Randomized Trial

Auto-Targeted Neurostimulation Is Not Superior to Placebo in Chronic Low Back Pain: A Fourfold Blind Randomized Clinical Trial

Maria Encarnación Aguilar Ferrándiz, PhD[2,5], Jo Nijs, PhD[1-3], Yori Gidron, PhD[6], Nathalie Roussel, PhD[1,7], Rob Vanderstraeten, MSc[4], Dries Van Dyck, MSc[4], Eva Huysmans, MSc[1,2], and Margot De Kooning, MSc[1,2,4]

From: [1]Pain in Motion International Research Group, www.paininmotion.be; [2]Department of Physiotherapy, Human Physiology and Anatomy, Faculty of Physical Education & Physiotherapy, Vrije Universiteit Brussel, Belgium; [3]Department of Physical Medicine and Physiotherapy, University Hospital Brussels, Belgium; [4]Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium; [5]Department of Physical Therapy, University of Granada, Spain; [6]Center 4 Neuroscience, Faculty of Medicine & Pharmacy, Vrije Universiteit Brussel, Brussels, Belgium; [7]Faculty of Medicine, University of Antwerp, Belgium

Address Correspondence:
Jo Nijs, PhD
Vrije Universiteit Brussel,
Building F-kima
Laarbeeklaan 103, BE-1090
Brussels, Belgium
E-mail:
Jo.Nijs@vub.ac.be

Disclaimer: This study was funded by Nervomatrix Ltd., 4a Hagavish st., Netanya, 4250704, Israel.

Manuscript received: 11-04-2015
Revised manuscript received: 12-23-2015
Accepted for publication: 01-18-2016

Free full manuscript:
www.painphysicianjournal.com

Background: Myofascial trigger points (MTrPs) are common in people with musculoskeletal pain and may play a role in chronic nonspecific low back pain (CLBP). One of the potential treatments of MTrPs is the Nervomatrix Soleve® auto-targeted neurostimulation device, providing targeted transcutaneous electrical nerve stimulation (TENS) to MTrPs in the lower back muscles. To date, no controlled studies have evaluated the effectiveness of this device for the pain management of this population.

Objective: To examine whether the Nervomatrix Soleve® auto-targeted neurostimulation device is superior over placebo for the treatment of CLBP.

Study Design: A fourfold-blind randomized controlled trial was conducted.

Setting: Brussels University Hospital, health care centers and pharmacies around Belgium.

Methods: Participants with CLBP for at least 3 months were randomly assigned to the experimental (the Nervomatrix Soleve® auto-targeted neurostimulation device providing TENS-stimulation and mechanical pressure) or placebo group (the Nervomatrix Soleve® auto-targeted neurostimulation device providing mechanical pressure alone without current). The treatment protocol in both groups consisted of 6 treatment sessions per patient. Participants were evaluated at baseline prior to the intervention, immediately following treatment, and at one month follow-up. Pain and pain behavior (steps climbed) were assessed as primary outcome measures. Secondary outcome measures were pain functioning, health beliefs, symptoms of central sensitization, pain catastrophizing, and kinesiophobia.

Results: In total, 39 participants were included in the study. Participants in both groups improved significantly for pain and functioning, but no significant differences were observed between groups. These improvements were not clinically meaningful for any of the reported measures. The health beliefs changed significantly in both groups ($P < 0.05$), with superior results at follow-up in the placebo group.

Limitations: The follow-up period is limited to one month.

Conclusions: Treatment of MTrPs with the Nervomatrix Soleve® auto-targeted neurostimulation device in patients with CLBP does not result in a better outcome than placebo-treatment in terms of pain, pain behavior, functioning, central sensitization, pain catastrophizing, and health beliefs.

Key words: Low back pain, chronic pain, randomized controlled trial, electric stimulation therapy, trigger points

Pain Physician 2016; 19:E707-E719

Chronic nonspecific low back pain (CLBP) represents a significant burden on the health care system that results in substantial costs to society (1). Up to 84% of the general population experience low back pain during their lifetime and in most cases no specific disease or clear pathological cause of the pain is found (2). Several factors can contribute to spinal pain including mechanical, structural, functional, psychological, and neuromuscular dysfunctions. Of all these factors, the myofascial system seems to play an important role in the development of low back pain (3-6).

Myofascial trigger points (MTrPs) might be a common source of musculoskeletal pain within the low back pain population (2-5). MTrPs are defined as a taut band of skeletal muscle which is painful during compression and that, when stimulated (i.e., by compression, percussion, or needling), can evoke a characteristic pattern of referred pain and related autonomic phenomena (7). A recent systematic review evaluating the prevalence and incidence of MTrPs in spinal pain concluded that MTrPs can be found as a prevalent clinical entity in people with spinal pain (8).

The underlying physiological and pathophysiological mechanism in MTrPs remain unknown (9). However, observations of an acidic milieu and raised biochemical (mainly pro-inflammatory) substances are made in local and remote tissues surrounding these MTrPs (8,10). Different studies have reported the presence of stiffer muscle tissue (11,12), retrograde diastolic blood flows due to an increase in vascular volume (11,13), and spontaneous muscle activity at rest in MTrPs (14).

Besides MTrPs, central sensitization or hyperexcitability of the central nervous system is present in a subgroup of the CLBP population (15). Central sensitization is a common process presenting in different chronic pain conditions and is defined as "an augmentation of responsiveness of central pain-signaling neurons to input from low-threshold mechanoreceptors" (16). Features of central sensitization include poor functioning of central analgesic mechanisms (17) and increased activity in brain areas responsible for the production of pain (known as the pain matrix) as shown in patients with CLBP (18).

One possible therapeutic answer is transcutaneous electrical nerve stimulation (TENS) – a low frequency electrical current that stimulates the spinal pain modulating system (as initially described by the "gate control theory of pain") and central analgesic mechanisms (endorphin and enkephalin release) through the application of localized high-intensity neurostimulation that stimulates peripheral nerve endings (Aδ- and C-fibres) (19). Therefore, TENS has been suggested as a candidate treatment for decreasing the hyperexcitability of the nervous system as seen in central sensitization pain (20). Studies that include central sensitization as a possible influencing factor are needed to evaluate the effectiveness of TENS in chronic pain conditions.

TENS may result in an immediate relief of MTrPs, even though there is contradicting evidence for the use of TENS as an isolated treatment for CLBP (21). Nowadays, new devices have been developed to use TENS in a more specific way for the treatment of MTrPs in patients with CLBP. Nervomatrix Soleve® auto-targeted is such a new device that detects MTrPs by using skin resistance measurements and subsequently applying TENS treatment on the detected MTrPs. The idea is that TENS provides an analgesic effect by changing the biochemical environment of MTrPs in order to reduce the primary source of nociception (10-14). This auto-targeted neurostimulation is based on the physiological understanding that biochemical changes in MTrPs (8,10) result in autonomic reactions such as increased sweat secretion from sweat glands and ducts, which leads to variations in skin resistance (22). An uncontrolled pilot study, examining the pre- versus post-treatment changes in low back pain patients using the Nervomatrix Soleve® auto-targeted device (23), found positive results in relation to self-reported pain. However, we are unaware of randomized controlled trials examining the effectiveness of this new treatment device. The findings from the uncontrolled pilot study were promising (23), but require a deeper and more sound investigation via a randomized controlled design, to examine whether auto-targeted neurostimulation is superior to placebo for the treatment of CLBP.

