Research Article

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Reduction of Pain and Fatigue after Use of Over-The- Counter Socks Embedded With Haptic Vibrotactile Trigger Technology: Results from the Invigor Study

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ABSTRACT

Introduction: *The prevalence of pain, pain-related diseases, and fatigue related issues are so vast that they are the leading reasons patients visit their primary care provider. Over 100 million people are estimated to live with chronic or recurrent pain and fatigue is estimated to affect more than 50% of the population of older adults. Conventional pharmacological treatments targeting the symptoms of pain and fatigue have been associated with dangerous adverse effects. Clinicians are continuously trying to identify effective, alternative treatment strategies to address pain and fatigue, especially those that are non-invasive and non-pharmacologic with limited side effect profiles. It is proposed that humans have a widely distributed and perhaps unique neural network or "neuromatrix" that contributes to the multidimensional experience of pain. This neuromatrix is genetically determined and influenced by multiple factors, of which sensory (nociceptive) input is only one. Researchers have shown that these pathways and areas of the brain that are associated with the neuromatrix can change in response to external stimuli.*

Understanding this complex pain neuromatrix may assist in identifying alternative approaches that reduce pain severity and interference and improve patient outcomes. There are various types of nerve fibers responsible for sensation and pain. A-β nerve fibers transmit information from Pacinian and Meissner corpuscles, which convey vibratory/sensory perception from the skin. According to the gate control theory of pain hypothesized decades ago by Melzack and Wall, vibration can stimulate inhibitory interneurons in the spinal cord that in turn act to reduce the amount of pain signal transmitted by A-δ and C transmitting pain fibers. The application of vibration has long been trialed for its analgesic effects. When you get a text or a call on your mobile phone, the vibration you feel is a form of haptic feedback. An enhanced technique known as haptic vibrotactile trigger technology (VTT) is designed to target the nociceptive pathways and theorized to disrupt the neuromatrix of pain. The technology is non-pharmacological and non-invasive, and has been incorporated into topical patches, wearable clothing, and other routes of delivery.

The purpose of this IRB-approved, minimal risk observational study was to evaluate and compare patients' experiences, perceptions and response for those who received haptic vibrotactile trigger technology (VTT) embedded non-pharmacologic, non-invasive, over-the-counter wearable device in the form of socks (Superneuro Haptic Vibrotactile Trigger Technology (VTT) Enhanced Socks; Srysty Holding Co, Toronto, Canada) versus those who did not.

Methods: *Baseline, 7- and 14-day data were recorded in 90 subjects who presented with pain and/or fatigue related issues or associated symptoms. The 'active' treatment group (TG) was comprised of eighty-five (85) adult subjects (61 females and 24 males) with a mean age of 54.8 years; there were five (5) adult subjects (3 females and 2 males) in the 'inactive' control group (CG). The study evaluated changes in overall pain severity, pain interference, and fatigue severity via validated scales including the BPI (Brief Pain Inventory) and the BFI (Brief Fatigue Inventory) as well as changes in the use of prescription and OTC medications, patient satisfaction, energy levels, and any side effects reported while using the VTT Enhanced socks. Future analysis will compare the outcomes reported here with a larger control as well as the addition of a crossover treatment group.*

Results: *In the Treatment Group, the results showed statistically significant decreases in mean BPI and BFI severity and interference scores after using the VTT embedded socks. After 14 days, the vast majority of patients reported "less" or "a lot less" usage of prescription oral medications and were very/extremely satisfied with the wearable device/socks, and the number of hours of daily pain decreased significantly. Results also showed statistically significant and positive outcomes in all measured Quality of Life (QoL) components with improvements in general activity, mood, relations with other people, sleep, normal work, walking ability, and enjoyment of life. In the Control Group, BPI severity scores increased, use of oral prescription medication stayed the same, patients were not satisfied with the 'inactive' socks, and the number of hours of daily pain decreased only minimally, perhaps as a result of a placebo effect.*

Conclusions: *Study results indicate that these non-pharmacologic, non-invasive, haptic vibrotactile trigger technology (VTT) embedded socks reduce pain severity and interference, fatigue, improve energy levels, and reduce the use of concurrent prescription or other pain medications for those experiencing symptoms of pain and fatigue. The VTT embedded socks improved quality-of-life components. Results suggest that this non-invasive, non-pharmacological VTT wearable has potential to be added to current approaches to symptomatic treatment of pain and fatigue with no side effects. Further evaluation, including more data from control and crossover groups are forthcoming and should support the use of this OTC sock as a first-line non-pharmacological treatment option as part of a multimodal treatment approach.*

Keywords

Haptic vibrotactile trigger technology, Pain, Fatigue, Brief pain inventory, Brief fatigue inventory, BPI, BFI, Superneuro Haptic Vibrotactile Trigger Technology (VTT) Enhanced Socks, VTT, Pain modulation, Neuromatrix of pain, Pain management, Analgesic.

Introduction

The symptoms of pain and fatigue are common, troubling, and frequently overlapping. They can occur independent of or almost ubiquitously associated with systemic disorders and comorbidities. Further understanding of pain and fatigue is clinically important as they are among the most frequent symptoms reported by patients [1]. When these symptoms are 'persistent' or 'unexplained', they are associated with poorer quality of life and higher costs than other patient groups [2].

