Received: April 6, 2017 Revised: July 4, 2017 Accepted: July 17, 2017

(onlinelibrary.wiley.com) DOI: 10.1111/ner.12684

Effective Relief of Pain and Associated Symptoms With Closed-Loop Spinal Cord Stimulation System: Preliminary Results of the Avalon Study

Marc Russo, MBBS FFPMANZCA*; Michael J. Cousins, MD, DSc†; Charles Brooker, MBBS‡§; Nathan Taylor, BSc(Med), MBBS¶; Tillman Boesel, MBBS, BMedSc (hons); Richard Sullivan, MBChB††; Lawrence Poree, MD, PhD‡‡; Nastaran Hesam Shariati, PhD§§; Erin Hanson, MPH§§; John Parker, PhD§§¶¶**

Objectives: Conventional spinal cord stimulation (SCS) delivers a fixed-input of energy into the dorsal column. Physiologic effects such as heartbeat, respiration, spinal cord movement, and history of stimulation can cause both the perceived intensity and recruitment of stimulation to increase or decrease, with clinical consequences. A new SCS system controls stimulation dose by measuring the recruitment of fibers in the dorsal column and by using the amplitude of the evoked compound action potentials (ECAPs) to maintain stimulation within an individualized therapeutic range. Safety and efficacy of this closed-loop system was evaluated through six-month postimplantation.

Materials and Methods: Chronic pain subjects with back and/or leg pain who were successfully trialed received a permanent system (Evoke; Saluda Medical, Sydney, Australia). Ratings of pain (100-mm visual analogue scale [VAS] and Brief Pain Instrument [BPI]), quality of life (EuroQol instrument [EQ-5D-5L]), function (Oswestry Disability Index [ODI]), and sleep (Pittsburgh Sleep Quality Index [PSQI]) were collected at baseline and repeated three and six months after implantation.

Results: Fifty-one subjects underwent a trial procedure; permanent implants were placed in 36 subjects. The proportion of subjects with $\geq$50% relief was 92.6% (back) and 91.3% (leg) at three months, and 85.7% (back) and 82.6% (leg) at six months. The proportion with $\geq$80% pain relief was 70.4% (back) and 56.5% (leg) at three months, and 64.3% (back) and 60.9% (leg) at six months. Statistically significant improvements in mean BPI, EQ-5D-5L, ODI, and PSQI were also observed at both time points.

Conclusions: The majority of subjects experienced profound pain relief at three and six months, providing preliminary evidence for the effectiveness of the closed-loop SCS system. The exact mechanism of action for these outcomes is still being explored, although one likely hypothesis holds that ECAP feedback control may minimize recruitment of Aβ nociceptors and Aδ fibers during daily use of SCS.

Keywords: back pain, closed loop, closed-loop, dose, Evoked Compound Action Potential (ECAP), feedback, feedback stimulation, leg pain, neuromodulation, Spinal cord stimulation

Address correspondence to: Erin Hanson, MPH, Saluda Medical Americas, Inc., Clinical Dept., 1350 American Boulevard E, Bloomington, MN 55325, USA. Email: erin.hanson@saludamedical.com

* Hunter Pain Clinic, Broadmeadow, New South Wales, Australia;
† Pain Management Research Institute and Kolling Institute, University of Sydney at the Royal North Shore Hospital, St Leonards, NSW, Australia;
‡ Department of Pain Medicine, Royal North Shore Hospital, St Leonards, NSW, Australia;
§ Northern Clinical School, University of Sydney, Sydney, NSW, Australia;
¶ Northern Private Pain Centre, St. Leonards, NSW, Australia;
** Inner West Pain Center, Newtown, NSW, Australia;
†† Precision Brain, Spine, and Pain Centre, Kew, VIC, Australia;
‡‡ University of California, San Francisco, CA, USA;
§§ Saluda Medical Pty Ltd., Artarmon, NSW, Australia; and
¶¶ Graduate School of Biomedical Engineering, University of New South Wales, Kensington, NSW, Australia

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

Source(s) of financial support: Saluda Medical provided funding for the study, statistical support in analyzing the data with input from Drs. Russo and Professor Cousins, and also provided funding for editorial support.

Conflict of Interest: Dr. Russo is a consultant for Saluda Medical; Professor Cousins is a consultant for Saluda Medical; Dr. Poree, PhD is a consultant for Saluda Medical; Parker, Hanson, and Shariati are employees of Saluda Medical. Dr. Brooker previously consulted for Sequirus. He also served as an investigator on sponsored research for Saluda Medical, Abbott, Medtronic, Phosphagenics and RRMedsciences. Drs. Boesel and Taylor have no relevant financial relationships to disclose.

INTRODUCTION

Spinal cord stimulation (SCS) has been used to provide relief from chronic pain for 50 years. Despite advances in the technology, reported success rates for traditional SCS have not improved significantly over the years (1) and the failure rate of SCS due to loss of efficacy in patients initially responsive to SCS remains at approximately 10.1–13.7% (2,3). Although there is recent evidence of improved pain reduction with newer stimulation paradigms (e.g., high-frequency, burst, and dorsal root ganglion [DRG] stimulation), little is still known about their mechanism(s) of action. The gate control theory (4) is used to explain much of what is currently understood, but that framework is not sufficient in isolation to describe all of the phenomena associated with SCS-induced pain relief, including paresthesia-free paradigms and the phenomenon of residual pain relief after cessation of stimulation (1).

Regardless of the stimulation paradigm, all currently-available SCS therapies have two common features: 1) they use a fixed-input configuration (i.e., constant waveform as defined by continuous and unchanging amplitude, pulse width, frequency, burst setting) in which input is delivered to the neural target without sensing or automatically adjusting to the nerve fibers' response to stimulation (also called open-loop stimulation); and 2) they impact the electrophysiological response of targeted neurons and such changes can be detected with carefully designed experiments and action potential recordings (5). Several studies have been conducted to understand the neurophysiology of SCS (see reviews in Refs. 1,6). When a sensory fiber is activated by a single stimulus of sufficient strength, it produces a single fiber action potential. The sum of single fiber action potentials responding to stimulation is an evoked compound action potential (ECAP). The ECAP amplitude grows as the stimulation current is increased and more fibers are recruited. ECAPs provide a directly quantifiable measure of the response of nerve fibers to stimulation, they can reveal a great deal about the neurophysiology and neuroanatomy of these fibers as well as potentially the pain relief experienced by SCS patients (Parker JL, Obradovic M, Shariati N et al. Evoked compound action potentials [ECAPs] reveal spinal cord dorsal column neuroanatomy. Neuroanatomy, Submitted for publication February 2017) (7).