With this background, the primary aim of this study was to perform a randomized controlled trial to investigate whether auto-targeted neurostimulation is superior to placebo for improving pain, pain behavior, functioning, health beliefs, symptoms of central sensitization, pain catastrophizing, and kinesiophobia, in patients with CLBP. The secondary aim was to determine whether central sensitization had a prognostic value in auto-targeted neurostimulation in patients with CLBP.

Methods

Participants

A fourfold-blind randomized controlled trial was conducted between November 2013 and February

2015. In order to prevent recruitment bias and increase participation, patients were recruited through several routes. In addition to the patients with CLBP recruited from the Brussels University Hospital (Jette, Belgium), patients were also recruited through French and Dutch flyers and posters spread in health care centers and pharmacies in and around Brussels. Potential participants were screened during a telephone interview for inclusion criteria prior to participation.

To be eligible, patients had to meet the following inclusion criteria: (1) aged between 18 – 65 years; (2) to have chronic, nonspecific, non-radicular low back pain localized between the last rib and gluteal region; (3) time since onset was at least 3 months; (4) had a visual analogue scale (VAS) pain score in the past 24 hours of ≥ 4/10; and (5) stable treatment regime for at least one month. Exclusion criteria included (1) complaints of radiculopathy with clear symptoms of radiating pain and weakness in one or both legs; (2) low back pain potentially associated with presence of serious or progressive neurologic deficits or symptoms of other serious underlying conditions such as a tumor, infection, vertebral compression fracture, or ankyloses spondylitis or clinically significant spinal stenosis; (3) implantation of cardiac pacemaker, (4) defibrillator, or other metallic or electronic devices; (5) pregnant women or women until one year postnatal; (6) patients with epilepsy, cancer, arthritis (except osteoarthritis); (7) those awaiting surgery or having had surgery in the past 6 months; (8) sensory loss in the skin; (9) skin inflammation or edema in the region where the treatment is applied; in order to apply the device treatment safely and the criteria; and (10) body mass index ≥ 30 due to the fact that high level of adipose tissue could influence the effectiveness of the electrical stimulation.

Included participants were asked to continue current treatments, without starting a new treatment during the time period of study participation. The protocol was approved by the local human research committee (University Hospital/Vrije Universiteit Brussel) and registered with clinicaltrials.gov (NCT02256410). The study was performed in accordance with the Helsinki Declaration on research projects and all participants signed an informed consent form prior to their inclusion in the study.

Procedure

Participants provided demographic and clinical information and completed a number of self-report measures. Before and after being randomized to one of the 2 conditions, data were gathered on pain intensity and pain behavior as primary outcome measures. Secondary outcome measures comprised of functioning, symptoms of central sensitization, pain catastrophizing, illness perception, and kinesiophobia. All outcome measures were assessed at 3 time points: baseline (immediately before the first treatment session), post-treatment (immediately following the final treatment session), and after one month of follow-up. In addition, pain intensity was also measured at the beginning and end of each treatment session (a total of 6 sessions). Table 1 provides a schedule of enrollment, interventions, and assessments of the study.

Primary Outcomes

First, participants were asked to rate their current pain intensity and average pain in the last 7 days using a 100 mm Visual Analogue Scale (VAS) which has been demonstrated to have a good test-retest reliability (24).

Pain behavior was assessed by the one minute stair climbing test (1MSCT). The patient was asked to climb and descend 5 stairs during one minute as fast as possible, but in a safe way and without running. The total number of stairs climbed and descended was counted and registered. For all assessments, the same stairs in the hospital were used. The staircase was barely used and no passage of other persons was allowed during the test. This test has a good test-retest reliability, inter-rater reliability, and responsiveness to change (25).

Secondary Outcomes

The Quebec Back Pain Disability Scale (QBPDS) was used to assess the patients' limitations in functioning due to the CLBP. This questionnaire is found to be valid, reliable, sensitive, and responsive, and is recommended for the use in the CLBP population (26,27). Symptoms of central sensitization were evaluated with the Dutch Central Sensitization Inventory (CSI) (28,29), a questionnaire having good clinimetric properties for assessing symptoms of central sensitization in patients with chronic pain (29,30). The Pain Catastrophizing Scale (PCS) measures the patient's pain catastrophizing (31) in a reliable and valid way (32). The Illness Perception Questionnaire-Revised Version (IPQ-R) was used to assess the patients' illness perceptions. The IPQ-R was found to have good test-retest reliability and predictive validity (33). Finally, the Tampa Scale of Kinesiophobia (TSK) is a questionnaire developed to measure fear of movement and (re)injury in patients with CLBP (34) in a reliable and valid way (35).

Randomization and Blinding

Patients were randomly assigned to receive either auto-targeted neurostimulation (experimental treatment; n = 19) or the placebo-control treatment with a sham protocol (n = 19). Before data collection was initiated, concealed allocation (ratio 1:1) was performed using a computer-generated allocation schedule executed by a researcher not involved in the recruitment or treatment of patients. The allocation schedule was concealed for the investigator who screened potential participants and the investigator who measured outcome data. This randomization procedure prevented selection bias and guaranteed a blind outcome assessment.

In addition to the blinded allocation and assessment, patients and the researcher who performed the statistical analyses were also blinded. Patients were blind to the group allocation throughout the study, including the follow-up. The researcher who performed the statistical analysis was blinded to group status following a fourfold-blind methodology. All treatments were carried out by 5 physical therapists who were blind to scores of the outcome measures and baseline examination findings, but not to the treatment allocation due to the manual setting of the treatment with the device. Therapists worked in pairs so each patient was treated by no more than 2 different therapists.

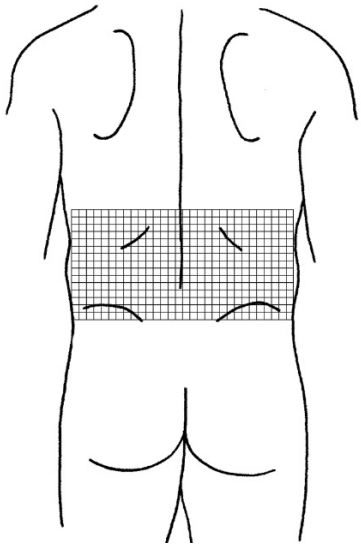

Fig. 1. *Screened region of the lower back.*

Interventions

Both study groups followed a very similar treatment protocol (balanced treatment arms), which consisted of 6 sessions twice a week (not on 2 consecutive days) during 3 consecutive weeks. At the beginning of each treatment session, patients were placed in a prone position on a treatment table. The lower back was bare and cleaned before the device was installed. The array of 26 miniature probes was placed over the spina iliaca posterior superior. Each treatment session started with the device screening the lower back to locate the presence of MTrPs and to select the 10 most active locations (i.e., with the lowest impedance levels). Afterwards, the treatment was initiated and was maintained during 20 minutes.