Worldwide, pain and pain-related diseases are the leading causes of disability and disease burden. In the United States, pain is the most common reason patients consult primary care providers and an estimated 100 million people live with pain everyday [3]. Acute, chronic, and mild to moderate pain issues are widely prevalent throughout the US and have been shown to impact quality of life and activities of daily living (ADLs) [4-6]. Fatigue is a common symptom reported by 27%-50% of community-dwelling older adults [7] and 98% of long-term care older adults [8]. Fatigue has been shown to predict decreased mobility [9] and instrumental activities of daily living (IADL's) [10]. It has also been shown to predict an increased risk of functional decline, hospitalization [11], future home care [12], and incident disability [13-16]. Further, fatigue is a main or secondary reason for 10–20% of all consultations with a primary care physician and can be the result of any of a broad spectrum of diseases, including decompensation of already known conditions. Patients describe fatigue as listlessness, lack of energy, exhaustion, tiredness, early fatigability, sleepiness, a tendency to fall asleep during the day, physical weakness, or a feeling of running on empty [17]. It is associated with mental, physical, and occupational impairment [18,19], and negatively impacts family life and social relationships [20-22]. Besides physiological explanations for fatigue, it could also be the result of drugs or psychotropic substances. Fatigue can slow down reaction times, reduce attention or concentration, limit short-term memory, and impair judgment, as well as contribute to work-related and motor vehicle injuries [23]. Conventional pharmacological treatments to address both pain and fatigue have been associated with significant and dangerous adverse effects. Identifying effective and safe alternative treatment strategies, including those that are non-invasive and non-pharmacologic and that have reduced or limited side effect profiles, will provide options that may be preferable in how clinicians treat patients experiencing these symptoms.

In an effort to minimize the toxicities of pharmacologic treatments, there has been a focus on investigating novel non-pharmacologic treatment options for patients as part of a multi-modal treatment approach to maximize effectiveness, improve a patient's quality of life (QoL), and restore function. Current treatment guidelines for pain management recommend a multi-modal approach that includes non-invasive and non-pharmacological therapies as first line treatment options before consideration of other approaches [24,25]. A variety of non-pharmacologic treatments have been reported to be successful in addressing a patient's pain with limited, if any, side effects. These include physical therapeutic modalities, behavioral, and topical drug and device therapies [26-28]. Evidence supports that topical analgesic and other non-invasive therapies and devices are safe and effective for pain conditions and should be considered as part of a multi-modal treatment strategy [29-31].

There are known networks of neuronal pathways and circuits along with "neurosignature" patterns of nerve impulses generated by a widely distributed neural network in the brain responding to sensory (nociceptive) stimulation [32-34]. These neurosignature patterns may be triggered by inputs such as tactile sensations. Tactile perception is an innate mechanism for human survival and represents our evolved and adaptive sensorial ability to capture information via haptics – the active touch for object recognition and perception by higher centers of the brain [35,36]. The somatosensory experience is determined by a set of channels and receptors sensitive to thermal, tactile, and mechanical stimuli shown to be critical to survival, balance control, and pain modulation, among other modalities [35-37].

Neuronal signals are measurable by the electroencephalogram (EEG) [34,38,39]. EEG research has shown that haptic vibrotactile trigger technology (VTT) can influence and modulate brain centers and neuronal pathways [40]. In recent years, haptic skin-stimulation technology has been incorporated into several over-the-counter products with different routes of delivery that include patches, apparel (socks), braces, wrist bands, and compression sleeves, among others. Recent research has shown that VTT has been safe and effective for pain and sleep conditions [31,41,42]. Identifying and studying other non-invasive routes of delivery, like haptic vibrotactile trigger technology, that has been shown to address pain and sleep symptoms, will allow for clinicians to determine if VTT can be successful in addressing pain and other symptoms such as fatigue, and perhaps assist in reducing the use of prescription or other OTC pain medications, and be an important option and part of a multi-modal treatment strategy [31,41,42].

The Brief Pain Inventory (BPI) is a brief, simple, and easy to use tool for the assessment of pain in both clinical and research settings. The BPI is used to assess the severity of pain and the impact of pain on daily functions in patients with cancer pain and pain due to other conditions [43-45]. The assessment areas of BPI include severity of pain, impact of pain on daily function, location of pain, pain medications, and amount of pain relief in the past 24 hours or the past week. The BPI uses simple numeric rating scales from 0 to10 that are easy to understand and easy to translate into other languages. On the BPI, mild pain is defined as a worst pain score of 1 - 4, moderate pain is defined as a worst pain score of 5 - 6, and severe pain is defined as a worst pain score of 7 - 10 [45]. This corresponds to literature on the classifications of pain conditions [46].

Fatigue

Persistent fatigue is a frequent complaint of individuals with many systemic disorders including chronic pain [47]. In various patient populations experiencing both fatigue and pain, studies have reported wide differences in prevalence and show that it can be as high as 60%. Persistent fatigue has been broadly defined as overwhelming sense of tiredness, lack of energy and a feeling of exhaustion that is unrelated to the recent activity [48]. A relation between pain intensity and persistent fatigue has been reported in several populations where pain is a significant symptom including osteoarthritis [49], rheumatoid arthritis [50], fibromyalgia [51], cancer [52], headache [53], and low back pain [54]. Approximately half of individuals with chronic pain report fatigue as their most debilitating symptom [48,55].