In open-loop conventional SCS systems, patients manually adjust stimulation current to maintain coverage and to minimize over- and under-stimulation that occurs during posture changes. Specifically, postural movements change the distance between the stimulating electrodes and the dorsal column (8). Even small movements caused by breathing or the heartbeat result in changes in neural recruitment (9). With decreased distance between the spinal cord and the electrode comes an increase in the volume of tissue stimulated. This volume of tissue will contain a mix of fibers with varied excitability, including low threshold mechanosensory fibers, higher threshold Aβ nociceptors, and Aδ fibers. Higher threshold fibers are recruited as the lead moves closer to the dorsal columns and perceived as over-stimulation with side effects including uncomfortably strong paresthesia, paresthesia in unwanted areas, or muscle activation and/or cramping. Conversely, movements that increase the separation (distance) between the leads and the spinal cord may be perceived as insufficient stimulation with reduced pain relief. The result is that patients often decrease stimulation amplitude to avoid painful stimulation at the expense of optimized pain relief. Closed-loop SCS aims to avoids these issues by automatically adjusting stimulation input (current) to achieve constant neural recruitment.

A closed-loop SCS system has been developed and uses measured ECAPs as a feedback control mechanism to automatically maintain desired dorsal column fiber recruitment levels. The ECAP amplitude is compared to a set point (i.e., a comfortable patient-determined target level that provides optimal pain relief) in a feedback algorithm, and calculates a new stimulus amplitude by changing the input current (Fig. 1). This process is repeated for every stimulus, with the net result being continuously adjusted current that maintains a constant ECAP amplitude. Experience with animal models and human subjects to date has established the feasibility of

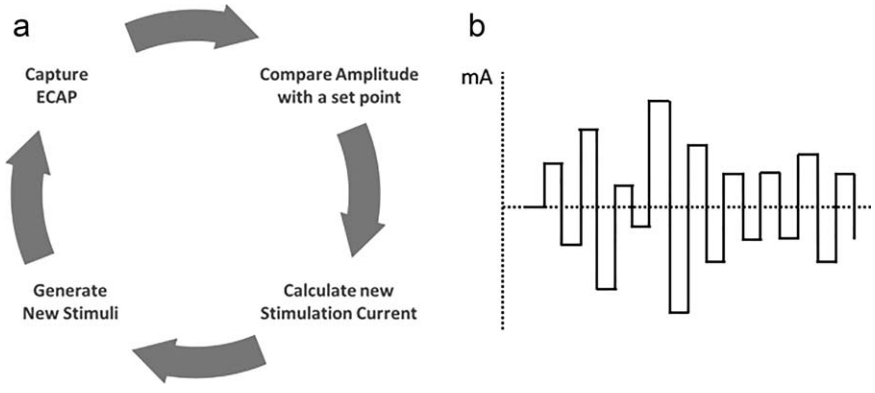

Figure 1. Visual representation of the closed-loop system (a). Input current showing dynamic changes in current amplitude with each pulse as measured in milliamps. The current amplitude may change significantly from pulse to pulse depending on the level of postural (and other physiologic) variations at the time, in an attempt to keep the feedback variable constant (b).

using ECAP measurements for feedback control in SCS (10,11). Clinical evidence has demonstrated that closed-loop SCS provides an improved experience in a temporary setting over fixed-input systems (12,13). For the patient, this means that the level of dorsal column recruitment (defined as the dose of stimulation) is better maintained within the therapeutic window or usage range—the range between their perception and discomfort thresholds (the threshold at which stimulation recruits the dorsal roots or Aβ nociceptors) (14–16). Most importantly, this feedback mechanism potentially allows the precision necessary to stimulate the low back without painful stimulation of the thoracic dorsal root entry zone. Thus, dose control is obtained using a novel waveform in which the ECAP recorded from the immediately preceding pulse informs the amplitude of the input current, which adjusts on every pulse, in real-time. The safety and performance of the closed-loop SCS system was evaluated in this prospective, multi-center, single-arm study.

METHODS

Subjects

Subjects were recruited from five clinical sites in Australia from August 2015 to September 2016 and gave their written informed consent. To be enrolled in the study, subjects had to be 18 or older; diagnosed with chronic pain of the back and/or legs that was refractory to conservative therapy for at least three months; and have had stable prescription pain medication dosage(s) for at least one month. Enrolled subjects experienced failed back surgery, radiculopathy, or other diagnoses including discogenic back pain/internal disc disruption, lumbar spondylosis, neuropathic pain, sciatica and gluteal tendinopathy, and possible lumbar spine defect.

Subjects were excluded if they had a contraindication to SCS; a medical, psychiatric, or social condition that was likely to interfere with study conduct or to confound data interpretation; addiction; or were pregnant or nursing. Subjects were also excluded if they were participating in another clinical study or involved in litigation regarding their pain condition.

Study Design and Data Collection

The Avalon Study was a prospective, multi-center, single-arm study. Study design and procedures aligned with international ethical and regulatory guidelines and were approved by local ethics committees prior to subject enrolment. The protocol was publicly registered as ACTRN12615000713594.

Baseline assessments included ratings of pain (100-mm visual analogue scale [VAS]) (17), impact of pain (Brief Pain Inventory [BPI]) (18), function (Oswestry Disability Index [ODI]) (19), sleep (Pittsburgh Sleep Quality Index [PSQI]) (20), and quality of life (EuroQol instrument [EQ-5D-5L]) (21). Subjects were asked to rate their pain intensity for their pain specific to the back and legs, and for overall pain. Adverse events were assessed throughout the study.

Assessments were repeated at the end of the trial period and at one, three, and six months postimplantation. At the time of writing, 31 subjects had completed the three-month visit and 32 subjects had completed their six-month follow-up visit.

Device and Implantation

The Evoke SCS system (Saluda Medical, Sydney, Australia) consists of a closed-loop rechargeable implantable pulse generator (closed loop stimulator [CLS]) and two 12-contact percutaneous leads with 7-mm contact-to-contact spacing. An external pulse generator (external closed loop stimulator [eCLS]) is used during the trial period.

Subjects were implanted with 12-contact trial leads in the epidural space over the dorsal column at the thoracic vertebral level associated with pain. Subjects used the external stimulator for up to 10 days (average seven days) to evaluate its effect. If deemed successful ($\geq$40% reduction in either baseline back, leg, or overall pain), subjects were given the option to receive a fully-implanted system. Programming was completed shortly thereafter and the subject was trained in using their remote control and charging system.