Auto-targeted Neurostimulation

A SoleveTM device (Nervomatrix, Ltd.; Akron, Ohio, U.S.) was used to provide TENS stimulation directed at the MTrPs in the lower back. This computer-controlled device performs a skin conductance measurement over the lower back by using an array of 26 miniature probes (diameter of 0.4 cm) that make contact with the skin. These probes make an automated screening over 15 levels of the lower back (total area of 20 x 30 cm^2) and measure impedance at each point as represented in Fig. 1. An image processing software and algorithms are used to detect the 10 most dominant MTrPs based on a decreased skin resistance over these MTrPs (low impedance compared to the surrounding area).

Following this detection, the device treats these 10 MTrPs one by one by using a high-intensity, low-frequency neurostimulation (TENS) on the identified MTrPs areas for 2 minutes (wave form: pulsed biphasic non-symmetrical sq. wave; shape: rectangular; positive phase maximum output voltage [± 5%]: 320 V; negative phase maximum output voltage: 24 V; positive phase output current [± 5%]: 16 mA at 500 Ω; negative phase maximum output current: 0.125 mA; pulse width: 300 μS; frequency: 8 Hz; maximum phase charge: 9.6 μC). The amplitude of the current is determined for each patient by a sensation tolerability test. First, the device selects a point from the 10 points whose resistance is the most representative. Secondly, the amplitude of the stimulus is determined by delivering an electrical pulse to this point for one second with the lowest intensity after which the amplitude is gradually increased by the user until the patient reports a strong but tolerable awareness. The amplitude of the stimulus varies between 0.4 mA and 16 mA. Once the amplitude was

determined, each of the 10 selected points was treated with this amplitude during 2 minutes. This brought the total treatment time to 20 minutes and the duration of the whole session to 45 minutes. Skin impedance measurement and the sensation tolerability test were repeated each session to adapt to daily variations.

Placebo Treatment

The placebo control group received an identical protocol with the same device and positioning of the patient. Analogue to the active treatment, the device measured the skin impedance and selected 10 treatment points. Following the impedance measurement, the device made contact with each of the 10 points for 2 minutes, however, without giving any active TENS treatment (i.e., the device did not provide electrical stimulation during the treatment). Each treatment session lasted 45 minutes as in the experimental group. Despite the lack of TENS current provided by the device, the provided treatment in the experimental and placebo groups were identical and patients were unaware of the group allocation.

Treatment Side Effects

Patients were asked to report any adverse event experienced after the intervention and during the one month follow-up. Adverse events were defined as sequelae of medium-term duration with any symptom perceived as distressing and unacceptable to the patient. In addition, pain intensity with VAS was also registered at the end of each session in order to detect possible worsening in pain related to the treatment procedure.

Sample Size

Two separate sample size calculations were performed using G*Power 3.1.5 (Kiel, Germany) (36) in order to detect changes in the 2 primary outcomes measures, VAS and pain behavior. A calculation for a matched randomized controlled design, which was previously planned and registered, was not performed due to the varying responses during the patient recruitment. Thus, sample sizes were recalculated and obtained using the data from the pilot study phase of this project, which included a total of 9 patients. Since the protocol has not changed, these patients were also analyzed together with the final sample. For VAS, the power analysis revealed that 16 patients were necessary in each group to obtain an effect size of d = 1.07 and provide a power of 80% with a two-tailed significance level (α) of 0.05. For pain behavior, a sample size of 33 participants per arm was needed with an effect size of d = 0.72, a statistical power of 80%, and a significant level α = 0.05 two tailed.

Statistical Analysis

The statistical analysis was performed using the SPSS statistical software (SPSS Inc, Chicago, IL) version 22.0. An intention-to-treat analysis was followed and missing data were filled in by imputing the "last observation carried forward" method. Normality of the variables was tested with a Kolmogorov-Smirnov-test. Linearity was examined using bivariate scatter plots of observed residual values against the expected values. Baseline demographic and clinical variables were compared between both groups using an independent Student t-test or a Mann Witney U-test depending on the normality of the data for continuous variables. $\chi 2$ tests were used to analyze the categorical data between groups.

Repeated measures analyses of variance (ANOVA) were used to analyze the effects of group (experimental versus placebo), time (pre-, post-treatment, and follow-up for most measures, or pre and post each session for pain), and to analyze the group x time interaction effects for all outcome measurements (pain intensity in the last 7 days, pain behavior, functioning, central sensitization, pain catastrophizing, illness perception, and kinesiophobia). The evolution in current pain intensity was analyzed at baseline, at each VAS-score obtained after each of the 6 treatments sessions, and at follow-up (8 time-points). If a significant time x group interaction was identified, planned pairwise comparisons were performed to examine differences from baseline to each follow-up point, within each group separately.

Finally, we examined for whom the device may be most effective, and the sample was classified according to baseline levels of central sensitivity (Cent-S), search for a triple Group * Time * Cent-S interaction. Changes in variable scores within and between groups were measured by means (95% confidential interval) of t-tests for paired or independent samples as appropriate.

The effect size was calculated according to Cohen's d statistic. An effect size < 0.20 reflects a negligible effect; between 0.20 and < 0.50 a small effect; between 0.50 and < 0.80 a moderate effect; and 0.80 a large effect. $P < .05$ was considered statistically significant in all tests.

Results

Participant Characteristics

Thirty-nine (n = 39) consecutive CLBP patients (mean ± SD age: 40.76 ± 13.3 years; 63.2% female) met all the eligibility criteria, agreed to participate, and were randomized to either the experimental (n = 19) or placebo group (n = 20). Of the total number of patients included in the study, 3 patients in the experimental group and one patient in the placebo group did not attend all treatment sessions. No mental health issues or depression/anxiety were reported in any of the CLBP patients. Figure 2 provides a flow diagram of patient recruitment and retention. Baseline features between groups were similar for all variables at the beginning of the study (Table 1).