Research conducted to date suggests that there might be a temporal relation between pain and fatigue [55,56]. Fishbain et al. [47] reported that in 5 of the 6 prospective studies they reviewed, the development of fatigue occurred after pain onset, suggesting that pain might be causally related to fatigue. There are also indications that symptoms of fatigue might precede the onset of pain. Siivola et al. [57] reported that symptoms of fatigue were prospectively associated with the onset of musculoskeletal pain in a sample of healthy young adults. It is critical to assess fatigue using reliable and valid instruments that can be administered in a variety of settings including rehabilitation and medical facilities, clinical trials, and longitudinal studies.

The Brief Fatigue Inventory (BFI) is a brief screening tool designed to assess the severity and impact of fatigue on daily functioning. It is simple, easy-to-understand language and limited administration time (<10 minutes) [58] make it an ideal measure for older adults. Originally designed for use in English-speaking patients with cancer [59,60] the BFI has been validated in multiple languages [60-69]and used in other samples including individual with rheumatoid arthritis [70] and community-dwelling adults [58,70-72]. However, the BFI has not yet been validated in adults over the age of 65. Acute, chronic, mild to moderate, and severe pain and fatigue-related issues are widely prevalent throughout the US and that can greatly impact quality of life [73-75]. It is important to explore all treatment options for patients as part of a multi-modal treatment approach to maximize effectiveness and improve a patient's quality of life (QoL). Treatment strategies for pain and fatigue should cause minimal harm to the patient while providing the best results.

This INVIGOR ("Interrupting the Neuromatrix with Haptic Vibrotactile Trigger Technology: Improvement of Fatigue and Pain: Gathering Data and Observing Response") observational study evaluated a non-invasive pain- and fatigue-relieving sock that incorporates haptic-vibrotactile trigger technology (VTT) (skin stimulation technology) that may prove effective with minimal side effects compared to traditional approaches. It is an Institutional Review Board (IRB) -approved Study that utilized specialized over the counter (OTC), non-invasive socks embedded with haptic vibrotactile trigger technology (Superneuro Haptic Vibrotactile Trigger Technology (VTT) Enhanced Socks). The socks are embedded with proprietary sensory patterns incorporating VTT and are designed to trigger neural pathways and circuits associated with the neuromatrix of pain and other cortical networks. These patterns within the socks are designed to be in close symmetry between known EEG patterns and their role in modulating EEG and neuronal circuits within higher brain centers, including those that target pain [76]. This study included patients with mild/moderate/severe, and acute or chronic pain, and/or fatigue symptoms, and evaluated their overall perceptions of pain treatment and associated pain and/or fatigue symptoms with the use of the VTT socks. The data presented here are mostly for those who received 'active' socks, and a small group of patients who received as control 'inactive or regular' socks not embedded with the VTT technology. Future planned analyses will include a larger control as well as a crossover group of patients and explore differences between each group.

Methods

Study Design

In this prospective, Institutional Review Board-approved Observational Study, pain management and fatigue symptoms were reported by patient answers to validated pain measurement and fatigue symptom scales (e.g., Brief Pain Inventory (BPI)) and

the BFI (Brief Fatigue Inventory) The Brief Pain Inventory short form (BPI) and the Brief Fatigue Inventory (BFI) validated tools were used to assess patient-reported changes in pain severity, pain interference, and fatigue severity scores, change in the use of pain medications at 7- and 14-days following treatment, as well as other questions relating to energy levels, satisfaction, quality of life, and resumption of their normal activities. Additional survey questions regarding patient satisfaction, patient quality of life, energy levels, and resumption of their normal activities were also collected for patients receiving 'active' socks and a control group of patients who received 'inactive or regular' socks (those that do not have the embedded VTT technology).

Baseline Demographic and Clinical Characteristics of Patients

A total of 85 patients (61 females, 24 males) at 3 US investigator sites were enrolled in the treatment group arm (TG) of the study and completed the baseline, day 7, and day 14 surveys. Demographic results were similar for gender and age at the baseline survey for all groups of patients. The mean age at baseline was 54.8 years. For this analysis, there were an additional 5 patients who were enrolled in the Control Group arm (CG) of the study and completed baseline, day 7, and day 14 surveys. The mean age at baseline for the CG was 45.9 years and included 2 males and 3 females. Both groups of study subjects (TG and CG) were blinded as to which arm and which product (socks with or without VTT technology) they received.

Patients who met the eligibility criteria and who were treated with the socks embedded with the haptic vibrotactile trigger technology (VTT) comprised the study's treatment group (TG). For the treatment group, patient inclusion criteria were as follows: 1) ages 18 to 85 years, inclusive; 2) ability to provide written informed consent; 3) received the active VTT embedded study socks; and 4) had been diagnosed with pain or fatigue related symptoms. Patients who had had a history of use drug or alcohol abuse, patients who had an implantable pacemaker, defibrillator or other electrical devices, or patients who were pregnant, were ineligible to participate in the study.

Primary Pain Complaint

Out of the 85 patients in the treatment group, 36% (n=31) indicated that their primary pain complaint was myofascial/musculoskeletal pain, followed by 34% (n=29) who indicated that they had neuropathy or radiculopathy, and 29% (n=25) who indicated that their primary pain complaint was arthritis. The control group for this analysis included 3 patients with myofascial/musculoskeletal pain, and 2 patients with neuropathy/radiculopathy as their primary pain complaint.

