Improved Psychosocial and Functional Outcomes and Reduced Opioid Usage Following Burst Spinal Cord Stimulation

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ABSTRACT

Objective: Burst spinal cord stimulation (B-SCS) has been shown to reduce neuronal firing in the anterior cingulate cortex through selective modulation of the medial pain pathway tract. This pain pathway communicates the affective component of pain processing. The purpose of this study was to assess the effect of B-SCS on psychosocial functioning and its influence on pain and quality of life.

Materials and Methods: Eligible patients with chronic, intractable pain of the trunk, and/or lower limbs were enrolled. After a successful trial period, subjects received a permanent implant and returned for follow-up at 6- and 12-months.

Results: In total, 269 patients were enrolled at 22 centers. Trial success rate was 90%. Significant improvements in pain, physical, mental, and emotional functioning were observed from baseline to the 6- and 12-month follow-up ($p < 0.001$). Overall, patients had improved quality of life, became more active, and the negative impact of pain on daily life was decreasing. At one year, 81% of subjects were satisfied or very satisfied with their therapy. Subjects showing significant improvements on mental health outcomes reported enhanced pain relief and quality of life scores compared with subjects with continued impaired mental health at follow-up. At one year, 89% of subjects who were taking opioids at baseline decreased or stayed at the same level of opioid use; 19% stopped taking any opioids. No unanticipated adverse events have been reported.

Conclusions: One-year outcomes after B-SCS show improvements across all evaluated psychological measures with the largest impact observed on catastrophizing and depression (the affective component of pain processing). These pain-related beliefs and behaviors, and not pain intensity, have been shown to put patients at greatest risk of a poor prognosis and quality of life.

Keywords: Burst, chronic pain, medial pain pathway tract, opioid therapy, patient reported outcomes

Conflict of Interest: Steven Falowski serves as a consultant for Abbott, Vertiflex, Medtronic, and Saluda. He also serves on the advisory boards for Abbott and Medtronic. Dr. Falowski owns equity in Saluda, SPR therapeutics, Thermaquil, and SpineThera and conducts research for Medtronic, Abbott, Biotronik, and Nuvectra. Gregory Moore received consulting fees and a research grant from Boston Scientific Corporation. Eric Cornidez received consulting fees from Abbott. He also conducts research for Abbott, Nevro, and Nuvectra. Kelby Hutcheson received research support from Abbott and Medtronic. Kenneth Candido and Isaac Peña declare no conflict of interest. Bram Blomme and Robyn Capobianco are employees of Abbott (formerly St. Jude Medical).

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INTRODUCTION

Chronic pain affects approximately 30% of adults worldwide and is consistently associated with psychological disorders across all geographies (1, 2). Patients seek medical care for pain not only for diagnostic evaluation and symptom relief, but also because pain interferes with daily activities, causes worry and emotional distress, and undermines confidence (1). The association between major depression and chronic low back pain is particularly well known among pain physicians, and several studies recommend targeting depression as an integral component of pain management programs (3-5).

Spinal cord stimulation (SCS) is an established therapy for patients suffering with chronic neuropathic pain. It has been shown to reduce pain, improve quality of life, reduce analgesic use, allow patients to return to work, and result in significant cost savings over time compared to conventional medical management (6). Within the last decade, new stimulation designs have emerged that deviate from low-frequency tonic SCS. These novel therapies include high-frequency tonic SCS and BurstDR™ SCS (B-SCS; Abbott, Plano, TX, USA) stimulation (7, 8).

A large amount of preclinical and clinical data is available that provides insight into the different mechanism of action and neurophysiological effects of B-SCS compared with tonic stimulation patterns (9-16). Importantly, in addition to somatosensory modulation, multiple neuroimaging and direct neuronal recording studies have revealed that B-SCS modulates the medial spinothalamocortical pathways, having a greater effect than tonic SCS on targets of the brain that are associated with the affective/attentional or emotional aspects of pain processing (12, 17-20). The full clinical implications of these differences have not been established, although B-SCS has shown to be more effective than tonic stimulation in several comparative studies (8, 17, 21-26).

Although pain relief is the primary outcome in many SCS studies, quality of life may be more significantly affected in chronic pain patients. The importance of non-pain measures has been stressed by the IMMPACT group and the CDC; both entities encourage the evaluation of functional improvement and psychosocial factors beyond pain relief alone (27, 28). Expanding the literature on quality of life outcomes will provide clinicians additional data to better educate patients about the benefits of SCS and set comprehensive goals for treatment outcomes. In addition, subjects with substantial depression at baseline were not eligible to participate in the SUNBURST trial, and the study consequently did not demonstrate significant differences for catastrophizing and SF-36 quality of life assessment between the burst and tonic arms (8). Depression has been shown to be directly correlated with catastrophizing, among other psychosocial factors. The main purpose of the TRIUMPH study was therefore to examine psychosocial functioning and its influence on pain relief and quality of life after implantation of a B-SCS system in real-world settings. Finally, the SUNBURST study used only tonic in the trial phase resulting in an enriched cohort that were initial responders to tonic stimulation (8). This study set out to assess outcomes for B-SCS when burst, and not tonic stimulation, is presented as the initial SCS experience.

MATERIALS AND METHODS

TRIUMPH is an ongoing prospective, multi-center, international study being conducted at sites in the United States, Canada, and Europe (ClinicalTrials.gov registration NCT03082261). Enrollment completed in June 2018 and is currently in the follow-up phase, which will extend to 24 months. This study was performed according to Good Clinical Practices, the Declaration of Helsinki, and before initiating the study, Institutional Review Board or Ethics Committee approval was received at each site.

Patients

Centers were instructed to approach all eligible patients and ask for their interest in participating in the study. Patients (≥18 years of age) with chronic, intractable pain of the trunk, and/or lower limbs, recommended by a physician for SCS therapy, were recruited for this study. This included patients with radiculopathy, failed back surgery syndrome (FBSS), and other chronic pain conditions who passed a psychological screening according to the standard of care of individual sites. Eligible patients had a baseline score on the Numeric Rating Scale (NRS) ≥ 6 over the past 24 hours for average pain specific to the area(s) of chronic pain being treated with SCS. Patients with an existing SCS system, who previously failed SCS, were planning to have a different neurostimulation system or drug pump implanted, or had a primary diagnosis of peripheral vascular disease, angina pectoris, or chronic migraine were excluded from the study.

Procedures

After providing written informed consent, subjects underwent an SCS trial according to the investigator's clinical practice. B-SCS stimulation parameters (i.e., monopolar burst at 500 Hz delivered in groups of five pulses, with passive discharge between bursts, repeated at a 40 Hz frequency, with a 1 ms pulse width) were configured using the clinician programmer and delivered using an external pulse generator. Trial success was determined by the investigator and defined as 50% pain relief and the subject's interest in placement of a permanent implant. Subjects who went on to permanent implant received either a rechargeable (Prodigy, Abbott, Plano, TX, USA) or recharge-free (Proclaim, Abbott, Plano, TX, USA) SCS system at the physician's discretion. Subjects subsequently returned for follow-up at 3, 6, and 12 months. Future follow-up visits are planned at 18 and 24 months. The three-month follow-up did not include the full battery of psychosocial and functional outcome measures and are not reported here.