Evoke is the only SCS system with an integrated feedback control system. The recording electrode for measuring the ECAP can be any electrode not used for stimulation on either lead. Further, either or both leads may be used for stimulation. The ECAP elicited by the therapy pulses is sensed and the electrical signal is sampled and processed by the stimulator to measure the ECAP amplitude. For each patient, initial programming involves first optimizing the stimulation location by identifying appropriate electrodes, and then identifying the ECAP amplitude that delivers preferred pain coverage. Coverage of the painful area with paresthesia is not necessary for pain relief.

The range between a patient's perception of sensation at any location, and discomfort at any location is considered the therapeutic window for the desired operating amplitude. Perception of sensation varied from patient to patient, with some patients not conscious of stimulation. The device captures and stores ECAP amplitude data and these data can be analyzed to determine the percentage of time that stimulation was delivered within a patient's therapeutic window.

Data Management and Analysis

Throughout the study, data were captured on forms and were processed according to standard data management procedures. Periodic monitoring by an independent clinical research organization ensured data quality.

Questionnaire instruments were analyzed consistent with their validated methodology. Summary statistics were calculated as appropriate, including means, medians, standard errors of the mean and proportions, VAS data were presented as raw scores, percentage change from baseline, responders ($\geq$50% pain relief), and profound-responders ($\geq$80% pain relief). Subjects who reported significant ($\geq$60 mm) back pain at baseline, without significant ($>$60 mm) leg or foot pain, were analyzed as a separate "primary back pain" cohort. Hypothesis testing that the mean change from baseline was significantly different from 0 using paired *t*-tests and an alpha of 0.05 was performed in Minitab, Version 17 (Minitab, Inc., State College, PA, USA).

Efficacy outcome data were presented for the permanently implanted subjects only; safety data were presented for all enrolled subjects.

RESULTS

Subjects, Demographics, and Baseline Characteristics

A total of 51 subjects underwent a trial procedure. Of these, 49 (96.1%) completed the end-of-trial assessments and were evaluable. Forty-four (89.8%) of the 49 subjects with assessment data had a successful trial (40% reduction from baseline VAS rating) and 36 elected to move forward to implant (see Fig. 2).

Demographics and baseline characteristics of the cohort of subjects who underwent a trial procedure are presented in Table 1. Most

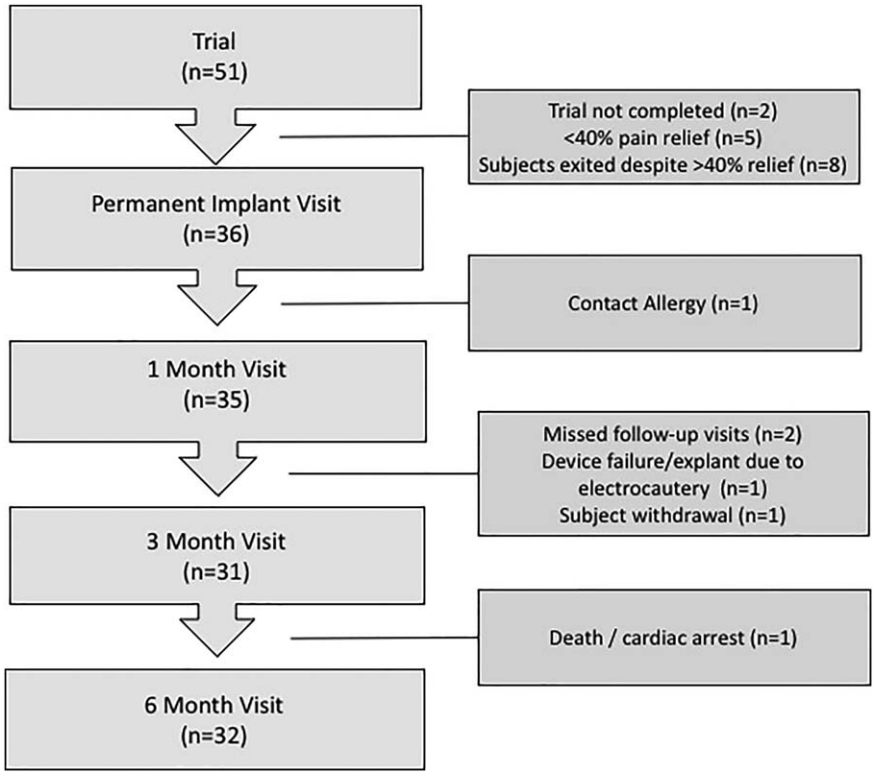

Figure 2. Subject progression through the study. Of the subjects receiving >40% pain relief but who were exited, reasons for exit included: One patient opted for back surgery; one patient was withdrawn by the investigator; one patient was unsatisfied with the stimulation as they received 50–60% relief; one patient decided to investigate other treatment options besides SCS; one subject did not like the sensation; 3 subjects had only axial back pain and received unwanted stimulation in legs.

subjects had persistent or recurrent pain following spinal surgery, and the majority of subjects reported the low back as the site of their most significant pain. Three subjects had used SCS previously.

Pain Relief Outcomes

Across all subjects, mean rating of back pain was 80.9 mm (± 1.8) at baseline. Back pain was reduced to 17.4 mm (± 3.3) after three months of treatment, a statistically significant mean reduction of 64.1 mm (± 3.5, $p < 0.0001$) and a mean percent reduction of 78.9% (± 3.9). After six months of treatment, back pain rating was reduced by 64.1 mm (± 3.6, $p < 0.0001$) and a mean percent reduction of 80.1% (± 4.3). At three months, the proportion of subjects who were back pain responders was 92.6%, and 70.4% of subjects were profound-responders (≥80% pain relief). At six months, 85.7% of patients were back pain responders, with 64.3% being classified as profound-responders. Individual subject responses for back pain at three and six months are shown in Fig. 3.

Mean ratings of leg pain were 76.3 mm (± 2.2) at baseline. Leg pain was reduced to 16.8 mm (± 3.8) after three months of treatment, a statistically significant mean reduction of 60.1 mm (± 4.4, $p < 0.0001$) and a mean percent reduction of 78.0% (± 4.9). After six months of treatment, leg pain rating was reduced by 59.6 mm (± 4.9, $p < 0.0001$) and a mean percent reduction of 77.4% (± 5.8). The proportion of subjects who were leg pain responders at three months was 91.3%, and 56.5% of subjects were profound-responders. At six months, 82.6% of patients were leg pain responders, with 60.9% being classified as profound-responders.

