correlation between PGIC scores and standard outcomes among FM patients, but encouraged the use of the PGIC in studies none the less. At the time of recruitment, all the subjects were told that they would be assigned to either a high intensity TENS or a low intensity TENS. The subjects were not told that there would be a sham condition. We know that persons with FM show hypersensitivity to stimulation (56) and many elected to use lower intensities of the TENS based on their hypersensitivity. This might have contributed to the perception that most (85%) felt they had been assigned to the low intensity (sham) condition. It is difficult to understand what benefit minimal stimulation might offer in improving symptoms, but based on the qualitative comments, many believed that infrequent stimulation from the sham device offered benefit. It may be possible that minimal stimulation can have a positive effect among persons with wide-spread pain due to FM and that our study offered two regimens that were effective for this population rather than a sham and an active therapy regimen.

It is also known that placebo treatments are effective among those with FM (33,57). This effect is increased with increased strength of treatment, especially among older adults with higher baseline pain severity, although less of an effect has been found among women and for those with longer duration of pain due to FM (33,57). Many of the participants in this study were hopeful that the treatment would improve their symptoms, and this expectation for a positive result may also have contributed to their perceived benefit. Previous trials have lent support for the need to use adequate dosing of TENS to contribute to improvements in pain (26,54,58). Studies have demonstrated a significant reduction in inflammation-induced sensitization with the use of TENS (22) and examined high and low frequency TENS to reduce hyperalgesia in rodents (25), with evidence that low-frequency TENS can release endogenous opioids (23,24).

This study demonstrated that those with FM who were most hypersensitive based on QST results significantly benefitted the most from a TENS. It has been proposed that greater sensitivity indicates impaired descending inhibition and delayed recovery from central sensitization in persons with chronic pain (59). Assessing these deficits through sensory testing can be useful in determining who might benefit the most from TENS treatment. It is possible that TENS exerts its beneficial effects in part by reducing central sensitization, which may explain the greater reported benefit among the most pain-sensitive patients in this study (13,26).

The participants in this study had significant levels of pain hypersensitivity, illustrated by the very short amounts of time the

Table 5. Patient Post-Study Helpfulness Questionnaire Responses After Three Months for Those With the Active TENS and Sham TENS.

Variable (0–10)	Active TENS (*N* = 52)	Sham TENS (*N* = 44)	*p* value	95% confidence interval
How helpful was the TENS for your fibromyalgia?*	4.8 ± 3.5	4.8 ± 2.6	0.881	−1.15, 1.34
How helpful was the TENS for other pain sites?*	4.0 ± 3.3	4.4 ± 2.9	0.462	−1.74, 0.79
How bothersome was the TENS to use?†	2.9 ± 2.5	2.0 ± 2.3	0.072	−0.08, 1.89
How easy was it to recharge the TENS?‡	9.1 ± 1.9	9.1 ± 2.0	0.828	−0.69, 0.87
How willing would you be to using the TENS in the future?§	7.6 ± 3.2	8.5 ± 2.4	0.148	−1.94, 0.30
How helpful was the TENS app?*	8.5 ± 2.1	7.9 ± 2.2	0.195	−0.30, 1.44
How often did you use the TENS to treat your pain?¶	9.1 ± 1.6	9.1 ± 2.0	0.893	−0.68, 0.78
Which group do you think you were assigned to? (% who chose SHAM)	82.2	87.5	0.399	−0.11, 020

*0 = not at all helpful; 10 = very helpful; mean, SD.
†0 = not at all bothersome; 10 = very bothersome; mean, SD.
‡0 = not at all easy; 10 = very easy; mean, SD.
§0 = not at all willing; 10 = very willing; mean, SD.
¶0 = only as needed; 10 = daily routine; mean, SD.

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subjects would tolerate their hands in cold water (55). As a result, many of the participants chose not to tolerate higher levels of stimulation on the TENS device, even though, as demonstrated in other chronic pain patient populations, greater stimulation may have been beneficial in reducing their pain in the long run (21,58).

Subjective comments and feedback by the participants suggest that some did not believe that the TENS was helpful for their pain, even though they might have shown improvement based on pre-post testing results. Thus, even though the TENS might have contributed to a beneficial outcome, the individuals did not perceive that the beneficial effects were striking. These individuals were found in both the active and sham groups. The fact that many expressed a willingness to use the TENS in the future despite minimal changes in outcome also indicates that many believed that the TENS had some benefit for their pain.