Measures

Endpoints of this study are psychosocial and functional outcomes and pain relief (on NRS) at 6- and 12-month follow-up. Psychometrics were assessed using the following validated clinical questionnaires: Pain Catastrophizing Scale (PCS), Patient Health Questionnaire Depression scale (PHQ-9), State-Trait Anxiety Inventory (STAI), Tampa Scale for Kinesiophobia (TSK), EuroQol 5-Dimensions (EQ-5D), 8-item PROMIS physical function short form (PROMIS-8), and Medical Outcomes Survey (MOS) Sleep Index II.

Additional outcome measures included Patient Global Impression of Change (PGIC), patient reported pain relief (PRPR), therapy satisfaction, and activity level. Chronic pain medication use was collected at baseline and at all follow up timepoints. This included opioids, analgesics, anticonvulsants, muscle relaxants, nonsteroidal anti-inflammatory drugs, and psychiatric mediation. Given the epidemic of abuse and overdose related to opioids in

Table 1 Published Clinical Impact Scores, Clinically Meaningful Changes, and Population Norms.

Outcome	Clinical impact score(s)	Reference	Clinically meaningful change or MCID	Reference	Population norm (mean ± SD)	Ref
PCS	≥30	(43)	PCS reductions of approximately 38%-44% were best associated with returning to work and low pain severity ratings	(44)	13.87 ± 10.11	(45)
PHQ-9	No or mild depression: 1–9 Moderate depression: 10–14 Moderately severe depression: 15–19 Severe depression: 20–27	(46)	Decrease of ≥5 points	(47)	2.91 ± 3.52	(48)
STAI state	≥40	(49)	NA	NA	34.5 ± 10.3 (Male 50-69 y) 32.2 ± 8.67 (Female 50-69 y)	(50)
TSK	≥38	(51)	Decrease of ≥4 points	(52)	21.7 ± 6.3	(53)
EQ-5D	NA	NA	Increase of ≥0.074	(54)	0.86 ± 0.23	(55)
PROMIS-8	≥43.1 on T-score	(56)	Increase of ≥ 5 points on T-score	(56)	T-score of 50 ± 10	(57)
MOS Sleep Scale II	>33.3	(58)	NA	NA	25.8	(59)

NA, not available; MCID, minimal clinically important difference; SD, standard deviation.

the United States and various other countries, we focused on presenting the usage of these substances. Opioid medication use was standardized by converting each drug to morphine milligram equivalents (MMEs) using CDC validated conversion factors (29).

Adverse device effects (ADEs) and serious adverse device effects (SADEs), defined as adverse events related to the device or procedure, were collected for all enrolled subjects.

Statistical Analysis

Outcomes were analyzed by calculating the absolute and percentage change (%) from baseline. Two-tailed paired t-test was used for continuous variables, such as patient reported outcomes, and Chi-square test was used to compare the frequency of proportions between two groups. The Kruskal-Wallis test was used for multiple comparisons between groups. All statistical analyses were performed with a significance level of $p < 0.05$. No adjustments for multiplicity have been made. Imputations methods were used as appropriate to account for missing data, subject dropouts, and withdrawals.

Published clinical impact scores (i.e., values at or above which significant intervention is required) and/or clinically meaningful changes, including minimal clinically important difference (MCID),

Table 2 Demographics and Baseline Characteristics.

	All patients (n = 269)
Sex, n (%)	
Female	166 (61.7%)
Male	103 (38.3%)
Age (years)	
Mean ± SD	59 ± 14
Range (Min-Max)	18–89
Years with chronic pain	
Mean ± SD	9.7 ± 8.6
Range (Min-Max)	0–54
Impact of pain, n (%)	
Minimal	5 (1.9%)
Moderate	53 (19.7%)
Major	211 (78.4%)
Activity level, n (%)	
Sedentary	42 (15.6%)
Minimally active	146 (54.3%)
Moderately active	73 (27.1%)
Very active	8 (3.0%)
Work status, n (%)*	
Full time	37 (13.8%)
Part time	16 (5.9%)
Home maker	17 (6.3%)
Volunteer	2 (0.7%)
Retired	109 (40.5%)
Disabled	70 (26.0%)
None of the above	26 (9.7%)
Pain diagnosis, n (%)†	
Radiculopathy	156 (58.0%)
Failed back surgery syndrome	131 (48.7%)
Complex regional pain syndrome	18 (6.7%)
Intervertebral disc disorder	15 (5.6%)
Other	19 (7.0%)

SD, standard deviation.
*Subjects could select more than one category.
†A subject might have up to two pain diagnoses.
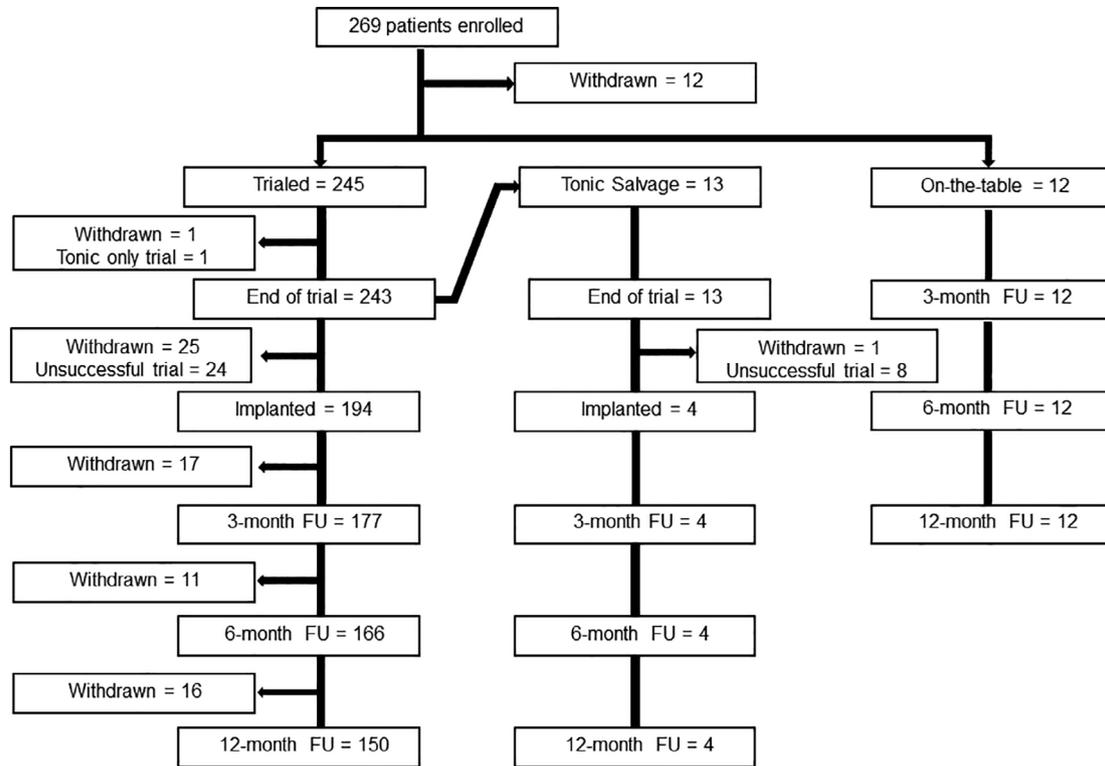
Figure 1 Subject disposition.

were collected for a responder rate analysis. Population norms for all patient reported outcomes (PROs) are also reported; an overview is provided in Table 1.