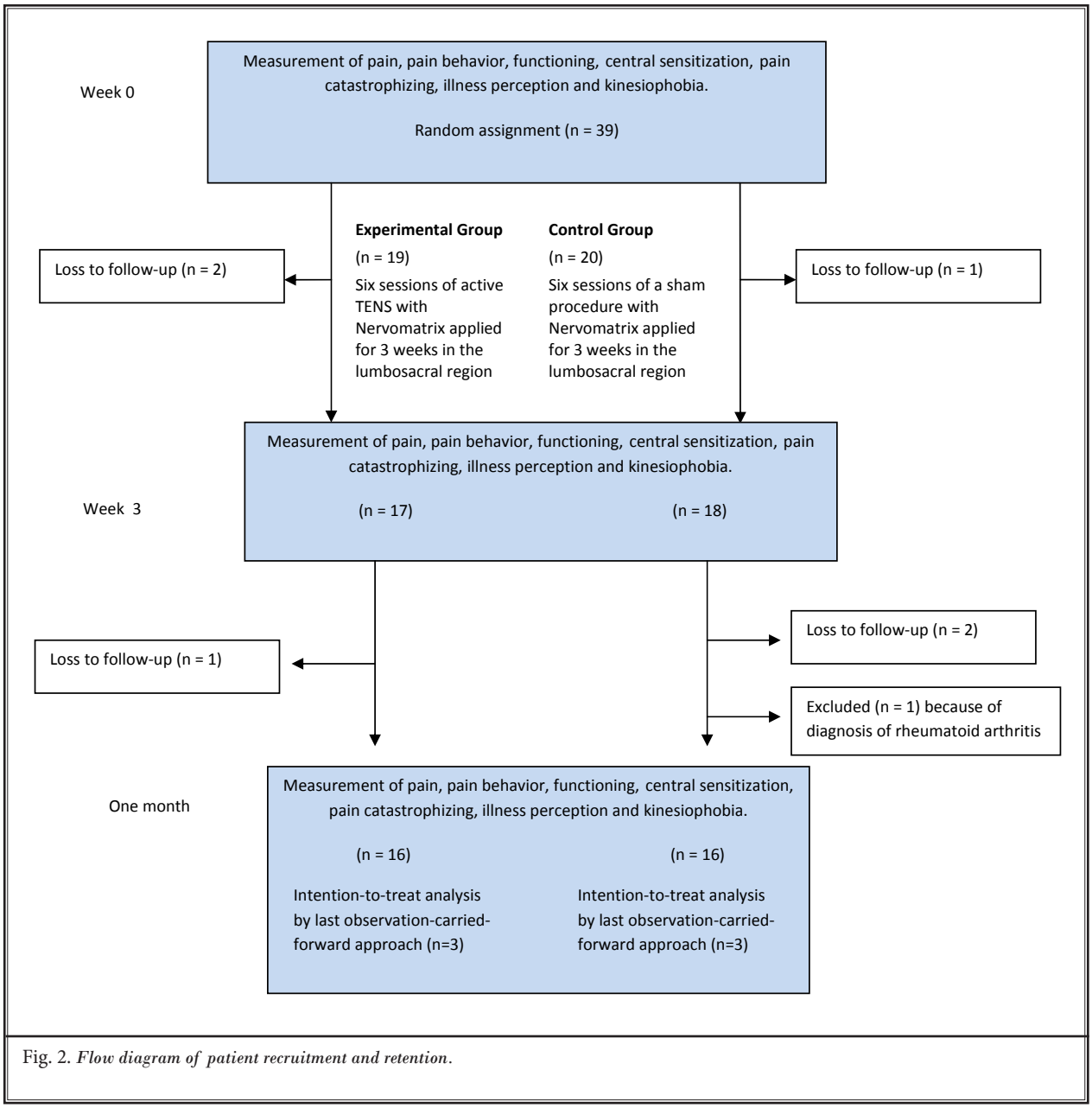

Fig. 2. *Flow diagram of patient recruitment and retention.*

Table 1. *Schedule of enrollment, interventions, and assessments of the study.*

	Enrollment	Allocation		Post-allocation		
TIMEPOINT	**Pre-treatment**	**Time 0**	**Baseline**	**At the beginning/ end of each session**	**3 weeks post-treatment**	**1 month follow-up**
Enrollment:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
Interventions:						
Experimental group			→	→	→	
Placebo group			→	→	→	
Assessments:						
Sociodemographic and clinical data			X			
Current Visual analogue scale			X	X	X	X
Visual analogue scale last seven days			X		X	X
One minute stair climbing test			X		X	X
Quebec Back Pain Disability Scale			X		X	X
Pain Catastrophizing scale			X		X	X
Central Sensitization Inventory			X		X	X
Illness perception questionnaire			X		X	X
Tampa Scale of Kinesiophobia			X		X	X

Primary Outcomes Pain and Pain Behavior

The group * time interaction for the 2 × 8 repeated measure ANOVA was not significant, suggesting that changes in pain and pain behavior between the experimental and placebo groups over time on the primary outcome of current pain intensity were not significant (pain: F = 1.31; *P* = 0.267; pain behavior: F = 0.11; *P* = 0.816). Regarding the slope of the mean pain scores, patients in both groups experienced similar decreases in pain intensity (Fig. 3). The effect sizes were high immediately after treatment for both groups (Experimental: mean ± SD change score = 27.11 ± 24.68, d = 1.05; Placebo: mean ± SD change score = 23.26 ± 21.33, d = 0.91). At one month follow-up, effect sizes were moderate for the experimental and high for the placebo group (Experimental: mean ± SD change score = 16.15 ± 29.49, d = 0.57; Placebo: mean ± SD change score = 22.76 ± 24.52, d = 0.97). Similar results were achieved for VAS pain severity during the last 7 days. This group * time interaction for the 2 × 3 repeated measures ANOVA was not significant, suggesting no significant differences between groups in change in pain during the past week (F = 0.53; *P* = 0.590). The effect sizes of this measure differed from the current VAS results, namely for the outcome of VAS pain during last 7 days, both groups reported a moderate effect immediately after treatment (Experimental: mean ± SD change score = 15.78 ± 24.42, d = 0.67; Placebo: mean ± SD change score = 11.10 ± 16.10, d = 0.64) and small change at one month follow-up (Experimental: mean ± SD change score = 14.78 ± 34.90, d = 0.52; Placebo: mean ± SD change score = 6.47 ± 19.50, d = 0.27). The large SDs seen in these outcomes suggest large heterogeneity of therapeutic responses within each group.

Secondary Outcomes – QBPDS, IPQ, CSI, and PCS

At the end of the follow-up period, the group * time interaction for the 2 × 3 ANOVA was not significant, suggesting no significant difference between groups in the changes of the outcome measures QBPDS (F = 0.25; *P* = 0.775), CSI (F = 1.75; *P* = 0.180), PCS (F = 0.40; *P* = 0.670), and TSK (F = 2.43; *P* = 0.109). This means that there were no differential changes over time between groups on any of these secondary outcomes as well (Table 2).