In the treatment group, 66% (n=56) of patients indicated that they had severe pain, 26% (n=22) of patients indicated they had moderate pain, and 7% (n=6) indicated that they had mild pain. For the control group, 3 patients indicated they had moderate pain and 2 patients indicated that they had severe pain. The vast majority of patients in both the treatment group (71%) and control group (60%) indicated that they had their pain for over 1 year, 25% of patients in the treatment group and 20% of patients in the control group indicated that they had their pain for between 3 months and 1 year, and only a few (3 patients) in the treatment group indicated that they had pain for between 1 and 3 months. One patient in both the treatment and control group indicated that they had their pain for less than one month.

Location of Pain

For those patients who indicated that their primary complaint was arthritis were experiencing their pain in the back, hips, and lower extremities (legs and feet). Those who indicated neuropathy/radiculopathy were experiencing pain in their back, in their lower extremities (knees, legs and feet), in addition to some indicating sciatica. For those with myofascial/musculoskeletal pain, they indicated pain in their back, hips, and lower extremities (legs and feet).

Each site provided patients an identification number, and a confidential file containing the informed consent forms and patient identification numbers were kept and maintained in a secured cabinet only accessible to the principal investigator and authorized personnel. Patient survey responses were provided with no identifying patient information.

Fatigue Symptoms

At baseline, 86% (n=73) in the treatment group, and all of the patients in the control group, indicated that they felt unusually tired over the past week. Also at baseline, the mean/10 'current' level of pain for the treatment group and control group was reported as 4.11 and 4.40, respectively. The mean/10 'worst' level of pain reported in the past 24 hours at baseline was 5.13 for the treatment group and 5.80 for the control group.

Patients could withdraw from this study at any time with the assurance of no unfavorable impact on their medical care. All diagnostic tests and treatment decisions were made at the discretion of clinicians, with no tests, treatments, or investigations performed as part of this study. Patients were provided the treatment at no cost and were not compensated for their participation in the study.

The study protocol was approved by ADVARRA institutional review board and was performed in full accordance with the rules of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the principles of the declaration of Helsinki and the international council of Harmonisation/GCP. All patients gave informed and written consent.

Wearable Intervention

The active, non-invasive, non-pharmacological socks are embedded with proprietary sensory pattern imprints and incorporate haptic vibrotactile trigger technology (VTT). The active socks contain no drug or energy source. Patients in the treatment group were instructed to wear one pair of socks and change them each day over the study period (See Picture 1). The study subjects could choose to wear the socks in the evening and overnight while sleeping if they desired. The non-active socks look similar to the

active socks but do not incorporate the haptic vibrotactile trigger technology (VTT).

Picture 1: Superneuro Haptic Vibrotactile Trigger Technology (VTT) Enhanced Socks.

Study procedures and assessments

Following consent and enrollment, patients were asked to complete surveys of the BPI and BFI at baseline (day 0) and follow-up on days 7 and 14 of the study period. The surveys were comprised of questions to address and document pain and fatigue severity and level of interference on their quality-of-life components and in their daily lives. Any reported side effects were also documented. Study participants were instructed to wear the socks and questions relating to the amount of time worn (e.g., 1) day only, 2) day and evening, 3) day, evening, and overnight) were also collected.

The BFI is a 9-item, 11-point rating scale developed to assess subjective fatigue. The first three questions measure fatigue severity from 0, indicating "no fatigue," to 10, indicating "as bad as you can imagine," at current, usual, and worst levels. The following six questions assess fatigue interference with daily activities including general activity, mood, walking ability, normal work (both inside and outside the home), relations with other people, and enjoyment of life. Response options range from 0, indicating "does not interfere," to 10, indicating, "completely interferes." Higher scores on the BFI correspond to greater self-reported levels of fatigue. The time period for all questions is over the past 24 hours. Factor analysis for the original validation study found the scale to be uni-dimensional. Reliability was excellent with an internal consistency coefficient of 0.96 for scale items.

Patients were asked to indicate their preference between the socks and any other medications that they had been taking for pain or fatigue relief at the time of the baseline, day 7, and day 14, as well as their satisfaction and ease of use of the socks.

Study End Points

The primary endpoints included changes in patient responses to The Brief Pain Inventory (BPI) and the Brief Fatigue Inventory (BFI) scores among treatment and control group, as well as preference in the use of prescription and OTC medications. We also assessed patient satisfaction with patch treatment and any side effects reported by patients during the trial. Future analysis will compare the non-active control and crossover treatment groups with the outcomes reported here.

Statistical Analysis

For all variables, descriptive statistics were calculated, including frequencies and percent for categorical variables and means with standard deviation (SD) for continuous variables. The maximum sample size available was used for each statistical analysis.

Changes from baseline in BPI and BFI scores to day 7 and day 14 were analyzed using the paired *t*-test to identify any statistically significant differences within the treatment group.

Each survey collected responses to questions regarding patient satisfaction, side effects of treatment, and current medication usage. Descriptive statistics were used to determine patient satisfaction with the VTT embedded socks within those treated. Descriptive statistics were also used to report any side effects experienced by patients. A two-tailed alpha was set to 0.05 for all statistical comparisons. SPSS v. 27 was used for all analyses.