Mean ratings of overall pain were 81.0 mm (± 1.7) at baseline. Overall pain was reduced to 17.0 mm (± 2.8) after three months of treatment, a statistically significant mean reduction of 64.0 mm (± 2.9, $p < 0.0001$) and a mean percent reduction of 79.3% (± 3.3). After six months of treatment, overall pain rating was reduced by 64.3 mm (± 3.8, $p < 0.0001$) and a mean percent reduction of 78.9% (± 4.4). The proportion of subjects who were overall pain responders

Table 1. Baseline Demographics and Characteristics.

	Enrolled Subjects $N = 51$
Age (years) at enrolment	
Mean (SD)	56.7 (13.0)
Gender (n,%)	
Male	26 (51.0%)
Female	25 (49.0%)
Primary diagnosis (n, %)	
FBSS/FNSS	29 (56.9%)
Radiculopathy	10 (19.6%)
Other*	12 (23.5%)
Primary region of pain (n/N, %)	
Lower Back	37 (72.5%)
Leg	10 (19.6%)
Foot	4 (7.8%)
Prior History of SCS†	
Yes	3 (6.0%)
No	47 (94.0%)
Duration (years) of Pain	
Mean (SD)	13.6 (11.0)

*Other diagnoses: Discogenic back pain/internal disc disruption (n = 4), lumbar spondylosis (n = 3), neuropathic pain (n = 3), sciatica & gluteal tendinopathy (n = 1), and possible lumbar spine defect (n = 1).
†One subject reported prior history with neuromodulation but did not provide details on exact therapy; this subject is counted as missing for SCS therapy.

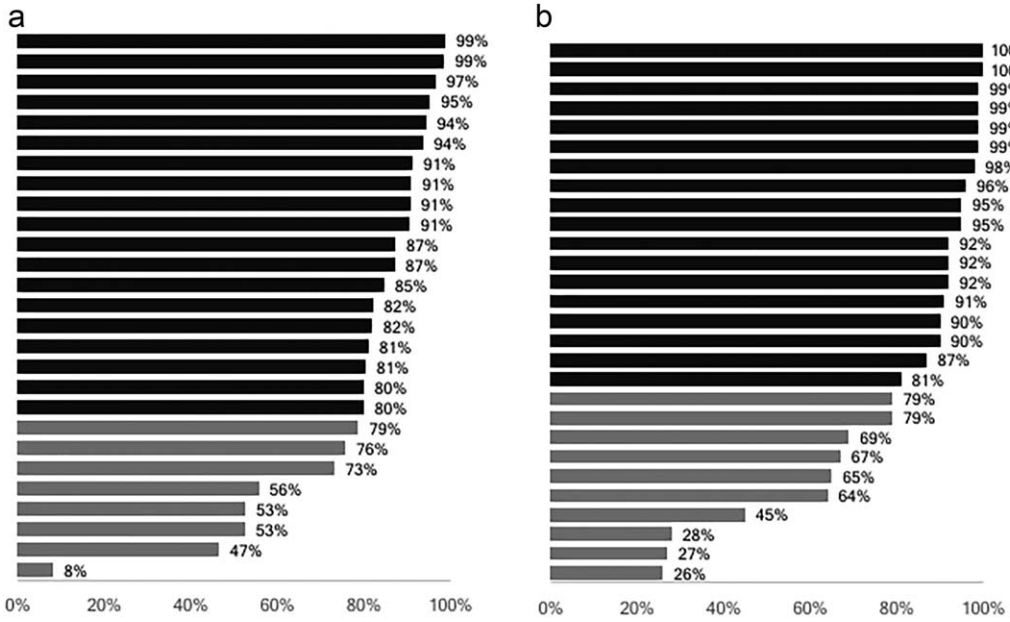

Figure 3. Individual subject responses for back pain VAS reduction at three months (a) and six months (b).

at three months was 93.5%, and 54.8% of subjects were profound-responders. At six months, 87.5% of patients were overall pain responders, with 62.5% being classified as profound responders. Back, leg, and overall pain outcomes are presented in Table 2 and Fig. 4.

Pain Relief Outcomes for Axial Back Pain Only

For the axial back pain only cohort (back pain without significant leg pain, $N = 9$), the mean rating of back pain was 78.2 mm (± 3.2) at baseline. Axial back pain was reduced to 13.4 mm (± 4.3) after three months of treatment and 11.1 mm (± 3.9) after six months of treatment, reductions of 82.9% (± 5.5) and 86.6% (± 4.1), respectively. The proportion of subjects who were responders at both three and six months was 100%, with 85.7% and 62.5% of subjects being classified as profound-responders, respectively.

For the same cohort, mean VAS rating of overall pain was 81.2 mm (± 3.8) at baseline. Primary back pain was reduced to 15.6 mm (± 6.1) after three months of treatment and 10.5 mm (± 3.8) after six months of treatment, reductions of 82.1% (± 6.5) and 87.8% (± 4.2), respectively. The proportion of subjects who

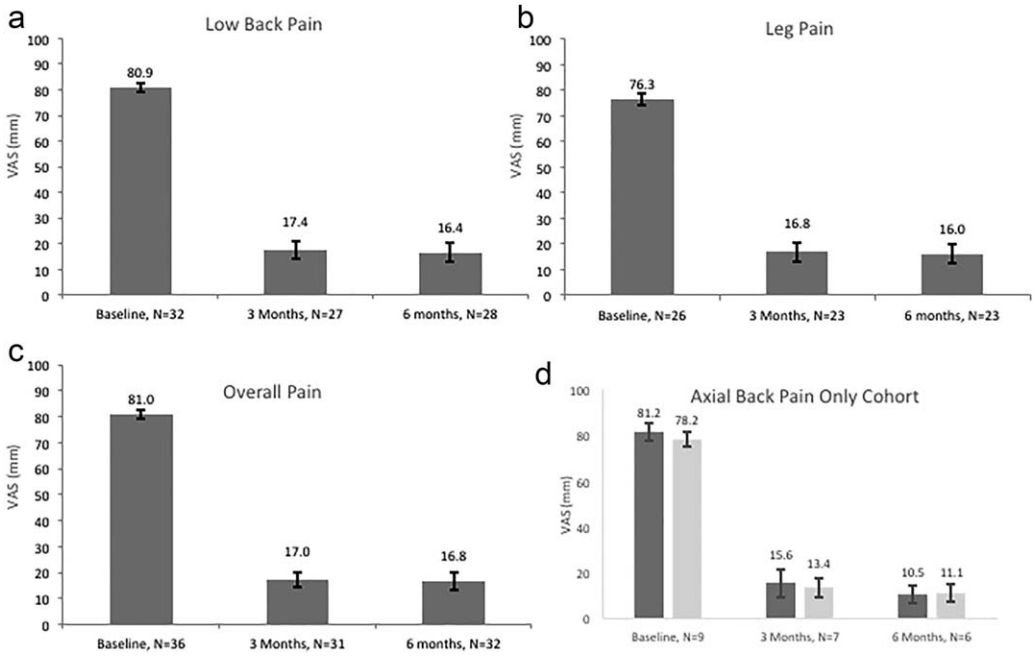

Figure 4. Mean VAS ratings over time for back (a), leg (b), and overall (c) pain. Mean VAS ratings over time for back and overall pain in the primary back pain cohort only (d). Error bars represent SEM.