This study found no serious and few minor adverse events from the TENS consistent with other investigations (21). There is a call for nonpharmaceutical interventions to help manage symptoms associated with FM (60). TENS has been shown to be inexpensive and safe and can be self-administered with minimal difficulty (18). The results presented in this study are similar in strength of efficacy to outcome trials of pharmaceutical interventions for FM (61) and a combination of pharmacological and nonpharmacological interventions has been recommended in order to offer the best chance for improvement among persons with widespread pain (62).

There are several limitations of this study that should be acknowledged. First, this study included a limited number of subjects and we followed them for only three months. It is possible that with larger numbers of subjects in each group and the opportunity to follow the subjects for a longer period, other findings may have emerged. In addition, given that placebo effects can be quite powerful in studies of interventions to treat painful conditions, a longer follow-up period might have demonstrated separation between the active treatment and sham groups. Those who participated in this study tended to be female, Caucasian, well educated, and with a long history of FM-related pain of almost 18 years. Most of the subjects had exhausted many other treatments for their pain. It would have been interesting to explore findings of individuals who had been newly diagnosed with FM. It would have also been valuable to have recruited more males and more persons with ethnic diversity to expand the generalizability of the findings. Second, we used agreed-upon criteria for the diagnosis of FM but did not incorporate an in-person medical history and physical examination in the study. Wolfe et al. (34) have argued that a physical examination is not always necessary to accurately diagnose FM; however, a more rigorous assessment of FM may have changed who were included in the study (58,63). Third, it should be highlighted that the participants in this study had significant levels of pain hypersensitivity. As a result, many of the participants chose not to tolerate higher levels of stimulation on the TENS device, even though, as demonstrated in other chronic pain patient populations, higher levels of stimulation may have been more effective (20,58).

Fourth, the subjects in this study reported other medical comorbidities and were pursuing other treatments for their pain during this trial despite being encouraged to not change their treatment during the study period. Although we made every effort to track the other treatments or external factors, including use of medication, it is hard to know how other treatments or environmental factors (such as changes in the weather) might have affected the outcome of this study. Outside treatments were shown to be evenly divided between the active and sham groups, so one group did not have an advantage in receiving more pain-related treatments compared with the other. Although we did not find a significant effect of the use of pain medication on the overall report of pain, some of the participants were taking stronger pain medication to treat their pain that might have affected the results.

Finally, we did not require assessment of the symptoms of FM at the same time that the TENS was being used (64), and we did not assess other symptoms such as physical and cognitive fatigue (65), or pain with movement (18,21). This might have accounted for the differences in the results of this trial compared with other outcome trials of TENS (18,66). It may have also been useful to include daily assessments using ecological momentary assessment to more accurately assess momentary changes (67).

In summary, while this study found no outcome differences between an active TENS with standard stimulation frequency and a sham TENS with minimal stimulation frequency for persons diagnosed with FM, those with more hypersensitivity showed most improvement. Also, among subjects with higher pain sensitivity, those in the active group showed more benefit with TENS compared with the sham treatment. The expectations of benefit from any device cannot be ruled out. Future studies are needed to gain a better understanding of the mechanisms of action of the effect stimulation using a TENS has in treating pain and symptoms associated with FM.

Acknowledgement

The authors wish to thank Marise Cornelius, Kara Fields, Shai Gozani, and Xuan Kong for their assistance with this study.

Authorship Statement

Robert Jamison and Robert Edwards contributed to the trial design and supervised conduct of the trial. Samantha Curran and Limeng Wan conducted the data collection. All authors contributed to the data interpretation. Robert Jamison wrote the manuscript and was responsible for statistical analyses. All authors edited, reviewed, and approved the final manuscript.

How to Cite this Article:

Jamison R.N., Curran S., Wan L., Ross E.L., Gilligan C.J., Edwards R.R. 2021. Higher Pain Sensitivity Predicts Efficacy of a Wearable Transcutaneous Electrical Nerve Stimulation Device for Persons With Fibromyalgia: A Randomized Double-Blind Sham-Controlled Trial.
Neuromodulation 2021; E-pub ahead of print. DOI:10.1111/ner.13463

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COMMENT

This is a well-structured study, although as stated by the authors a longer time scale of greater than 3 months may have shown a difference between sham at active treatment. It is difficult to do sham TENS, however as stated in the manuscript the sham treatment was a form of treatment.

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