Results

Treatment Group

Treatment group paired data were collected; only patients that completed 14 days of treatment were included in the analysis. Study subjects in the TG reported on how long each day they wore the socks. At day 14, 46% of subjects indicated that they wore the socks "*almost all of the time during the day,"* and 47% of subjects indicated that they wore the socks "*almost all of the time during the day and also while sleeping."* Four percent (4%; n=6) indicated that they wore the socks "*until the pain was gone, then again when the pain came back*." (Table 1).

In the Treatment Group, patients experienced a decreased level of pain of 3.7 hours of pain per day from baseline to day 7 (P<0.001, CI: -4.45 – -2.89, n=85), and a decrease level of pain of 5.1 hours per day from baseline to day 14 (P<0.001, CI: -5.84 – -4.23, n=85).

Over 14 days, the mean BPI Severity score decreased 57% (4.14 to 1.80/10;P< .001), mean BPI Interference score decreased 54% (2.33 to 1.07;P< .001**)** (Figure 1), and mean BFI Fatigue score decreased 63% (2.89 to 1.07; P<.001) (Figure 2). Results also showed an increase in energy among all TG study subjects and changes in all measured BPI and BFI (QoL) components with reductions in BFI fatigue (weariness/tiredness) of 62% (4.11 to 1.55; P<.001), and statistically significant (P<.001) BPI and BFI score improvements including in enjoyment of life, sleep, mood, general activity, normal work, walking ability, and relations with other people (P<.001 (BFI); P<.003 (BPI)) after use of the VTT socks. In addition, medication usage among TG subjects showed a statistically significant decrease (70%) in the number of patients (45 to 13) using prescription NSAIDS from Baseline to Day 7 (P<0.001) and an 89% decrease (45 to 5) to Day 14 (P<0.001). There was also a statistically significant increase in the number of patients not using any pain relievers, OTC or prescription, from Baseline to Day 7 (P<0.001; 3 to 27) and to Day 14 (P<0.001; 3 to 27).

Table 1: Follow-up Only Q4. How did you use the Socks? (n %).

	Test Group		Control Group	
	Day 7	**Day 14**	**Day 7**	**Day 14**
I wore them almost all of the time during the day.	39, 45.9%	39, 45.9%	3, 60.0%	---
I wore them almost all of the time during the day; I wore them also while sleeping.	37, 43.5%	40, 47.1%	---	2, 40.0%
I wore them also while sleeping.	1, 1.2%		---	---
I wore them until the pain was gone, then again when the pain came back.	7, 8.2%	6, 4.1%	1, 20.0%	---
I wore them until the pain was gone, then again when the pain came back; I wore them also while sleeping	---	1, 1.2%	---	---
I tried it, but it did not work for me, so I stopped using it.	---	---	---	2, 40.0%
Other (please describe)	1*, 1.2%		1**, 20.0%	---
N/A: I did not use the Socks.	---	3, 3.5%	---	1, 20.0%
N	85	85	5	5

*Developed headache after removing them. Skipped 1 day. Resumed using and developed another headache.
**Did not work but still used them to see if I noticed relief later on.

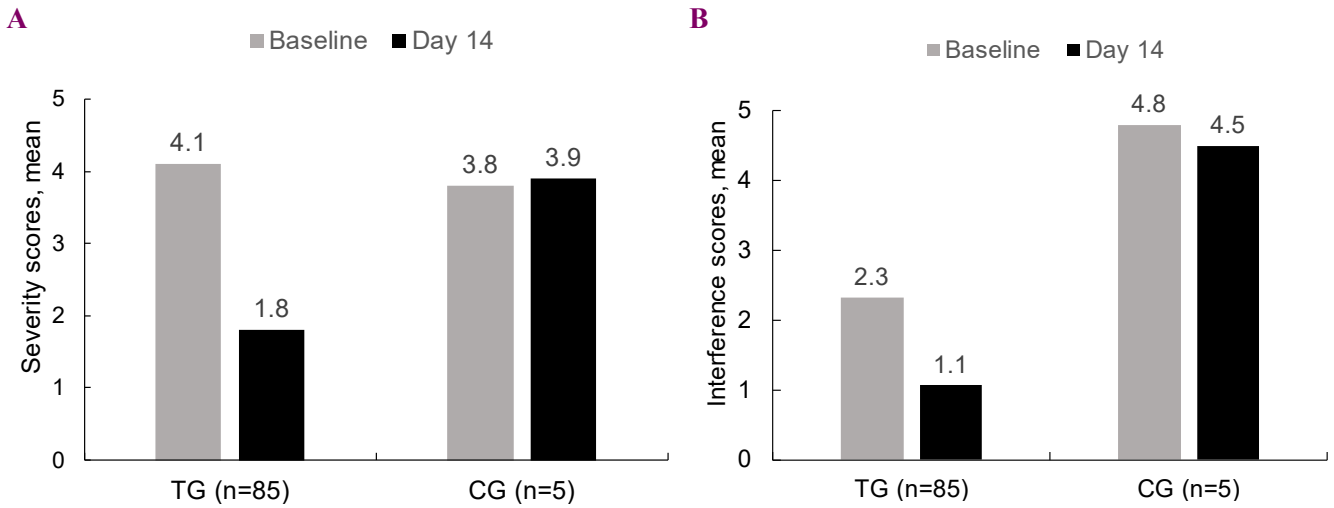

Figure 1: Baseline and Day 14 Overall Mean Brief Pain Inventory (**A**) Severity and (**B**) Interference Scores within the Treatment and Control Groups.