Table 2. Summary of Back, Leg, and Overall Pain VAS Scores Over Time for Permanently-Implanted Subjects.

	Baseline	Three Months	Six Months
Back Pain			
N	32	27	28
Mean Raw VAS Score, mm (SEM)	80.9 (1.8)	17.4 (3.3)	16.4 (3.7)
Mean Percent Improvement in VAS Scores (SBM)	–	78.9% (3.9%)	80.1% (4.3%)
Mean Improvement in VAS Scores. mm (SEM, *p* value)		64.1 (3.5, $p < 0.0001$)	64.1 (3.6, $p < 0.0001$)
Proportion of subjects responding at ≥50% improvement	–	92.6%	85.7%
Proportion of subjects responding at ≥80% improvement	–	70.4%	64.3%
Leg Pain			
N	26	23	23
Mean Raw VAS Score, mm (SEM)	76.3 (2.2)	16.8 (3.8)	16.0 (3.8)
Mean Percent Improvement in VAS Scores (SEM)	–	78.0% (4.9%)	77.4% (5.8%)
Mean Improvement in VAS Scores. mm (SEM, *p* value)	–	60.1 (4.4, $p < 0.0001$)	59.6 (4.9, $p < 0.0001$)
Proportion of subjects responding at ≥50% improvement	–	91.3%	82.6%
Proportion of subjects responding at ≥80% improvement	–	56.5%	60.9%
Overall Pain			
N	36	31	32
Mean Raw VAS Score. mm (SEM)	81.0 (1.7)	17.0 (2.8)	16.8 (3.3)
Mean Percent Improvement in VAS Scores (SEM)	–	79.3% (3.3%)	78.9% (4.4%)
Mean Improvement in VAS Scores. mm (SEM, *p* value)	–	64.0 (2.9, $p < 0.0001$)	64.3 (3.8, $p < 0.0001$)
Proportion of subjects responding at ≥50% improvement	–	93.5%	87.5%
Proportion of subjects responding at ≥80% improvement	–	54.8%	62.5%

were responders at both three and six months was 100%, with 71.4% and 87.5% of subjects being classified as profound-responders (Table 3 and Fig. 5).

Secondary Outcomes

BPI, EQ-5D-5L, ODI, and PSQI all showed statistically significant improvements at both three and six months, compared to baseline. Six-month outcomes are described below, and all outcomes can be found in Table 4 and Fig. 5. The mean BPI severity was 6.7 (± 0.19) at baseline and 2.8 (± 0.37) at six months, a statistically significant mean change of 3.8 (± 0.34 $p < 0.0001$). The mean BPI interference score was 7.3 (± 0.22) at baseline and 3.0 (± 0.49) at six months, a statistically significant mean change of 4.2 (± 0.46, $p < 0.0001$). The mean EQ-5D-5L score was 0.422 (± 0.0363) at baseline and 0.714 (± 0.0365) at six months a statistically significant mean change of 0.282 (± 0.0412, $p < 0.0001$). The mean ODI score was 52.3 (± 2.2) at baseline and 30.4 (± 3.2) at six months, a statistically significant mean change of 21.1 (± 2.7, $p < 0.0001$). At baseline, 19.5% of subjects rated themselves as minimally or moderately disabled on the ODI; at six months, this proportion increased to 73.3%. The mean PSQI score was 12.5 (± 0.68) at baseline and 8.4 (± 0.88) at six

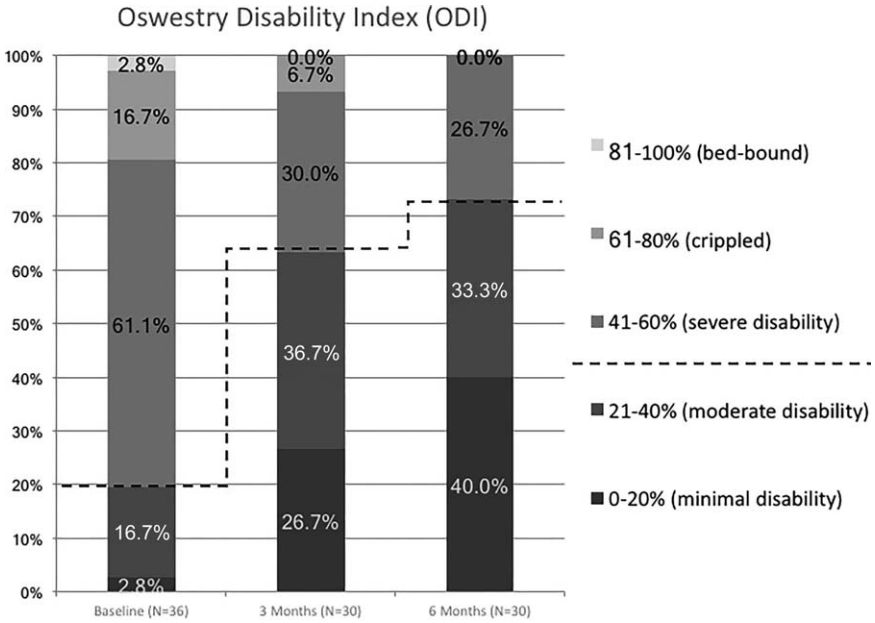

Figure 5. Proportion of subjects reporting each level of disability on the ODI at baseline, three months, and six months.

Table 3. Summary of Back and Overall Pain VAS Scores Over Time for Subjects With Axial Back Pain Only.