In addition, we performed a remitter analysis on mental health outcomes. A remitter was defined as a subject who met the impact score to detect clinically significant symptoms on PHQ-9 and STAI State scale at baseline and improved to a level below the impact score at 6- and/or 12-months; non-remitters remained above the impact score at 6- and/or 12-months. Subjects who were not clinically impacted at baseline were categorized as non-impacted. NRS and EQ-5D outcomes were compared across the three groups: remitter, non-remitter, and non-impacted.

The primary cohort consists of subjects who successfully completed the trial phase with B-SCS, had a permanent system implanted, and completed the 12-month visit. Subjects who underwent an on-the-table trial and completed the 12-month visit are also included in this cohort. Subjects who did not respond to B-SCS during the trial phase were given the opportunity to extend the trial period using tonic stimulation. These subjects who were implanted after a successful tonic trial were analyzed separately.

RESULTS

The study enrolled 269 subjects at 22 investigational sites between March 2017 and February 2018. The mean ± SD age was 59 ± 14 years, and 62% of the subjects were female. Subjects had experienced pain for a mean ± SD of 9.7 ± 8.5 years at the time of study enrollment. Demographics and baseline characteristics are summarized in Table 2. Radiculopathy and FBSS, diagnosed separately or combined with another chronic pain

condition, were the most frequent etiologies in the study. Fig. 1 shows the disposition of the subjects.

Trial Phase

Nearly all trials were performed with percutaneous leads (98.1%; 252/257); only five subjects were trialed with a paddle lead. The trial success rate was 90% (219/243). The mean ± SD reported pain relief was 70% ± 16, and 97% of subjects were satisfied or very satisfied with the therapy at the end of the trial period. The median trial length was seven days (Q1, five days; Q3, seven days). Trial success in subjects with baseline values meeting the clinical impact score on mental health outcomes (PHQ-9 [≥ 10] and STAI State [≥ 40]) did not differ significantly from subjects with baseline values below the clinical impact score on these scales (91% vs. 89%, $p = 0.68$ and 90% vs. 91%, $p = 0.69$, respectively). Thirteen subjects who failed to achieve ≥50% pain relief using B-SCS underwent an extended trial with tonic stimulation. Of these 13 extended trials, five (38%) were successful; one subject with a successful tonic trial withdrew from the study, four received a permanent implant and were analyzed separately.

Primary Cohort

After a successful B-SCS trial, 194 subjects received a permanent IPG. Of these, 160 subjects (82%) received a recharge-free IPG; 125 subjects (64%) received percutaneous leads, and 69 subjects (36%) received a paddle lead. Significant improvements from baseline to the 6- and 12-month follow-up period were observed for all psychosocial and functional measures ($p < 0.0001$) (Table 3). The mean PCS score improved by 48% to 13.2 at six months, and by 44% to 14.2 at 12 months, and mean PHQ-9 score improved 28% and 25%. Mean EQ-5D score improved 51%

Table 3 Six- and 12-Month Psychosocial and Functional Outcomes (Primary Cohort), Reported as Mean ± SD (n).

Outcome	Baseline	6 Months	p-value*	12 months	p-value*
Catastrophizing (PCS)	25.5 ± 12.7 (162)	13.2 ± 12.0 (158)	$p < 0.0001$	14.2 ± 12.9 (156)	$p < 0.0001$
Depression (PHQ-9)	10.4 ± 6.3 (162)	7.5 ± 6.4 (158)	$p < 0.0001$	7.8 ± 6.6 (156)	$p < 0.0001$
State anxiety (STAI state)	43.9 ± 13.5 (162)	38.2 ± 12.8 (158)	$p < 0.0001$	39.1 ± 14.4 (156)	$p < 0.0001$
Fear avoidance (TSK)	28.7 ± 7.8 (162)	24.7 ± 7.2 (158)	$p < 0.0001$	24.4 ± 7.2 (156)	$p < 0.0001$
Quality of life (EQ-5D)	0.44 ± 0.21 (162)	0.66 ± 0.20 (158)	$p < 0.0001$	0.63 ± 0.23 (156)	$p < 0.0001$
Physical capability (PROMIS-8)	17.6 ± 5.7 (155)	22.5 ± 7.9 (151)	$p < 0.0001$	21.6 ± 7.7 (149)	$p < 0.0001$
Sleep problems (MOS sleep index II)	53.0 ± 21.2 (162)	44.9 ± 23.0 (158)	$p < 0.0001$	45.7 ± 23.6 (156)	$p < 0.0001$

*p-values are from two-tailed paired-sample t-tests.
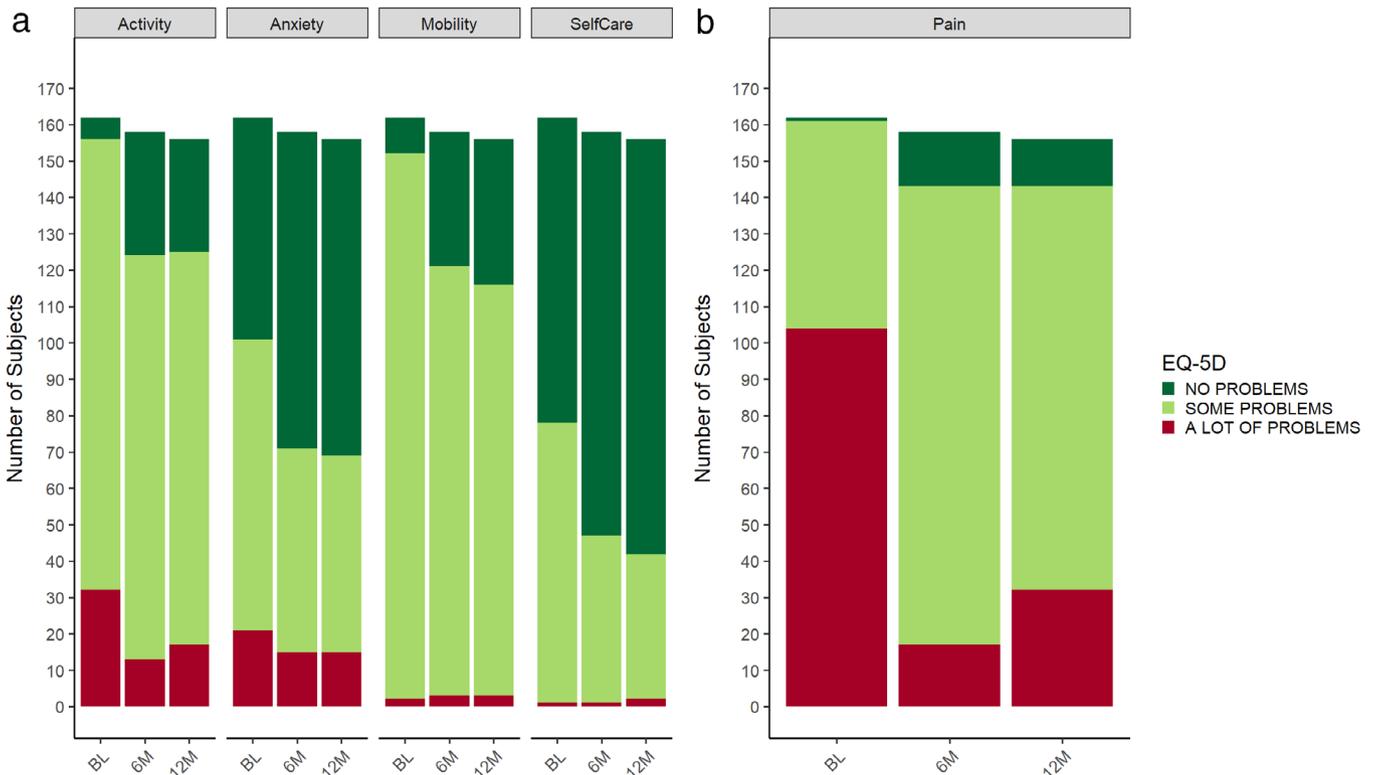
Figure 2 The five dimensions of the EQ-5D score at baseline and at 6- and 12-months follow-up. Activity, Anxiety, Mobility, and Selfcare are presented in panel a; Pain/Discomfort is presented in panel b. [Color figure can be viewed at wileyonlinelibrary.com]