*95% Confidence Interval of the difference, paired t-test.
Abbreviations: TG, treatment group; CG, control group.

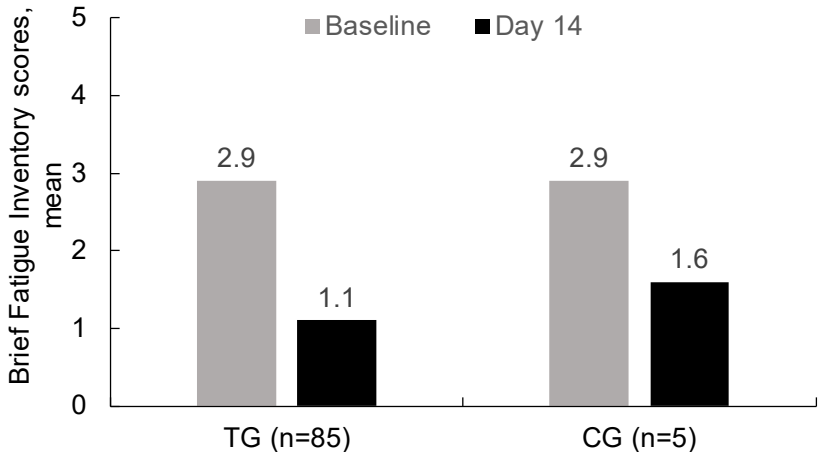

Figure 2: Baseline and Day 14 Overall Mean Brief Fatigue Inventory Scores within the Treatment and Control Groups.

*95% Confidence Interval of the difference, paired t-test.
Abbreviations: TG, treatment group; CG, control group

Table 2: Baseline Q5a, b, c, Follow Q14a, b, c. How many times during the Past Week did you do: (mean, SD, min., max., n).

	Test Group			Control Group		
Activity	**Baseline**	**Day 7**	**Day 14**	**Baseline**	**Day 7**	**Day 14**
a. Light physical activity for 30 min or more	3.5 2.8 0 18 85	4.2 2.3 0 18 85	5.1 2.2 0 18 85	4.4 2.0 2 7 5	4.6 1.8 2 7 5	3.8 2.3 1 7 5
b. Moderate physical activity for 30 min or more	1.7 2.1 0 10 85	1.9 1.7 0 10 85	2.0 1.5 0 7 85	2.6 1.1 1 4 5	2.8 1.5 1 5 5	2.8 1.5 1 5 5
c. Heavy physical activity for 30 min or more	0.9 1.5 0 7 85	1.2 1.2 0 7 85	1.4 1.2 0 7 85	0.4 0.9 0 2 5	0.4 0.9 0 2 5	0.4 0.9 0 2 5

Statistically significant increases (paired T-test) in the Test Group:
Light: Baseline to Day 7 (P=0.001). Baseline to Day 14, and Day 7 to Day 14: each statistically significant at P<0.001.
Moderate: Baseline to Day 14 (P=0.034)
Heavy: Baseline to Day 7 (P=0.002). Baseline to Day 14 (P<0.001). Day 7 to Day 14 (P=0.002).

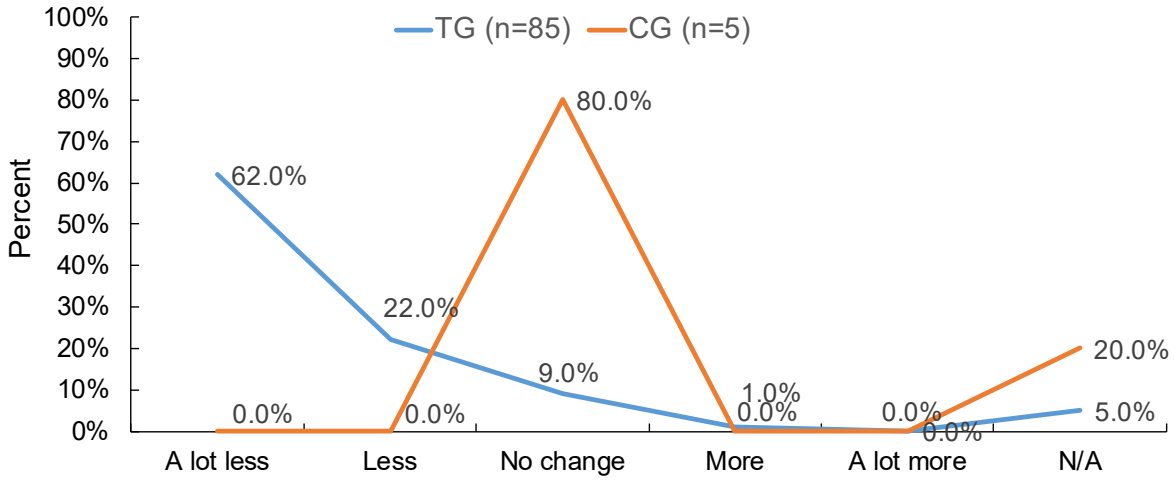

Figure 3: Change in Use of Oral Pain Medications on a Daily Basis from Day 7 to Day 14 within the Treatment and Control Groups.