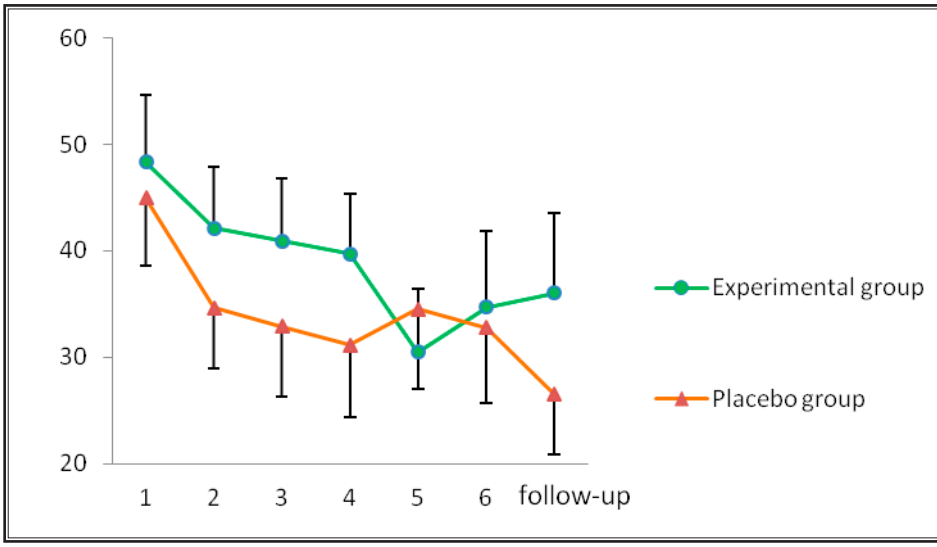

Fig. 3. *Evolution in pain intensity pre-treatment sessions and at follow-up does not differ between experimental group and placebo group. Effect of intervention on the mean current pain intensity score from pre-treatment 1 to one-month follow-up. Error bars represent standard error (SE) of the mean. No group by time interaction effect was achieved.*

Table 2. *Baseline demographics and clinical data for both groups.*

	Electrical stimulation group (n = 19)	Placebo group (n = 19)	*P* values
Gender (m/f)	6/13	8/11	0.737
Age (years)	43.9 ± 14.5	37.6 ± 11.5	0.149
Height (cm)	168.1 ± 8.9	172.2 ± 9.9	0.188
Weight (kg)	70.3 ± 9.3	74.5 ± 13.0	0.263
BMI (kg/m²)	25.0 ± 3.4	25.0 ± 3.0	0.950
Time with pain (years)	10.55 ± 10.91	7.42 ± 4.7	0.263
Self-reported measures			
Current VAS pain (0 – 100 mm)	48.36 ± 27.67	44.96 ± 27.68	0.707
VAS pain last 7 days (0 – 100 mm)	52.21 ± 23.76	49.26 ± 22.35	0.696
QBPDS (0 – 100 points)	37.36 ± 17.92	35.31 ± 17.18	0.721
CSI (0 – 100 points)	33.57 ± 13.02	32.26 ± 12.82	0.755
PCS (0 – 52 points)	23.88 ± 13.10	19.63 ± 10.47	0.281
TSK (17 – 68 points)	40.42 ± 8.32	39.05 ± 7.77	0.604
IPQ (0 – 80 points)	47.57 ± 16.65	47.89 ± 9.92	0.943
Physical outcomes			
1MSCT (Steps climbed)	89.68 ± 29.8	81.00 ± 30.8	0.894

Abbreviations: SD: standard deviation; VAS: Visual Analogue Scale; QBPDS: Quebec Back Pain Disability Scale; CSI: Central Sensitization Inventory; PCS: Pain Catastrophizing scale; TSK: Tampa Scale for Kinesiophobia; IPQ-R: Illness Perception Questionnaire-Revised version, 1MSCT: one minute stair climbing test.

Results on the IPQ demonstrated a significant improvement over time in both groups for functioning, showing a larger effect size in the placebo group ($F = 9.69$; $P < 0.001$). Analyzing baseline to post-treatment changes in illness perceptions, the experimental group showed no change ($F = 3.68$; $P = 0.071$) compared to a significant improvement ($F = 12.78$; $P = 0.002$) in the placebo group (Table 3).

Symptoms of Central Sensitization as a Possible Moderator of Therapeutic Effects

Finally, we examined whether symptoms of central sensitization may act as a moderator for any therapeutic effects of the experimental device. When using a median split on CSI scores, we observed a significant Group * Time * central sensitization interaction in relation to stair climbing ($F (2, 70) = 3.33$, $P < 0.05$). Fol-

Table 3. *Mean ± SD for pain behavior, functioning, central sensitization, pain catastrophizing, kinesiophobia, illness perception and within-between groups score change (95% CI) between baseline and one month follow-up.*

Outcome/ Group	3 weeks post-treatment	One Month follow-up	Within Group *P*	Cohen d	Within Group Change score	Between-Group Change score
1MSCT (Steps climbed)						
Experimental	102.26 ± 37.18	96.00 ± 33.95	.112	0.19	-6.31 (-19.67, 7.04)	1.68 (-20.66, 24.03)
Placebo	101.00 ± 30.91	94.31 ± 33.98	.101	0.41	-3.31 (-13.68, 7.05)	
QBPDS						
Experimental	32.15 ± 19.38	31.47 ± 17.75	.033*	0.33	5.89 (0.48, 11.30)	3.68 (-9.10, 16.47)
Placebo	30.78 ± 21.44	27.78 ± 20.99	.010*	0.39	7.52 (3.25, 11.76)	
CSI						
Experimental	33.84 ± 13.81	32.94 ± 15.02	.878	0.04	0.63 (-3.73, 4.99)	3.73 (-4.98, 12.46)
Placebo	28.05 ± 10.52	29.21 ± 11.22	.031*	0.25	3.05 (-0.60, 6.71)	
PCS						
Experimental	22.66 ± 15.00	21.72 ± 13.85	.461	0.16	2.16 (-2.04, 6.37)	6.36 (-2.37, 15.11)
Placebo	18.94 ± 12.46	16.10 ± 12.69	.031*	0.17	3.52 (0.37, 6.67)	
TSK						
Experimental	39.73 ± 10.12	40.31 ± 9.03		0.00	0.10 (2.15, 2.36)	3.15 (-2.44, 8.76)
Placebo	39.63 ± 7.62	37.15 ± 7.97		0.24	1.89 (-0.91, 4.70)	
IPQ						
Experimental	50.68 ± 16.61	45.05 ± 17.25		0.14	2.52 (-1.04, 6.09)	1.36 (-7.82, 10.56)
Placebo	42.00 ± 10.34	43.68 ± 9.63		0.43	4.21 (1.58, 6.83)	

*Significant ($P < 0.05$).

Abbreviations: SD: standard deviation; 1MSCT: one minute stair climbing test; QBPDS: Quebec Back Pain Disability Scale; CSI: Central Sensitization Inventory; PCS: Pain Catastrophizing scale; TSK: Tampa Scale for Kinesiophobia; IPQ-R: Illness Perception Questionnaire-Revised version.

lowing this interaction's simple effects revealed that in patients with low self-reported symptoms of central sensitization, people receiving the experimental device had superior (but not statistically significant) walking ability on the steps test (109.4 steps) compared to controls with low self-reported symptoms of central sensitization (91.4 steps). In contrast, in patients with high self-reported symptoms of central sensitization, people receiving the device had less (but not statistically significant) walking ability on the steps test (83.9 steps) compared to the patients having high self-reported symptoms of central sensitization in the control group (100 steps). Though the simple effects were not significantly different, possibly due to small sample sizes, the opposite pattern of results contributed to the observed triple interaction of group x time x CSI.