and 44%, within a SD of the population norm. Improvements were observed for each EQ-5D category from baseline to 6- and 12-months with the most prominent change in the pain/discomfort category (Fig. 2).

The responder analysis for each psychosocial outcome measure is presented in Table 4. At one year, 89% of subjects achieved a clinically significant improvement in at least one of the seven predefined outcome measures. Of note, 70% and 72% of subjects who were clinically catastrophizing and 80% and 70% of subjects who were showing fear avoidance behavior (on TSK) at baseline, were not at 6- and 12-months, respectively. MCID of 0.074 on EQ-5D was achieved by 68% and 60% of subjects at 6- and 12-months, respectively.

Mean PRPR was 58% and 59% at 6- and 12-months, respectively. Other outcome measures including activity level, impact of pain on daily life (Fig. 3 and B), and PGIC (Fig. 3C) show continued improvement across all measures up to one-year post-permanent

implant. Furthermore, 78% and 81% of subjects were satisfied or very satisfied with their therapy, 84% and 83% would have the procedure again at 6- and 12-months, and 89% would recommend the procedure at both follow-up timepoints.

Remitters and non-impacted subjects on the depression and state anxiety scales had considerably greater improvements in pain relief (NRS) and quality of life (EQ-5D) than non-remitters (Fig. 4).

Opioid Medication Use

At baseline, 79% of subjects in the six months cohort (125/159) and 77% of subjects in the 12 months cohort (121/157) were taking opioids. Of note, 88% (110/125) and 89% (108/121) of subjects decreased or stayed at the same level of opioid use at 6- and 12-months, respectively. There was a 26% reduction in the mean opioid dose from 49.2 MME pre-operatively to 36.2 MME at

Table 4 Six- and 12-Month Responder Analysis (Primary Cohort).

Outcome	Criterion	6 months	12 months
Catastrophizing (PCS)	Impact score: ≥ 30 at BL; < 30 at follow-up	41/69 (69.5%)	41/57 (71.9%)
	Clinical meaningful change: 44% decrease	97/158 (61.4%)	84/156 (53.8%)
Depression (PHQ-9)	Impact score: ≥ 10 at BL; < 10 at follow-up	45/81 (55.6%)	40/80 (50.0%)
	Clinical meaningful change: 5-point decrease	54/158 (34.2%)	52/156 (33.3%)
State anxiety (STAI state)	Impact score: ≥ 40 at BL; < 40 at follow-up	41/100 (41.0%)	42/98 (42.9%)
Fear avoidance (TSK)	Impact score: ≥ 38 at BL; < 38 at follow-up	16/20 (80.0%)	14/20 (70.0%)
	Clinical meaningful change: 4-point decrease	79/158 (50.0%)	86/156 (55.1%)
Quality of life (EQ-5D)	Clinical meaningful change: 0.074-point increase	108/158 (68.4%)	94/156 (60.3%)
Physical capability (PROMIS-8)	Impact score: < 43.1 at BL; ≥ 43.1 at follow-up	25/148 (16.9%)	22/146 (15.1%)
	Clinical meaningful change: 5-point increase	57/151 (37.7%)	47/149 (31.5%)
Sleep problems (MOS sleep index II)	Impact score: > 33.33 at BL; ≤ 33.33 at follow-up	25/125 (20.0%)	25/123 (20.3%)
	Responder in one or more domains*	139/158 (88.0%)	139/156 (89.1%)

BL, baseline.

*Calculated based on clinically meaningful changes for PCS, PHQ-9, TSK, EQ-5D, and PROMIS score and proportion of subjects who dropped below clinical impact score for State Anxiety and MOS Sleep Scale.
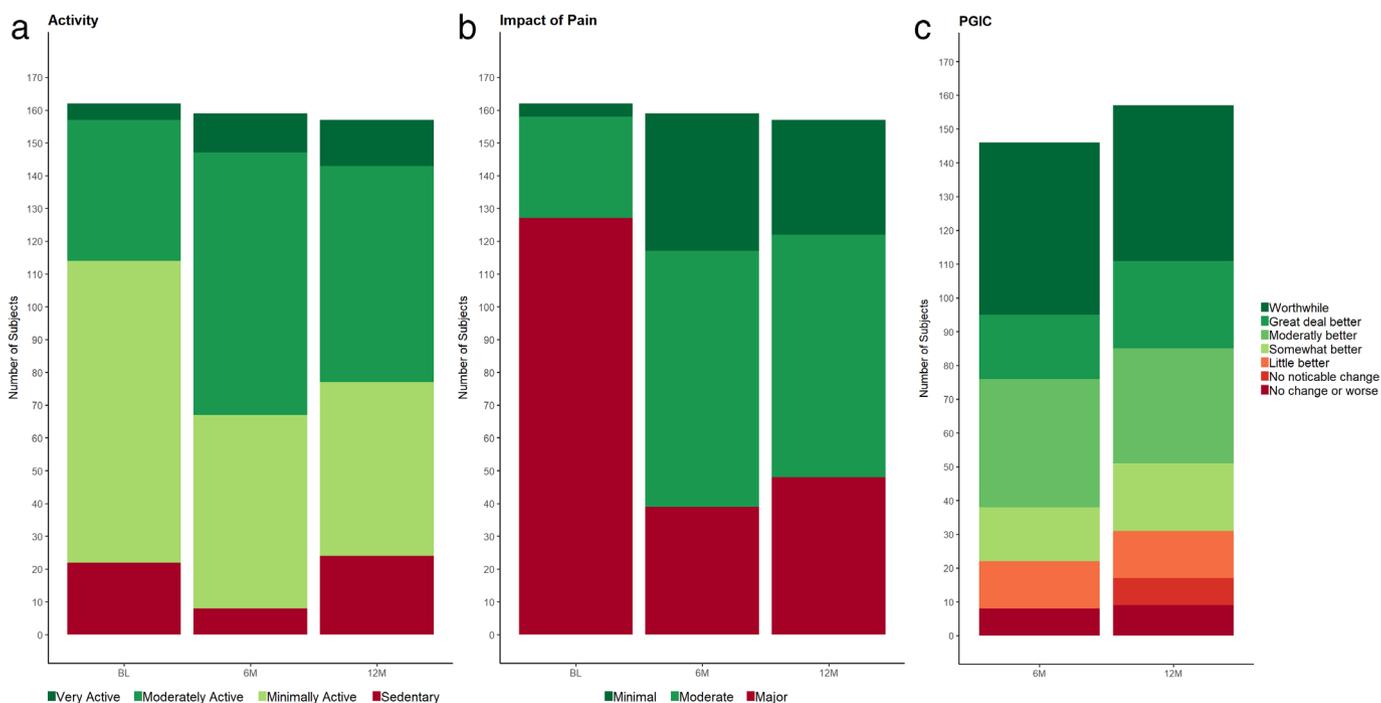
Figure 3 Activity level (a) and impact of pain on daily life (b) at baseline and at 6- and 12-months follow-up. Patient Global Impression of Change (c) at 6- and 12-months follow-up. [Color figure can be viewed at wileyonlinelibrary.com]