*95% Confidence Interval of the difference, paired t-test.
Abbreviations: TG, treatment group; CG, control group; N/A, not applicable

Changes in Energy Levels

Study subjects in the treatment group reported that they had more energy when they wore the socks at day 7 (77%; n=65) and at day 14 (86%; n=73). For the Control Group, not one of the 5 subjects reported an increase in energy at either the 7 day or 14 day follow up surveys.

Changes in Physical Activity

Subjects in the TG reported that they increased their physical activity over the 14-day study period while using the VTT embedded socks. Light physical activity for 30 min or more increased by 46% (P< .001; 3.5 to 5.1), moderate physical activity for 30 min or more increased by approximately 20% (P<.034; 1.7 to 2.0), and heavy physical activity for 30 min or more increased 56% (P< .001; .9 to 1.4) (Table 2).

Additional areas of Pain relief experienced

Several subjects (n=14) out of the 85 subjects in the Treatment Group reported that they experienced pain relief in other areas than their primary pain complaint. The additional areas of relief included hips (multiple), knees, legs, balls of feet, legs, lower back, shoulders, sinus, and upper back. There were no reported additional areas of pain relief from those in the Control Group.

Changes in Oral Pain Medications

Changes from baseline to day 7 and baseline to day 14 in the use of concurrent pain medications

Over 83% of study subjects in the TG reported that their use of oral pain medications was "*Less*" (22%) or "*A Lot Less" (62%)* from baseline to day 7 and to day 14 (Figure 3).

Use and Preference of the VTT Embedded Socks

Subjects were queried on specific satisfaction rating aspects regarding use of the VTT embedded socks (scale: 0 = N/A, 1 = Strongly disagree, 2 = Disagree, 3 = Neutral, 4 = Agree, 5 = Strongly agree). At day 14, approximately 97% of patients 'agreed' or 'strongly agreed' that the socks were "easy to wear" (n=82) and "convenient" (n=82), and approximately 92% of patients 'agreed' or 'strongly agreed' that they "preferred the socks over pills and other oral medication" (n=82) and "preferred over other pain-relieving treatments" (n=82). Over 87% of treatment group subjects (n=74) indicated that they would recommend the VTT embedded socks to their family and friends.

Control Group

For this interim analysis, there were 5 patients who, after consenting and enrollment, were designated to the Control Group and received regular socks that were not embedded with the VTT technology. As with all enrollees in the INVIGOR Study, subjects were blinded from which socks they received and to which group they were designated. In future planned analyses, this group of patients will be larger and also be included in the Crossover Group.

As compared to the Treatment Group of patients, the results from the control group of subjects included the following key differences (Table 3):

CONTROL GROUP	TREATMENT GROUP
Hours of pain decreased only slightly over the course of the 14- day study period 10.8 hours/day at Baseline to 10.2 hours/day at Day 14	Hours of pain decreased significantly over the course of the 14- day study period 8.4 hours/day at Baseline to 3.3 hours/day at Day 14
Physical activity stayed about the same as when they started the study for moderate and heavy activity and light physical activity decreased over the study period	Light, moderate, and heavy physical activity increased over the study period
4 out of 5 patients did not feel relief when they used the socks	Patients experienced a decreased level of pain of 3.7 hours of pain per day from baseline to day 7 and a decrease level of pain of 5.1 hours per day from baseline to day 14
None of the 5 patients reported more energy when they wore the socks	86% of patients reported more energy after wearing the socks
None of the 5 control group subjects would recommend the socks to their family or friends	87% of the patients would recommend the socks to their family or friends
Use of oral pain meds on a daily basis did not change (FIGURE 3)	Over 83% of study subjects reported that their use of oral pain medications was "Less" (22%) or "A Lot Less" (62%) from baseline to day 7 and to day 14.
Preference over pills/oral medication decreased Patients reported that they preferred oral medications to the 'non-active' socks. 2.60/5 at Day 7 to 2.2/5 at Day 14	92% of patients 'agreed' or 'strongly agreed' that they "preferred the socks over pills and other oral medication" 4.4/5 at Day 7 to 4.6/5 at Day 14
Overall satisfaction decreased 80% of patients reported being "not very" or "not at all" satisfied with the not active socks.	85% of patients reported being "very" or "extremely" satisfied with the VTT socks
BPI Severity Score increased 3% 3.80 at Baseline to 3.90 at Day 14	BPI Severity score decreased 57% (FIGURE 1) 4.14 at Baseline to 1.80 at Day 14
BPI Interference Score decreased less than 7% 4.80 at Baseline to 4.49 at Day 14	BPI Interference Score decreased 54% (FIGURE 1) 2.33 at Baseline to 1.07 at Day 14
Medication usage stayed exactly the same No Change in any Prescription medications	Prescription Opioids, Prescription NSAIDS, and Prescription Pain Relievers all decreased
BFI Score decreased 45% 2.93 at Baseline to 1.60 at Day 14	BFI Score decreased 63% (FIGURE 2) 2.89 at Baseline to 1.07 at Day 14

Table 3: Key Differences between Control Group and Treatment Group.