	Baseline	Three Months	Six Months
Back Pain			
N	9	7	8
Mean Raw VAS Score, mm (SEM)	78.2 (3.2)	13.4 (4.3)	11.1 (3.9)
Mean Percent Improvement in VAS Scores (SEM)	–	82.9% (5.5%)	86.6% (4.1%)
Proportion of subjects responding at ≥50% improvement	–	100%	100%
Proportion of subjects responding at ≥80% improvement	–	85.7%	62.5%
Overall Pain			
N	9	7	8
Mean Raw VAS Score, mm (SEM)	81.2 (3.8)	15.6 (6.1)	10.5 (3.8)
Mean Percent Improvement in VAS Scores (SEM)	–	82.1% (6.5%)	87.8% (4.2%)
Proportion of subjects responding at ≥50% improvement	–	100%	100%
Proportion of subjects responding at ≥80% improvement	–	71.4%	87.5%

months, a statistically significant mean change of 4.0 (± 0.8, $p < 0.0001$). Seventy-one percent (71.0%) of subjects at three months and 62.5% of subjects at three months had a clinically meaningful change in PSQI score (≥3 point reduction (22)) compared to baseline. After three and six months of treatment, 96.8% and 75.1% of subjects, respectively, rated themselves as "satisfied" or "very satisfied" with their treatment.

Closed-Loop Feedback Stimulation

During therapeutic stimulation, ECAPs were captured (Fig. 6) and amplitudes were filtered and processed by the stimulator; the amplitude was measured and converted into a single feedback variable, or neural recruitment target measured in uV, which was used as the target to automatically adjust stimulation amplitude in a closed-loop feedback system.

For feasibility purposes, device data for 10 subjects at the three-month follow-up and 15 subjects at the six-month follow-up were retrieved to identify the proportion of time that therapy was delivered within their therapeutic window. Subjects spent a mean of 72.6% (± 34.8) and 83.8% (± 21.4), respectively, of their time with stimulation amplitude in their therapeutic window.

Safety Outcomes

At the time of this report, two (3.9%) serious adverse events (SAEs) related to the study/device were reported. One subject developed a contact allergy to the titanium used in the implanted components, and second subject experienced severe new low back pain during the trial. Both SAEs resolved with treatment and subsequent system explant.

The most commonly occurring complications and side effects were implant site issues (such as irritation, pruritus, seroma, wound dehiscence) (eight events in six subjects; 6/51 [11.8%]), implant site tenderness/pain (6 events in 6 subjects; 6/51 [11.8%]) and lead migration (5 events in 4 subjects; 4/51 [7.8%]). One lead migration occurred during the trial phase. No infections were reported. None of these adverse events (AEs) were determined to be related to the feedback control mechanism (see Table 5). AEs were similar in nature and frequency to those seen with traditional SCS systems (23).

DISCUSSION

This prospective, multi-center, single-arm study intended to characterize safety, pain relief, and associated outcomes with a new SCS

Table 4. Summary of Secondary Outcomes Over Time.

	Baseline	Three Months	Six Months
BPI			
N	36	31	32
Mean severity score (SEM)	6.7 (0.19)	2.8 (0.33)	2.8 (0.37)
Mean change from baseline. severity score (SEM, *p* value)	–	3.9 (0.27, $p < 0.0001$)	3.8 (0.34, $p < 0.0001$)
Mean interference score (SEM)	7.3 (0.22)	3.3 (0.48)	3.0 (0.49)
Mean change from baseline. interference score (SEM)	–	3.9 (0.45, $p < 0.0001$)	4.2 (0.46, $p < 0.0001$)
EQ-5D-5L			
N	36	31	32
Mean EQ index score (SEM)	0.422 (0.0363)	0.658 (0.0376)	0.714 (0.0365)
Mean change from baseline - EQ index score (SEM, *p* value)	–	0.234 (0.0474, $p < .0001$)	0.282 (0.0412, $p < 0.000l$)
ODI			
N	36	30	30
Mean ODI score (SEM)	52.3 (2.2)	33.6 (2.8)	30.4 (3.2)
Mean change from baseline - final score (SEM)	–	17.9 (2.2, $p < 0.0001$)	21.1 (2.7, $p < 0.0001$)
PSQI			
N	36	31	32
Mean PSQI Score (SEM)	12.5 (0.68)	8.1 (0.81)	8.4 (0.88)
Mean change from baseline - global score (SEM)	–	4.2 (0.77, $p < 0.0001$)	4.0 (0.8, $p < 0.0001$)

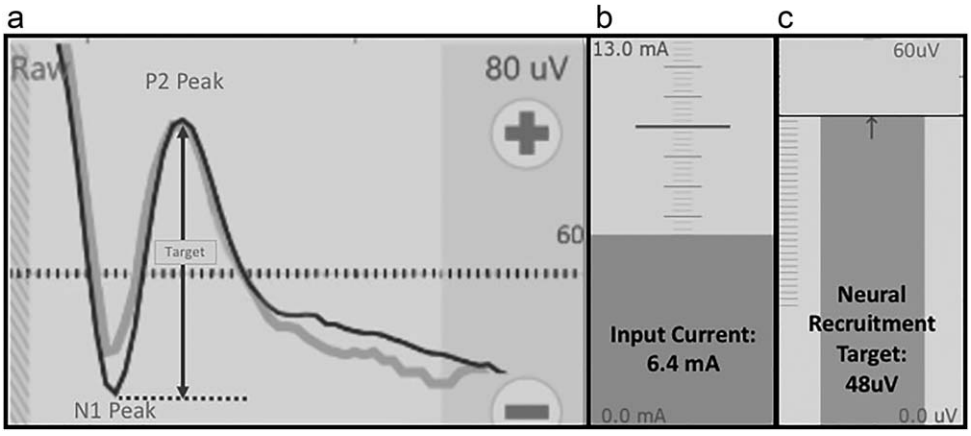

Figure 6. Sample ECAP: (a) ECAP Window Showing N1 and P2 peaks of an ECAP signal, (b) Input Current (mA), (c) Neural recruitment target (uV). During therapeutic stimulation, ECAP amplitude is continually measured and compared against the target. Thus, the input current on each pulse is automatically adjusted in a proportional fashion using a feedback algorithm, which maintains the ECAP amplitude at the patient's preferred "target."

system that employs closed-loop feedback control using ECAPs. The study enrolled a cohort of subjects with demographics consistent with the larger population undergoing neuromodulation (24). Conversion rate from trial to permanent system was also consistent with recent studies of modern SCS waveforms (25–29).