Adverse Events

No adverse events were registered during the course of the study or at the time of the one-month follow-up. Some patients in the experimental group reported discomfort at the end of the treatment sessions. However, analyzing the VAS scores after each treatment session revealed that this discomfort was not reflected by an increase in pain severity: all VAS scores were lower at the end of the treatment sessions in both groups (Table 4).

Discussion

This fourfold-blinded randomized placebo controlled trial examined the effectiveness of a new auto-targeted neurostimulation for the treatment of MTrPs in patients with CLBP. The results obtained immediately after treatment and at the one month follow-up suggest that 6 sessions of auto-targeted neurostimulation using local TENS stimulation and placebo treatment resulted in statistically similar improvements in pain and functioning in patients with CLBP. However, the observed improvements in both groups were not clinically meaningful, and patients in the placebo group showed significantly better health beliefs than patients receiving auto-targeted neurostimulation, after treatment

Table 4. *Mean ± SD pre- and immediately post-intervention for pain intensity (VAS) in each treatment sessions.*

Session Number	Group	Pre-session	Immediately post-session	Within Group *P*	Between Group *P*
1	Experimental	48.36 ± 27.67	36.15 ± 25.20	.006*	0.571
	Placebo	44.96 ± 28.68	35.89 ± 28.71	.031*	
2	Experimental	42.11 ± 23.80	28.76 ± 19.59	.003*	0.185
	Placebo	34.65 ± 24.81	28.68 ± 27.52	.146	
3	Experimental	40.94 ± 24.69	30.66 ± 23.70	.001*	0.388
	Placebo	32.87 ± 28.78	27.92 ± 27.28	.392	
4	Experimental	39.73 ± 24.40	28.52 ± 25.78	.001*	0.509
	Placebo	31.13 ± 28.86	23.14 ± 28.03	.068	
5	Experimental	30.47 ± 25.86	23.63 ± 23.93	.003*	0.773
	Placebo	34.53 ± 31.79	26.15 ± 28.52	.113	
6	Experimental	34.72 ± 30.19	27.38 ± 28.80	.107	0.822
	Placebo	32.76 ± 30.19	24.12 ± 29.04	.036*	

*Significant ($P < 0.05$).
Abbreviations: SD: standard deviation; VAS: visual analogue scale.

and at follow-up. In addition, auto-targeted neurostimulation did not produce any additional benefit over placebo in changing kinesiophobia, pain behavior, and symptoms of central sensitization and pain catastrophizing in patients with CLBP.

In this trial, both groups experienced a clinically meaningful reduction in current pain intensity, surpassing the minimal clinically important difference established for patients with CLBP (37) (18 – 19 mm), especially at short term (over 27 for the experimental group and 23 for the placebo group). However, for pain in the last 7 days, changes over time did not surpass the minimal clinically important difference, particularly not at one-month follow-up (over 14 and 6 mm for the experimental and placebo groups, respectively). Therefore, a placebo effect would support these results since the patients' self-perceived positive expectations towards therapy may have induced endogenous opiate brain activation. Placebo treatment has been found to facilitate inhibition of nociceptive reflexes through the periaqueductal gray matter (38).

A systematic review (39) about nonspecific treatment effects that occur following the use of sham interventions to treat nonspecific low back pain has shown that some placebo interventions such as oral medications produce a clinically meaningful change in pain scores, pointing to placebo as a tool that could be used to complement conventional therapies in CLBP patients. Some authors have also discussed the real value of electrotherapies as placebo procedures since patients can experience a physical sensation during its application (40,41).

In addition to the placebo effect, some of the observed improvements in both groups may have been due to a mechanical effect elicited by the device's 26 miniature probes contacting the patients' skin, overlying the lower back throughout the treatment sessions in both groups. Indeed, while the placebo group received no electrical stimulation, a mechanical effect could be related to the placement of the miniature probes, possibly producing a local ischemic pressure over MTrPs. A recent randomized controlled trial examined the effectiveness of manually applied ischemic compression over MTrPs in acute low back pain patients and found a significant improvement in pain severity, range of motion, and pressure pain thresholds over MTrPs in persons who received compression compared to a control group (42). In contrast, in patients with cervical pain, ischemic compression of MTrPs in combination with TENS provided more pain relief than ischemic pressure alone (43). This finding is contradictory to our results. The discrepancy can be explained by the different populations (neck versus low back pain) and the different ways of detecting MTrPs (identified through manual palpation versus automatically detected by the device in our study).

The lack of positive findings might be related to the treatment duration. Some authors (44) have emphasized that 30 to 40 minutes of stimulation twice a day for at least one month may be necessary to achieve

significant pain relief. Still, the treatment protocol is in line with the pilot study showing positive pre- versus post-treatment changes in low back pain patients (23). The findings of the present trial are not in contradiction with that earlier uncontrolled study, but rather explain that the observed changes were due to the placebo effect.

Similar results were achieved for functioning, with both groups improving without clinically meaningful changes. The minimal clinically important difference for patients with CLBP (45) is 8.5 to 24.6 points and the improvements were over 5 and 7 points for the experimental and placebo group, respectively. Changes in disability could be related to the improvement found in pain intensity. In addition, no significant changes over time were observed in pain behavior measured by the number of steps. This is important since this was an objectively measured behavioral outcome. Disability and other physical outcomes have been previously investigated in patients with CLBP using different electrotherapies and results have shown contradictory findings (46).

Although there was no significant group by time interaction for symptoms of central sensitization, subgroup analyses revealed that patients with more symptoms of central sensitization responded worse to the treatment in terms of pain behavior, while the opposite pattern emerged for those with low central sensitization, though the effects versus controls were not significant, possibly due to small sample sizes (47). The possible moderating role central sensitization had in treatment outcomes is in line with previous observations in patients with whiplash associated disorders (48) and total knee replacement surgery for osteoarthritis (49), but is not in line with the hypothesized physiological link between MTrPs and central sensitization (20,50) or with the idea that central sensitization is primarily driven by peripheral input (i.e., bottom-up sensitization) (51). An alternative view could be that central sensitization causes MTrPs activity (52), for instance via neurogenic inflammatory mechanisms (53). One possible mediator between central sensitization and peripheral MTrPs could be the vagus nerve (54) but further research is required to confirm or refute this hypothesis.

The observed changes in illness perception could be linked with the above placebo effect or with the existence of a Hawthorne effect. Participants in a research study may change their behavior simply because they are taking part in a study, not because of the provided treatment (e.g., changes due to deliberately or unwillingly trying to satisfy the researchers) (55). In addition, it is possible that subgroups of patients can respond differently to the intervention, depending on whether they perceive it to be of great or little therapeutic value (38).