This group of CG patients who received socks without the embedded VTT technology will cross over to the treatment group (TG) and will complete both 7- and 14-day follow up surveys after receiving socks with embedded VTT technology.

Safety

Patients reported no serious adverse events while wearing the socks. In the Treatment Group, there were 2 reports of users experiencing headaches, 1 reported (1/85) at the 7-day follow-up and 1 reported (1/85) at the 14-day follow-up. Among those in the Control Group, there were no side effects reported.

Discussion

Here we report initial results of this INVIGOR study, a prospective, non-randomized observational study evaluating the safety and efficacy of over-the-counter socks with VTT in patients presenting with pain or fatigue related symptoms. This analysis showed reductions in BPI pain severity scores, BPI pain interference scores and BFI Severity scores, and a preference for the socks over other pain medications from baseline to day 7, and to day 14.

Although there was a limited number of patients in the Control Group, the differences in statistically significant outcomes between the TG and CG in the BPI and BFI confirmed a logical separation of data that can be attributed to the impact of the socks embedded with VTT. The one aspect that was unexpected was the BFI outcomes in the CG, which showed a reduction of fatigue when wearing the socks not embedded with the VTT. This may be due to the placebo effect, and because those patients in the CG knew they were in a study and were asked specific questions on fatigue improvement over the study period. With a focus on their perception of fatigue improvement, they may have been more sensitive and attentive to acknowledging an improvement to their fatigue symptoms during the study period if compared to the same factors if they were not being studied.

Interestingly, as would be expected, over the counter use in the treatment group increased over the 14-day study period. This coincides with a reduction of prescription NSAIDS and stronger medications prescribed by the clinicians, including opioids, during that 14-day study period in the TG, confirming the fact that the socks embedded with VTT may have influenced the reduction in concurrent medication strength and use, perhaps lowering the patient need to use stronger pain medication.

Over the past several years, research of haptic vibrotactile trigger technology (VTT) indicates that there are changes in EEG patterns for those patients exposed to VTT [40]. The EEG mapping of the pain neuromatrix is corroborated with neuroimaging techniques such as functional analysis using magnetic resonance imaging (fMRI) in many experimental paradigms [76]. The sensory patterns within the patches are in close symmetry between known EEG patterns and their role in modulating EEG and neuronal circuits within higher brain centers [76]. In addition, researchers have developed a deeper understanding of the multiple neural networks impacted by VTT and have developed related theories of how different brain regions interact with VTT [32,76,77]. The brain centers targeted by VTT have been shown to be responsive to external stimuli that incorporate the VTT technology and have produced positive outcomes in pain, sleep, balance, stability, and with this report in addition to pain and function, improvements in fatigue measurements were shown [31,42,78].

Ronald Melzack first proposed and hypothesized that networks of neurons communicating in “large loops”, or through continuous cyclical processing, connect specific regions of the brain with the PNS (peripheral nervous system) during sensory processing [32]. He envisioned 3 distinct looping pathways: 1) a traditional sensory pathway with neural projections routed through the thalamus, 2) one that follows a path through the brainstem and parts of the limbic system, and 3) one associated with pathways that are routed through different Brodmann Areas (BA), particularly the somatosensory cortex. These loops were meant to explain the cognitive, emotional, and motor modalities through which humans experience sensations [32,76].

Limitations

Although blinded, this was a nonrandomized observational study based on a sample of patients attending diverse clinical settings for the treatment of pain- and fatigue-related symptoms who consented to participate in this study. The data of those patients who did not complete the follow up surveys after baseline, or patients who indicated that they did not use the socks after the baseline visit were removed from evaluation. Due to patients having different pain and fatigue symptoms and differences in how they report their pain and fatigue patterns and quality, overall generalization and consistency of results may be impacted due to the differences in pain and fatigue issues, the amount of time the patient utilized the socks, and subjective self-reporting by the patient. We have attempted to accurately evaluate and provide the most detailed reporting of the data while considering these limitations. Inclusion of a larger set of control group and crossover group data in future analyses will assist in confirming the validity of these results due to the nonrandomized nature of this clinical trial.

Conclusion

There remains an unmet need for alternative treatment options for patients experiencing pain- as well as fatigue-related symptoms. Multiple current treatment guidelines recommend topical, non-pharmacological and non-opioid medications as first line therapy. Study results indicate that these non-pharmacologic, non-invasive, haptic vibrotactile trigger technology (VTT) embedded socks reduce pain severity and interference, fatigue, improve energy levels, and reduce the use of concurrent prescription oral and other pain medications for those experiencing pain and fatigue related symptoms. The VTT embedded socks were shown to improve quality-of-life components. Results reported suggest that the non-pharmacological socks with VTT have significant potential to be added to the current approaches and treatments of noninvasive and nonpharmacological pain and fatigue therapies with minimal side effects. Further evaluation, including more data from control

and crossover groups are forthcoming and should support the use of this OTC sock as a first-line non-pharmacological treatment option as part of a multimodal treatment approach.

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Disclosure

Jeffrey Gudin MD has received compensation from Clarity Science LLC for his role as principal investigator and for providing protocol-required services for the study. Janet Fason DO received compensation from Clarity Science LLC for her role as an Investigator for the Study. Peter L Hurwitz is President of Clarity Science LLC. The authors report no other disclosures.

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