All subjects in this trial utilized the closed-loop feedback setting in the SCS system. Closed-loop feedback is a unique feature that automatically adjusts stimulation charge input to maintain neural recruitment at the predefined target, thereby delivering therapy that is consistently held within the therapeutic window. The pain relief experienced across this cohort of subjects was extensive: approximately 80% in the back, leg, and overall pain at three and six months. These results, both independently and when viewed in light of other recent SCS studies, suggest that closed-loop SCS is feasible, and this novel therapy has the potential to provide significant pain relief (23,28). Responder rates in this study were quite high, with more than 80% of subjects achieving 50% or better pain relief in the back, legs, and overall at six months. When identifying profound-responders as those receiving $\geq$80% pain relief, greater than 60% of subjects were profound-responders ($\geq$80% pain relief) at six months for back and leg pain, respectively. The choice to define a "profound-responder" population stems from the findings of the IMMPACT Guidelines (2008) which encourages future research to analyze reduction to lower pain intensity ratings for treatment success (30). By defining a "profound-responder" as achieving $\geq$80% pain relief, it is possible to identify patients who have achieved a level of mild pain (pain score of 1–3) that is "associated with less interference with physical and emotional function than higher ratings" (27). Given that subjects in this trial are required to have a baseline pain score of at least 6, a reduction from a baseline level of 7.5 to 1.5 (i.e., midpoint of the range from "no pain" to "mild pain" score) corresponds to an 80% reduction. There are other interventional pain medicine publications that establish a threshold level of pain reduction well more than 50%, in response to therapy. Kumar et al. (2008) identified 22% of patients who received SCS therapy achieved $\geq$80% pain relief (23). In the SENZA study, Kapural et al. (31) (2015) defined the population of patients achieving pain scores of $\leq$2.5 as remitters. It should be noted, of course, that data from these randomized, controlled trials have noncomparable statistical assumptions. Nevertheless, the outcomes presented herein suggest that closed-loop SCS may be a highly effective intervention.

Table 5. Adverse Event Rates.

Adverse Event Rates	Events *N*	Subjects *N* (%)
Study-Related SAEs	2	2/51 (3.9%)
Feedback-Related SAEs	0	0/51 (0%)
Unanticipated Adverse Device Effects	0	0/51 (0%)

Another notable feature of the pain outcomes in this study was the similarity of pain relief achieved in the back and the legs: the average reduction at six months was 80.1% for the former and 77.4% for the latter, and in fact, more subjects had 80% pain reduction in the back than did in the legs. It is generally accepted that leg pain is more amenable to SCS treatment than back pain, and thus greater reductions in leg pain are expected (for example, (23)). These outcomes demonstrating that back pain may be equally ameliorated by closed-loop feedback SCS suggest that this technology may allow more complete recruitment of back-specific dorsal column fibers than other systems. In the small subset of subjects with axial back pain only, there was an 86.6% reduction in back pain at six months. Overall, these outcomes are in contrast to the historical findings in the SCS literature, which indicate the difficulty in treating isolated back pain. For example, a multi-center study of high-frequency SCS reported approximately 49% pain relief in the back after six months of treatment (32).

Patient-reported outcomes of associated symptoms also showed significant improvements. For example, at baseline, 80.6% of subjects reported functional capacity on the ODI consistent with having a severe disability or worse condition. After six months of treatment, this proportion was reduced by two-thirds to 26.7%. Similarly, the pain interference and pain severity (BPI) showed a clinically significant improvement (33) with treatment, and the majority of subjects had a clinically meaningful improvement in sleep as measured by the PSQI (22). At baseline, mean EQ-5D scores (0.422) were much lower than the Australian population norm of 0.87 (34). After six months of treatment; however, mean scores had improved to 0.714. Additionally, more than 75% of subjects were satisfied or very satisfied with treatment.

The types and rates of adverse events in this study were within the expected ranges for this intervention and there were no reported AEs related to the closed-loop mechanism of the stimulator itself.

The conclusions that can be drawn from this report are limited by both the fact that the study did not employ a control group, and that the follow-up period is only six-months. A report of the long-term outcomes is planned, and preliminary data from early-enrolled subjects indicates that the trends reported here are durable. Further, the Evoke SCS system is currently being evaluated in a randomized, controlled, double-blind study in the United States. This study evaluates stimulation-naïve patients randomized and blinded to either conventional SCS or SCS with feedback (i.e., closed-loop SCS), with the primary endpoint being the percentage of patients with a reduction in pain of $\geq$50% with no increase in pain medication usage (clinicaltrials.gov ID #: NCT02924129).

Subjects receiving feedback control stimulation afforded by this SCS system experienced excellent pain relief and associated outcomes. Because the amplitude of each stimulation pulse is automatically adjusted based on the neural recruitment target, it is highly likely that the overall pain coverage, i.e., tolerable paresthesias or absence of pain in the location of reported pain, remains within an optimal range for each subject. Maintaining the recruitment levels, or dose, within the therapeutic window is important for achieving therapeutic levels of stimulation as well as for avoiding the discomfort of over-stimulation and the cessation of therapy due to under-stimulation (14,15). Closed-loop feedback SCS results in more time spent with amplitudes maintained within the therapeutic window than standard open-loop SCS (12).

In open-loop, conventional SCS systems, physiological changes such as heartbeat, respiration, and CSF flow, along with postural changes result in increased stimulation intensity as well as recruitment of nociceptors and potentially dorsal roots leading to aversive sensations. A key advantage of the closed-loop feedback-based SCS system may be its prevention or limitation of stimulation amplitudes reaching the high levels required to recruit Aβ nociceptors. This may result in a more comfortable therapy and may have an overall modulating effect on the frequency-based central sensitization by avoiding recruitment of the nociceptive pathways. Further study is required to better understand the neurophysiology of the nerve fibers affected by SCS.

CONCLUSIONS

ECAPs are a directly quantifiable measure of the response of nerve fibers to stimulation that can be used to maintain stimulation intensity within a therapeutic range of programming parameters that have the highest likelihood of achieving pain relief. In this study, stimulation with a closed-loop feedback SCS system employing real-time ECAP assessment resulted in profound pain relief and reduction in associated symptoms. The exact mechanism of action for these outcomes is still being explored; however, a key potential component of this mechanism may involve the Aβ nociceptor. The outcomes observed in this study could likely be the result of the closed-loop system maintaining stimulation dosage at therapeutic levels. Further study is required to confirm that the improved efficacy is the result of limiting the activation or potential windup of Aβ nociceptors in the dorsal column. Further research is required to continue to evaluate the efficacy of this novel therapy as well as elicit more information about the neuropathology of chronic neuropathic pain in the spine and the precise mechanisms of action of spinal cord stimulation. A multicenter, double-blind, randomized controlled trial is currently underway in the United States (clinicaltrials.gov ID #: NCT02924129).

Acknowledgements

The authors would like to thank the following for their dedication to the study and attention to detail in collecting data: Dominic Bailey and the team at Genesis Research, Linda Critchley and the team at Royal North Shore Hospital Pain Management and Research Centre, Tom Perkins at Precision Brain Spine and Pain Centre, and Rosemary Kingston at Inner West Pain Centre. In addition, the authors would like to acknowledge Dr. Martine O'Neill, Dr. Rebecca Martin, Dr. Lewis Holford, and Professor Peter Teddy for the contribution to enrollment. Thank you to Dr. Robert M. Levy, PhD for his review of the manuscript.