The current study has a number of limitations that should be considered. Firstly, we only collected data at a short-term follow-up. The treatment device is designed to be an isolated treatment and therefore is was tested in isolation when in reality therapists use a multi-modal approach to CLBP. The result of the present study clearly suggest that auto-targeted neurostimulation should not be used as a sole treatment for CLBP. One of the hallmarks to treatments of CLBP due to myofascial issues is to first undergo some of the very basic interventions like massage, TENS, non-steroid anti-inflammatory drugs, and exercise therapy. The study participants were not monitored for previous treatments; therefore it remains unclear whether the study participants already tried those modalities before initiating the experimental (or control) treatment. Secondly, we did not include a no-treatment control group, so it cannot be determined if the improvements seen in both groups can be attributed to the interventions or simply to the natural history of the disease. However, patients with CLBP do not spontaneously experience pain reduction even over a 5-year period (41). Thirdly, the sample size was small, affecting the power of the statistical analyses for the primary outcome of pain behavior, and for testing moderator effects such as those with central sensitization.

The strengths of the study include its placebo-controlled randomized design with concealed allocation, fourfold-blinding, a priori trial registration, its relying on intention-to-treat analyses and effect sizes, and the carefully balanced treatment groups. After that the company was informed about the study findings, they claimed that technical failure of the device in some of the participants included in the experimental group explained the negative study findings. However, neither therapists nor researchers were able to know when the device was not working properly. Clinical trials are designed to examine whether available treatments are effective in the clinical setting, i.e., without a technician checking the functioning of the device. Researchers reporting clinical trials should adhere to the a priori registered study protocol (including the way of analyzing and reporting the data).

Conclusion

The results of the current fourfold-blind randomized trial showed that 6 sessions of auto-targeted neurostimulation with the Nervomatrix device did not result in any clinically important short-term benefits over placebo for pain, functioning, health belief, kinesiophobia, pain behavior, symptoms of central sensitization, or pain catastrophizing in patients with CLBP. In addition, the results suggest that auto-targeted neurostimulation may work better for CLBP patients having no (or fewer) symptoms of central sensitisation. CLBP is a more complex problem including psychosocial factors that could not be solved with treatment of MTrPs alone. A biopsychosocial approach is therefore recommended to improve health beliefs and maladaptive processes in patients with CLBP.

Conflict of Interest

This study was funded by Nervomatrix Ltd., 4a Hagavish st., Netanya, 4250704, Israel. The authors have declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Linton SJ. The socioeconomic impact of chronic back pain: Is anyone benefiting? *Pain* 1998; 75:163-168.
2. Cassidy JD, Carroll LJ, Cote P. The Saskatchewan health and back pain survey. The prevalence of low back pain and related disability in Saskatchewan adults. *Spine (Phila Pa 1976)* 1998; 23:1860-1866; discussion 1867.
3. Fricton JR, Kroening R, Haley D, Siegert R. Myofascial pain syndrome of the head and neck: A review of clinical characteristics of 164 patients. *Oral Surg Oral Med Oral Pathol* 1985; 60:615-623.
4. Han SC, Harrison P. Myofascial pain syndrome and trigger-point management. *Reg Anesth* 1997; 22:89-101.
5. Ramsook RR, Malanga GA. Myofascial low back pain. *Current Pain and Headache Reports* 2012; 16:423-432.
6. Skootsky SA, Jaeger B, Oye RK. Prevalence of myofascial pain in general internal medicine practice. *West J Med* 1989; 151:157-160.
7. Simons DG, Travell JG, Simons LS. *Travell & Simons' Myofascial Pain and Dysfunction: The Trigger Point Manual.* 2nd edition. Williams & Wilkins, Baltimore, 1999.
8. Lluch-Girbes E Nijs J, De Kooning M, Van Dyck D, Vanderstraeten R, Struyf F, Roussel NA. Prevalence, incidence, localization and pathophysiology of myofascial trigger points in patients with spinal pain: A systematic literature review. *Journal of Manipulative and Physiological Therapeutics* 2015;38(8):587-600
9. Quintner JL, Bove GM, Cohen ML. A critical evaluation of the trigger point phenomenon. *Rheumatology (Oxford, England)* 2015; 54:392-399.
10. Shah JP, Danoff JV, Desai MJ, Parikh S, Nakamura LY, Phillips TM, Gerber LH. Biochemicals associated with pain and inflammation are elevated in sites near to and remote from active myofascial trigger points. *Archives of Physical Medicine and Rehabilitation* 2008; 89:16-23.
11. Ballyns JJ, Shah JP, Hammond J, Gebreab T, Gerber LH, Sikdar S. Objective sonographic measures for characterizing myofascial trigger points associated with cervical pain. *J Ultrasound Med* 2011; 30:1331-1340.
12. Turo D, Otto P, Shah JP, Heimur J, Gebreab T, Zaazhoa M, Armstrong K, Gerber LH, Sikdar S. Ultrasonic characterization of the upper trapezius muscle in patients with chronic neck pain. *Ultrason Imaging* 2013; 35:173-187.
13. Sikdar S, Shah JP, Gebreab T, Yen RH, Gilliams E, Danoff J, Gerber LH. Novel applications of ultrasound technology to visualize and characterize myofascial trigger points and surrounding soft tissue. *Arch Phys Med Rehabil* 2009; 90:1829-1838.
14. Wytrazek M, Huber J, Lisinski P. Changes in muscle activity determine progression of clinical symptoms in patients with chronic spine-related muscle pain. A complex clinical and neurophysiological approach. *Funct Neurol* 2011; 26:141-149.
15. Smart KM, Blake C, Staines A, Thacker M, Doody C. Mechanisms-based classifications of musculoskeletal pain: Part 1 of 3: Symptoms and signs of central sensitisation in patients with low back (+/- leg) pain. *Manual Therapy* 2012; 17:336-344.
16. Meyer R CJ, Raja S. Peripheral neural mechanisms of nociception. In Wall PD MR (ed). *Textbook of Pain.* Fifth ed. Churchill Livingstone, Edinburgh, 1995, pp 13-44.
17. Yarnitsky D, Granot M, Granovsky Y. Pain modulation profile and pain therapy: Between pro- and antinociception. *Pain* 2014; 155:663-665.
18. Kregel J, Meeus M, Malfliet A, Dolphens M, Danneels L, Nijs J, Cagnie B. Structural and functional brain abnormalities in chronic low back pain: A systematic review. *Seminars in Arthritis and Rheumatism* 2015; 45:229-237.
19. Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): Its relevance for acute and chronic pain states. *Curr Opin Anaesthesiol* 2010; 23:611-615.
20. Nijs J, Malfliet A, Ickmans K, Baert I, Meeus M. Treatment of central sensitization in patients with 'unexplained' chronic pain: An update. *Expert Opinion on Pharmacotherapy* 2014; 15:1671-1683.
21. Vernon H, Schneider M. Chiropractic management of myofascial trigger points and myofascial pain syndrome: A systematic review of the literature. *J Manipulative Physiol Ther* 2009; 32:14-24.
22. Cho SH, Chun SI. The basal electrical skin resistance of acupuncture points in normal subjects. *Yonsei Med J* 1994; 35:464-474.
23. Gorenberg M, Schiff E, Schwartz K, Eizenberg E. A novel image-guided, automatic, high-intensity neurostimulation device for the treatment of nonspecific low back pain. *Pain Res Treat* 2011; 2011:152307.