6 months and from 49.7 MME pre-operatively to 37.0 MME at 12 months. Of note, 19% of subjects who were taking opioids at baseline were not at both follow-up timepoints. Table 5 summarizes the opioid medication data.

Tonic Cohort

The group of four subjects who were implanted after a successful tonic trial was too small for meaningful statistical analyses. Point estimates at baseline, and at 6- and 12-months are presented in Supporting Information Table S1.

Safety

No unanticipated adverse events have been reported. Among the 269 enrolled subjects, there were a total of 47 complications in 41 subjects (15.2%). Twenty events were considered SADEs and were reported in a total of 17 subjects (6.3%). Twelve events occurred during trial phase. The most common occurrence was change in stimulation due to loose electrical connections (n = 2) or lead migration (n = 2). Overall infection rate during trial phase was <1% (2/269). During the permanent implant phase, 35 events were reported; 12 of which were device-related. Most common adverse events during permanent implant phase were infection (n = 6), pain at IPG site (n = 5), and lead failure/lead migration (n = 5).
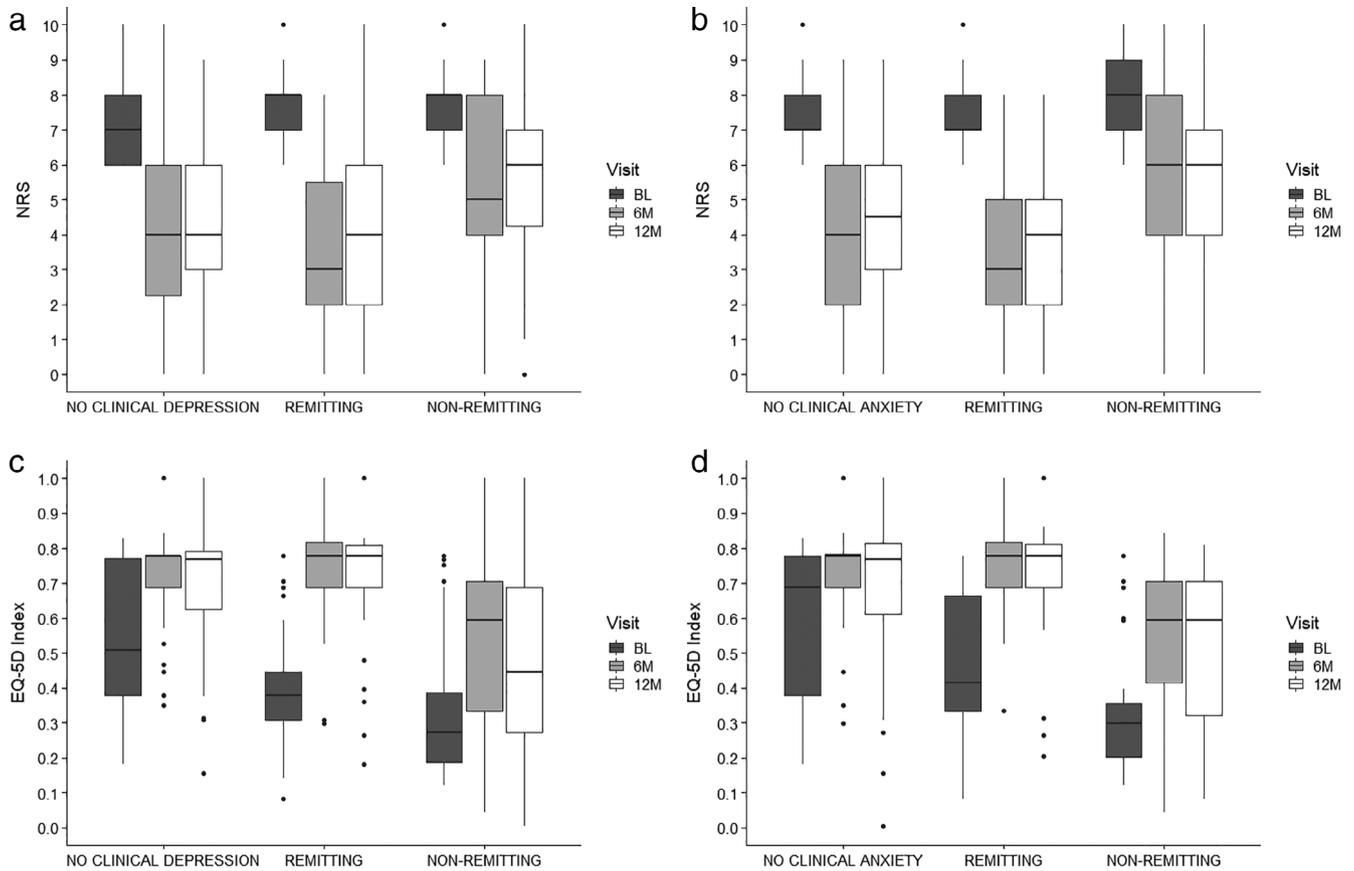
Figure 4 NRS (a and b) and EQ-5D (c and d) scores for non-impacted, remitters, and non-remitters on mental health outcomes (depression and state anxiety, respectively) at baseline and at 6- and 12-months follow-up. Box plots represent median and interquartile range (IQR, Q1-Q3). Outliers, represented by points, are ≥1.5 IQR.

Table 5 Opioid Medication Usage.