24. Wewers ME, Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. *Res Nurs Health* 1990; 13:227-236.
25. Andersson EI, Lin CC, Smeets RJ. Performance tests in people with chronic low back pain: Responsiveness and minimal clinically important change. *Spine (Phila Pa 1976)* 2010; 35:E1559-E1563.
26. Kopec JA, Esdaile JM, Abrahamowicz M, Abenhaim L, Wood-Dauphinee S, Lamping DL, Williams JI. The Quebec Back Pain Disability Scale: Conceptualization and development. *J Clin Epidemiol* 1996; 49:151-161.
27. Davidson M, Keating JL. A comparison of five low back disability questionnaires: Reliability and responsiveness. *Phys Ther* 2002; 82:8-24.
28. Mayer TG, Neblett R, Cohen H, Howard KJ, Choi YH, Williams MJ, Perez Y, Gatchel RJ. The development and psychometric validation of the central sensitization inventory. *Pain Practice* 2012; 12:276-285.
29. Neblett R, Cohen H, Choi Y, Hartzell MM, Williams M, Mayer TG, Gatchel RJ. The Central Sensitization Inventory (CSI): Establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. *The Journal of Pain* 2013; 14:438-445.
30. Kregel J, Vuijk PJ, Descheemaeker F, Keizer D, van der Noord R, Nijs J, Cagnie B, Meeus M, van Wilgen P. The Dutch Central Sensitization Inventory (CSI): Factor analysis, discriminative power and test-retest reliability. *The Clinical Journal of Pain* 2016;32(7):624-630.
31. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. *Psychol Assessment* 1995; 7:524-532.
32. D'Eon JL, Harris CA, Ellis JA. Testing factorial validity and gender invariance of the pain catastrophizing scale. *J Behav Med* 2004; 27:361-372.
33. Moss-Morris R, Weinman J, Petrie KJ, Horne R, Cameron LD, Buick D. The revised Illness Perception Questionnaire (IPQ-R). *Psychology & Health* 2002; 17:1-16.
34. Kori SH, Miller RP, Todd DD. Kinesiophobia: A new view of chronic pain behavior. *Pain Management* 1990; 35-43.
35. George SZ, Valencia C, Beneciuk JM. A Psychometric investigation of fear-avoidance model measures in patients with chronic low back pain. *J Orthop Sport Phys* 2010; 40:197-205.
36. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* 2007; 39:175-191.
37. Hagg O, Fritzell P, Nordwall A. The clinical importance of changes in outcome scores after treatment for chronic low back pain. *European Spine Journal* 2003; 12:12-20.
38. Dobrila-Dintinjana R, Nacinovic-Duletic A. Placebo in the treatment of pain. *Collegium Antropol* 2011; 35:319-323.
39. Puhl AA, Reinhart CJ, Rok ER, Injeyan HS. An examination of the observed placebo effect associated with the treatment of low back pain - a systematic review. *Pain Research & Management* 2011; 16:45-52.
40. Deyo RA, Walsh NE, Schoenfeld LS, Ramamurthy S. Can trials of physical treatments be blinded - the example of transcutaneous electrical nerve-stimulation for chronic pain. *Am J Phys Med Rehab* 1990; 69:6-10.
41. Hestbaek L, Leboeuf-Yde C, Engberg M, Lauritzen T, Bruun NH, Manniche C. The course of low back pain in a general population. Results from a 5-year prospective study. *Journal of Manipulative and Physiological Therapeutics* 2003; 26:213-219.
42. Takamoto K, Bito I, Urakawa S, Sakai S, Kigawa M, Ono T, Nishijo H. Effects of compression at myofascial trigger points in patients with acute low back pain: A randomized controlled trial. *European Journal of Pain (London, England)* 2015; 19:1186-1196.
43. Hou CR, Tsai LC, Cheng KF, Chung KC, Hong CZ. Immediate effects of various physical therapeutic modalities on cervical myofascial pain and trigger-point sensitivity. *Arch Phys Med Rehab* 2002; 83:1406-1414.
44. Cheing GLY, Tsui AYY, Lo SK, Hui-Chan CWY. Optimal stimulation duration of tens in the management of osteoarthritic knee pain. *Journal of Rehabilitation Medicine* 2003; 35:62-68.
45. van der Roer N, Ostelo RWJG, Bekkering GE, van Tulder MW, de Vet HCW. Minimal clinically important change for pain intensity, functional status, and general health status in patients with nonspecific low back pain. *Spine* 2006; 31:578-582.
46. Airaksinen O, Brox JI, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F, Mannion AF, Reis S, Staal JB, Ursin H, Zanoli G. Chapter 4. European guidelines for the management of chronic nonspecific low back pain. *Eur Spine J* 2006; 15:S192-S300.
47. Beckwee D, De Hertogh W, Lievens P, Bautmans I, Vaes P. Effect of tens on pain in relation to central sensitization in patients with osteoarthritis of the knee: Study protocol of a randomized controlled trial. *Trials* 2012; 13:21.
48. Jull G, Sterling M, Kenardy J, Beller E. Does the presence of sensory hypersensitivity influence outcomes of physical rehabilitation for chronic whiplash? – A preliminary RCT. *Pain* 2007; 129:28-34.
49. Baert IA, Lluch E, Mulder T, Nijs J, Noten S, Meeus M. Does pre-surgical central modulation of pain influence outcome after total knee replacement? A systematic review. *Osteoarthritis and Cartilage* 2016;24(2):213-223.
50. Cagnie B, Dewitte V, Barbe T, Timmermans F, Delrue N, Meeus M. Physiologic effects of dry needling. *Current Pain and Headache Reports* 2013; 17:348.
51. Smith AD, Jull G, Schneider G, Frizzell B, Hooper RA, Sterling M. Cervical radiofrequency neurotomy reduces central hyperexcitability and improves neck movement in individuals with chronic whiplash. *Pain Medicine (Malden, Mass)* 2014; 15:128-141.
52. Fernandez-de-las-Penas C, Dommerholt J. Myofascial trigger points: Peripheral or central phenomenon? *Current Rheumatology Reports* 2014;16(1):395.
53. Srbely JZ. New Trends in the treatment and management of myofascial pain syndrome. *Curr Pain Headache R* 2010; 14:346-352.
54. De Couck M, Nijs J, Gidron Y. You may need a nerve to treat pain: The neurobiological rationale for vagal nerve activation in pain management. *The Clinical Journal of Pain* 2014; 30:1099-1105.
55. McCambridge J, Kypri K, Elbourne D. Research participation effects: A skeleton in the methodological cupboard. *Journal of Clinical Epidemiology* 2014; 67:845-849.