		6 months (n = 159)	
	Subjects, n/N (%)	Baseline MME, mean ± SD	6 months MME, mean ± SD
Subjects with >0 MME	125/159 (78.6%)	49.2 ± 56.6	36.2 ± 53.5
Completely off	24/125 (19.2%)	30.9 ± 33.3	0.0 ± 0.0
Decrease	67/125 (53.6%)	54.5 ± 63.3	23.0 ± 47.1
Same	43/125 (34.4%)	47.0 ± 51.1	47.0 ± 51.1
Decrease/Same	110/125 (88.0%)	51.5 ± 58.7	32.4 ± 49.9
Increase	15/125 (12.0%)	32.2 ± 34.6	64.0 ± 71.2
		12 months (n = 157)	
	Subjects, n/N (%)	Baseline MME, mean ± SD	12 months MME, mean ± SD
Subjects with > 0 MME	121/157 (77.1%)	49.7 ± 57.3	37.0 ± 55.8
Completely off	23/121 (19.0%)	23.3 ± 19.2	0.0 ± 0.0
Decrease	69/121 (57.0%)	53.2 ± 64.4	25.3 ± 54.3
Same	39/121 (32.2%)	43.3 ± 47.8	43.3 ± 47.8
Decrease/Same	108/121 (89.3%)	49.6 ± 58.9	31.8 ± 52.5
Increase	13/121 (10.7%)	50.7 ± 43.7	80.4 ± 65.0

MME, morphine milligram equivalents; SD, standard deviation.

DISCUSSION

One-year after implantation of a B-SCS system, subjects showed significant and sustained improvements in physical, mental, and emotional functioning. Furthermore, physical activity levels were increasing and the impact of pain on daily life in this patient population was considerably diminished. The most impactful effect of the therapy was observed on mental health; catastrophizing returned to similar levels as observed in a healthy non-chronic pain population. Furthermore, individuals suffering from critical levels of depression no longer required intervention. These outcomes resulted in significant improvement in quality of life as measured by EQ-5D.

The trial success rate was high and was not affected by the subject's mental health state (i.e., depression or anxiety). Scores on all PROs significantly improved at 6- and 12-months follow-up. The highest relative changes were observed for pain catastrophizing (PCS), depression (PHQ-9), and quality of life (EQ-5D). The responder rate analysis confirmed the impact of B-SCS on these three outcomes, but additionally indicated that a high percentage (>70%) of subjects with clinically significant fear avoidance (on TSK) were not showing this behavior at follow-up. Multiple neuroimaging and direct neural recording studies have shown the selective effect of B-SCS on cortical areas (targets of the medial spinothalamic pathway) that modulate the attentional, emotional, and motivational aspects of pain and pain related cognition and behavior (12, 17-20); this study extends these neuroimaging findings with real-world effectiveness data.

A study on the influence of different types of SCS waveforms on somatosensory evoked potentials and electromyographic (EMG) signals further highlighted the unique characteristics of B-SCS (30). Unlike low-frequency tonic, burst activates the distal muscles first at lower amplitudes and more proximal muscles at higher amplitudes as well as creates a hyperexcitability state facilitating more robust responses when returning to tonic stimulation. In addition, B-SCS elicits only one large summated EMG signal, whereas other stimulation patterns with active recharge produce four equipotent EMG signals, and high-frequency tonic waveforms did not generate any observable EMG responses. These potent effects of B-SCS are generated at the lowest thresholds suggesting energy efficiency over other stimulation designs.

Interestingly, remitters on depression and anxiety outcomes reported significantly improved pain relief and quality of life scores compared with non-remitters, even outperforming subjects who were not clinically impacted at baseline. The absence of depression and anxiety at baseline seemed to result in favorable pain relief and quality of life after treatment; but, the results were no better than in subjects who were in remission for these psychological factors. Non-remitters remained associated with high levels of impairment.

Chronic pain is complex and multifactorial. Pain scores alone can be unreliable and often do not reflect a patient's current health state, or correlate with quality of life (31). Persistent pain can lead to emotional and behavioral consequences that are deleterious to pain recovery and functional rehabilitation (32). In a cohort study of 1208 patients, pain catastrophizing, and not pain intensity, was most closely associated with quality of life outcomes (33). In addition, other pain beliefs that have been shown to put patients at greatest risk of a poor prognosis are fear avoidance and poor expectations for recovery (34). The fear-avoidance model is a cognitive-behavioral account that integrates these

psychological factors (35). A cycle is initiated when pain is interpreted in a catastrophizing manner. These thoughts can lead to pain-related fear and associated avoidance behavior, eventually causing aggravated pain that becomes chronic due to disuse, depression, and disability. Breaking this vicious cycle by lowering pain catastrophizing is essential for recovery as patients accept and confront their pain. Our results show that B-SCS significantly decreases catastrophizing, depression, and fear avoidance behavior. In fact, pain catastrophizing dropped below the population norm (of 13.9 points) at follow-up.

PGIC, EQ-5D, and patient satisfaction are outcomes that have been evaluated in several SCS studies using different stimulation designs and modalities. In a study comparing tonic SCS plus optimal medical management (OMM) treatment to OMM only in a FBSS population (PROMISE study), subjects reported a PGIC of 59% at six months, compared with 68% satisfaction in our study (36). Our results show that B-SCS improves patient quality of life, as measured on EQ-5D; mean values at 6- and 12-months were 0.66 and 0.63, respectively. Similar to PGIC, our results compare favorably to data on other stimulation designs. The PROMISE study reported EQ-5D index scores of 0.49 and 0.48 at 6- and 12-months, respectively. In a small study of 20 patients that evaluated outcomes using multiple stimulation frequencies (PROCO study), EQ-5D index values ranged from 0.5 to 0.6 (37). The proportion of patients who were satisfied or very satisfied with their therapy is consistent across SCS studies and was around 80%, similar to results presented here (36, 38).

Opioid misuse and addiction in the United States is still peaking; more than 130 people die each day due to opioid overdose (39). As a non-pharmacologic option for chronic pain management, spinal cord stimulators have been put forward as one of the key therapies to counteract the opioid epidemic (40, 41). In our study, 90% of subjects decreased or stayed at the same level of opioids at follow up; an opioid reduction protocol was not in place. Of note, 19% of subjects who were taking opioids at baseline were not at the follow-up timepoints.

Of the 24 subjects (10%) who failed a trial with B-SCS, 13 were trialed with tonic stimulation, of which five (38%) were successful. This result raises questions about the utility of a tonic trial for nonresponders to B-SCS in the trial phase. Switching to tonic stimulation to obtain a successful trial does not mean that patients will only respond to tonic stimulation after permanent implant; the four subjects who were permanently implanted eventually chose to use both B-SCS and tonic to manage their pain.

Limitations

The TRIUMPH study was not designed to compare tonic and burst groups. The tonic group derived from subjects who received an extended trial showed less improved psychological outcomes at follow up compared with the burst group. However, given the large difference in sample size, it would be inappropriate to make comparisons or draw conclusions.

As this is a real-world study, stringent programming and cycling guidelines could not be imposed. Recent research has shown the benefits of optimizing clinical settings for B-SCS. The BOLD study revealed that lower-energy, intermittent doses of burst stimulation are as effective as continuous burst stimulation, thereby potentially mitigating therapy habituation (42).

The TRIUMPH study had broad inclusion criteria and minimal exclusion criteria. As a result, IPG systems and electrode

configurations were used according to physician preference. Thus, our study represents real-world outcomes, illustrating the effectiveness of B-SCS to address the affective component of pain in a representative population rather than in a tightly controlled environment. Future research is needed to further refine programming and stimulation configurations in the field of neuromodulation.

CONCLUSIONS

One-year outcomes after B-SCS show improvements across all evaluated psychological measures with the largest impact observed on catastrophizing and depression (the affective component of pain processing). These pain-related beliefs and behaviors, and not pain intensity, have been shown to put patients at greatest risk of a poor prognosis and quality of life.

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Authorship Statement

Steven Falowski, Gregory Moore, Eric Cornidez, Kelby Hutcheson, Kenneth Candido, and Isaac Peña contributed to the acquisition of the data and assisted with document preparation. Bram Blomme contributed to the analysis and interpretation of the data and document preparation. Robyn Capobianco contributed to the study conduct, analysis and interpretation of the data, and document preparation. All authors reviewed and approved the final manuscript for submission.

REFERENCES

1. Gureje O, Von Korff M, Simon GE et al. Persistent pain and well-being: a World Health Organization study in primary care. *JAMA* 1998;280:147–151.
2. Steingrimsdottir OA, Landmark T, Macfarlane GJ et al. Defining chronic pain in epidemiological studies: a systematic review and meta-analysis. *Pain* 2017;158: 2092–2107.
3. Robertson D, Kumbhare D, Nolet P, Srbely J, Newton G. Associations between low back pain and depression and somatization in a Canadian emerging adult population. *J Can Chiropr Assoc* 2017;61:96–105.
4. Sullivan MJ, Reesor K, Mikail S et al. The treatment of depression in chronic low back pain: review and recommendations. *Pain* 1992;50:5–13.
5. Carley JA, Karp JF, Gentili A et al. Deconstructing chronic low back pain in the older adult: step by step evidence and expert-based recommendations for evaluation and treatment: Part IV: Depression. *Pain Med* 2015;16:2098–2108.
6. Taylor RS, Van Buyten JP, Buchser E. Spinal cord stimulation for complex regional pain syndrome: a systematic review of the clinical and cost-effectiveness literature and assessment of prognostic factors. *Eur J Pain* 2006;10:91–101.
7. Kapural L, Yu C, Doust MW et al. Novel 10-kHz high-frequency therapy (HF10 therapy) is superior to traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain: The SENZA-RCT randomized controlled trial. *Anesthesiology* 2015;123:851–860.
8. Deer T, Slavin KV, Amirdelfan K et al. Success using neuromodulation with BURST (SUNBURST) study: results from a prospective, randomized controlled trial using a novel burst waveform. *Neuromodulation* 2018;21:56–66.
9. Chakravarthy K, Fishman MA, Zuidema X, Hunter CW, Levy R. Mechanism of action in burst spinal cord stimulation: review and recent advances. *Pain Med* 2019;20:S13–S22.
10. Swadlow HA, Gusev AG. The impact of 'bursting' thalamic impulses at a neocortical synapse. *Nat Neurosci* 2001;4:402–408.
11. Sherman SM. Tonic and burst firing: dual modes of thalamocortical relay. *Trends Neurosci* 2001;24:122–126.
12. De Ridder D, Vanneste S. Burst and tonic spinal cord stimulation: different and common brain mechanisms. *Neuromodulation* 2016;19:47–59.
13. Shyu BC, Vogt BA. Short-term synaptic plasticity in the nociceptive thalamic-anterior cingulate pathway. *Mol Pain* 2009;5:51.
14. Shum FW, Wu LJ, Zhao MG et al. Alteration of cingulate long-term plasticity and behavioral sensitization to inflammation by environmental enrichment. *Learn Mem* 2007;14:304–312.
15. Remy S, Spruston N. Dendritic spikes induce single-burst long-term potentiation. *Proc Natl Acad Sci U S A* 2007;104:17192–17197.
16. Crosby ND, Weisshaar CL, Smith JR, Zeeman ME, Goodman-Keiser MD, Winkelstein BA. Burst and tonic spinal cord stimulation differentially activate GABAergic mechanisms to attenuate pain in a rat model of cervical radiculopathy. *IEEE Trans Biomed Eng* 2015;62:1604–1613.
17. De Ridder D, Plazier M, Kamerling N et al. Burst spinal cord stimulation for limb and back pain. *World Neurosurg* 2013;80:642–9 e1.
18. Yearwood T, De Ridder D, Yoo HB et al. Comparison of neural activity in chronic pain patients during tonic and burst spinal cord stimulation using fluorodeoxyglucose positron emission tomography. *Neuromodulation* 2020;23: 56–63.
19. Bocci T, De Carolis G, Paroli M et al. Neurophysiological comparison among tonic, high frequency, and burst spinal cord stimulation: novel insights into spinal and brain mechanisms of action. *Neuromodulation* 2018;21:480–488.
20. Quindlen-Hotek JC, Kent AR, De Anda P et al. Changes in neuronal activity in the anterior cingulate cortex and primary somatosensory cortex with nonlinear burst and tonic spinal cord stimulation. *Neuromodulation* 2020. https://doi.org/10.1111/ner.13116.
21. De Ridder D, Lenders MW, De Vos CC et al. A 2-center comparative study on tonic versus burst spinal cord stimulation: amount of responders and amount of pain suppression. *Clin J Pain* 2015;31:433–437.
22. De Ridder D, Vanneste S, van der Loo E et al. Burst stimulation of the auditory cortex: a new form of neurostimulation for noise-like tinnitus suppression. *J Neurosurg* 2010;112:1289–1294.
23. Kriek N, Groeneweg G, Huygen FJ. Burst spinal cord stimulation in a patient with complex regional pain syndrome: a 2-year follow-up. *Pain Pract* 2015;15: E59-64.
24. Schu S, Slotty PJ, Bara G, von Knop M, Edgar D, Vesper J. A prospective, randomised, double-blind, placebo-controlled study to examine the effectiveness of burst spinal cord stimulation patterns for the treatment of failed back surgery syndrome. *Neuromodulation* 2014;17:443–450.
25. Tjepkema-Cloostermans MC, de Vos CC, Wolters R, Dijkstra-Scholten C, Lenders MWPM. Effect of burst stimulation evaluated in patients familiar with spinal cord stimulation. *Neuromodulation* 2016;19:492–497.
26. Courtney P, Espinet A, Mitchell B et al. Improved pain relief with burst spinal cord stimulation for two weeks in patients using tonic stimulation: results from a small clinical study. *Neuromodulation* 2015;18:361–366.
27. Grinberg AM, D'Eon MS, Ellison JK et al. A revised psychosocial assessment model for implantable pain devices to improve their evidence basis and consensus with updated pain management guidelines. *Pain Manag* 2019;9:139–149.
28. Turk DC, Dworkin RH, Allen RR et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2003;106:337–345.
29. National Center for Injury Prevention and Control. *CDC compilation of benzodiazepines, muscle relaxants, stimulants, zolpidem, and opioid analgesics with oral morphine milligram equivalent conversion factors, 2016 version*. Atlanta, GA: Centers for Disease Control and Prevention, 2016.
30. Falowski SM. An observational case series of spinal cord stimulation waveforms visualized on intraoperative neuromonitoring. *Neuromodulation* 2019;22: 219–228.
31. Ballantyne JC, Sullivan MD. Intensity of chronic pain: the wrong metric? *N Engl J Med* 2015;373:2098–2099.
32. Linton SJ, Shaw WS. Impact of psychological factors in the experience of pain. *Phys Ther* 2011;91:700–711.
33. Lame IE, Peters ML, Vlaeyen JW, Kleef M, Patijn J. Quality of life in chronic pain is more associated with beliefs about pain, than with pain intensity. *Eur J Pain* 2005;9:15–24.
34. Nicholas MK, Linton SJ, Watson PJ, Main CJ, "Decade of the Flags" Working Group. Early identification and management of psychological risk factors ("yellow flags") in patients with low back pain: a reappraisal. *Phys Ther* 2011;91: 737–753.

35. Leeuw M, Goossens ME, Linton SJ et al. The fear-avoidance model of musculo-skeletal pain: current state of scientific evidence. *J Behav Med* 2007;30:77–94.

36. Rigoard P, Basu S, Desai M et al. Multicolumn spinal cord stimulation for predominant back pain in failed back surgery syndrome patients: a multicenter randomized controlled trial. *Pain* 2019;160:1410–1420.

37. Thomson SJ, Tavakkolizadeh M, Love-Jones S et al. Effects of rate on analgesia in kilohertz frequency spinal cord stimulation: results of the PROCO randomized controlled trial. *Neuromodulation* 2018;21:67–76.

38. Al-Kaisy A, Van Buyten JP, Smet I et al. Sustained effectiveness of 10 kHz high-frequency spinal cord stimulation for patients with chronic, low back pain: 24-month results of a prospective multicenter study. *Pain Med* 2014;15:347–354.

39. United States Department of Health and Human Services. What is the U.S. opioid epidemic? Available from: https://www.hhs.gov/opioids/about-the-epidemic/index.html. Accessed December 6th, 2019.

40. Deer T, Kim C, Bowman R, Ranson M, Douglas CS, Tolentino W. Spinal cord stimulation as a method of reducing opioids in severe chronic pain: a case report and review of the literature. *W V Med J* 2010;106:56–59.

41. Deer TR. Neurostimulation should be used as a method of reducing or eliminating opioids in the treatment of chronic pain: the digital drug revolution. *Expert Rev Med Devices* 2013;10:697–699.

42. Deer TR, Patterson DG, Baksh J et al. Novel intermittent dosing burst paradigm in spinal cord stimulation. *Neuromodulation* 2020. https://doi.org/10.1111/ner.13143.

43. Sullivan M. *PCS: Pain Catastrophizing scale: User manual*. Montreal: Departments of psychology, medicine, and neurology, School of Physical and Occupational Therapy: McGill University, 2009.

44. Scott W, Wideman TH, Sullivan MJ. Clinically meaningful scores on pain catastrophizing before and after multidisciplinary rehabilitation: a prospective study of individuals with subacute pain after whiplash injury. *Clin J Pain* 2014;30:183–190.

45. Osman A, Barrios FX, Gutierrez PM, Kopper BA, Merrifield T, Grittmann L. The pain catastrophizing scale: further psychometric evaluation with adult samples. *J Behav Med* 2000;23:351–365.

46. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606–613.

47. McMillan D, Gilbody S, Richards D. Defining successful treatment outcome in depression using the PHQ-9: a comparison of methods. *J Affect Disord* 2010;127:122–129.

48. Kocalevent RD, Hinz A, Brahler E. Standardization of the depression screener patient health questionnaire (PHQ-9) in the general population. *Gen Hosp Psychiatry* 2013;35:551–555.

49. Julian LJ. Measures of anxiety: state-trait anxiety inventory (STAI), Beck anxiety inventory (BAI), and hospital anxiety and depression scale-anxiety (HADS-A). *Arthritis Care Res* 2011;63:S467-72.

50. Spielberger CD. *Manual for the state-trait-anxiety: STAI (form Y)*. Palo Alto, CA: Consulting Psychologists Press, 1983.

51. Branstrom H, Fahlstrom M. Kinesiophobia in patients with chronic musculoskeletal pain: differences between men and women. *J Rehabil Med* 2008;40:375–380.

52. Woby SR, Roach NK, Urmston M, Watson PJ. Psychometric properties of the TSK-11: a shortened version of the Tampa scale for Kinesiophobia. *Pain* 2005;117:137–144.

53. Houben RM, Leeuw M, Vlaeyen JW et al. Fear of movement/injury in the general population: factor structure and psychometric properties of an adapted version of the Tampa scale for Kinesiophobia. *J Behav Med* 2005;28:415–424.

54. Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Qual Life Res* 2005;14:1523–1532.

55. Kind P, Hardman G, Macran S. UK population norms for EQ-5D: Centre for Health Economics, University of York; 1999.

56. Jensen M. *The pain stethoscope: a clinician's guide to measuring pain*. Philadelphia, PA: Springer Healthcare, 2011.

57. HealthMeasures. PROMIS Score Cut Points: Northwestern University [Available from: http://www.healthmeasures.net/score-and-interpret/interpret-scores/promis/promis-score-cut-points].

58. Zagalaz-Anula N, Hita-Contreras F, Martinez-Amat A et al. Psychometric properties of the medical outcomes study sleep scale in Spanish postmenopausal women. *Menopause* 2017;24:824–831.

59. Cappelleri JC, Bushmakin AG, McDermott AM et al. Measurement properties of the medical outcomes study sleep scale in patients with fibromyalgia. *Sleep Med* 2009;10:766–770.

SUPPORTING INFORMATION

Additional supporting information may be found online in the supporting information tab for this article.

COMMENTS

The authors have astutely analyzed the subsets of data from this ongoing multicenter prospective study and provided a succinct review of their findings. Their results further validate the accepted theory of BurstDR waveform activating the medial pathway, which is essentially responsible for emotional pain perception and expression. This manuscript further adds to the growing body of evidence around opioid use reduction using advanced neuromodulation modalities. Registries similar to TRIUMPH can be really helpful in not only studying the effectiveness of therapy but also can be pivotal in expanding the indications in our field of neuromodulation.

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From a Psychological point of view this publication adds further evidence to support the notion that pain-related catastrophizing is a dynamic construct that is related to pain intensity. This has been looked at previously in patients undergoing total knee arthroplasty. It will be interesting to see if this is a sustained effect at follow-up periods.

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This is a very significant large size prospective trial of NLB stimulation showing an efficacy that seems better than tonic stimulation. It would appear that such stimulation exerts its effects through the affective pathway of pain. This and other studies may lead to changes of programming SCS with improved outcome.

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