Authorship Statements

Drs. Russo, Brooker, Taylor, Sullivan, and Boesel conducted the study, including patient recruitment, data collection, and interpretation of the data. Professor Cousins performed all previous tasks and assisted with study design and provided key input into the interpretation of the data. Dr. Russo also provided key input into the interpretation of the data [Correction added on 19 October 2017 after first online publication: the duplicated word "provided"after "Dr. Russo" has been deleted to correct the sentence.]. Dr. Poree is the medical monitor for the study and helped with the interpretation of the results and had key input into the text of the manuscript. Drs. Parker, Shariati, and Erin Hanson had significant contributions including drafting original text, analysis of data, and protocol design. All authors approved the final manuscript. Dr. Russo had complete access to the study data.

How to Cite this Article:

Russo M., Cousins M.J., Brooker C., Taylor N., Boesel T., Sullivan R., Poree L., Shariati N.H., Hanson E., Parker J. 2018. Effective Relief of Pain and Associated Symptoms With Closed-Loop Spinal Cord Stimulation System: Preliminary Results of the Avalon Study.
Neuromodulation 2018; 21: 38–47

REFERENCES

1. Zhang TC, Janik JJ, Grill WM. Mechanisms and models of spinal cord stimulation for the treatment of neuropathic pain. *Brain Res* 2014;1569:19–31.
2. Van Buyten J-P. *International spinal cord stimulation effectiveness study reveals longer-term outcomes of the therapy in 956 implants*. 19th Annual Meeting, North American Neuromodulation Society, Las Vegas, NV, January 2017.
3. Hayek SM, Veizi E, Hanes M. Treatment-limiting complications of percutaneous spinal cord stimulator implants: a review of eight years of experience from an academic center database. *Neuromodulation* 2015;18:603–609.
4. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965;150:971–979.
5. Parker J. *Effect of frequency on the recruitment of dorsal column fibers*. Edinburgh, Scotland: INS, 2017.
6. Linderoth B, Foreman RD. Physiology of spinal cord stimulation: review and update. *Neuromodulation* 1999;2:150–164.
7. Parker JL, Karantonis DM, Single PS et al. *Spinal cord potentials during neuromodulation for pain relief* [PH 445]. 14th World Congress on Pain, IASP. Milan, Italy, August 2012.
8. Holsheimer J, den Boer JA, Struijk JJ, Rozeboom AR. MR assessment of the normal position of the spinal cord in the spinal canal. *Am J Neuroradiol* 1994;15:951–959.
9. Figley CR, Stroman PW. Investigation of human cervical and upper thoracic spinal cord motion: implications for imaging spinal cord structure and function. *Magn Reson Med* 2007;58:185–189.
10. Parker JL, Karantonis DM, Single PS et al. Electrically evoked compound action potentials recorded from the sheep spinal cord. *Neuromodulation* 2013; 16:295–303.
11. Parker JL, Karantonis DM, Single PS, Obradovic M, Cousins MJ. Compound action potentials recorded in the human spinal cord during neurostimulation for pain relief. *Pain* 2012;153:593–601.

12. Kapural L, Parker JL, Obradovic M et al. *Direct assessment of dorsal column activity with electrically evoked compound action potentials (ECAPs) as a marker for patient outcomes*. 19th Annual Meeting, North American Neuromodulation Society, Las Vegas, NV, December 2015.
13. Rosen S, Parker JL, Obradovic M et al. *Randomized double-blind crossover study examining the safety and effectiveness of closed-loop control in spinal cord stimulation*. 19th Annual Meeting, North American Neuromodulation Society, Las Vegas, NV, December 2015.
14. North RB. Neural interface devices: spinal cord stimulation technology. *Proc IEEE* 2008;96:1108–1119.
15. Holsheimer J. Effectiveness of spinal cord stimulation in the management of chronic pain: analysis of technical drawbacks and solutions. *Neurosurg* 1997;40:990–999.
16. Djouhri L, Lawson SN. A [beta]-fiber nociceptive primary afferent neurons: a review of incidence and properties in relation to other afferent A-fiber neurons in mammals. *Brain Res Rev* 2004;46:131–145.
17. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain* 1983; Sep17:45–56.
18. Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the brief pain inventory for chronic nonmalignant pain. *J Pain* 2004;5:133–137.
19. Fairbank JC, Pynsent PB. The Oswestry Disability Index. *Spine* 2000;25:2940–2952; discussion 2952.
20. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
21. EuroQol Group. EuroQol–a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.
22. Buysse DJ, Germain A, Moul DE et al. Efficacy of brief behavioral treatment for chronic insomnia in older adults. *Arch Intern Med* 2011;171:887–895.
23. Kumar K, Taylor RS, Jacques L et al. The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. *Neurosurgery* 2008;63:762–770.
24. Taylor RS, Desai MJ, Rigoard P, Taylor RJ. 2014. Predictors of pain relief following spinal cord St.pdf [Internet]. http://onlinelibrary.wiley.com.ezproxy1.library.usyd.edu.au/store/10.1111/papr.12095/asset/papr12095.pdf?v=1&t=ij0n15m0&s=f321a97247d4bac7c944dfe641f49044715cd271. Accessed 5 January 2016.
25. Chagoya G. Abstract 816. [Internet]. 82nd Annual Meeting, American Association of Neurological Surgeons (AANS), San Francisco, CA, April 2014. http://www.medscape.com/viewarticle/824021
26. Murphy KR, Han JL, Hussaini SMQ et al. The volume-outcome effect: impact on trial-to-permanent conversion rates in spinal cord stimulation. *Neuromodulation* 2016;20:256–262. http://doi.wiley.com/10.1111/ner.12526. Accessed 13 March 2017.
27. De Ridder D, Lenders MWPM, 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.
28. Kapural L, Yu C, Doust MW et al. Comparison of 10-kHz high-frequency and traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain: 24-month results from a multicenter, randomized, controlled pivotal trial. *Neurosurgery* 2016;79:667–677.
29. Deer TR, Levy RM, Kramer J et al. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. *Pain* 2016;158:669–681.
30. Dworkin RH, Turk DC, Wyrwich KW et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 2008;9:105–121.
31. 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.
32. Russo M, Verrills P, Mitchell B, Salmon J, Barnard A, Santarelli D. High frequency spinal cord stimulation at 10 kHz for the treatment of chronic pain: 6-month Australian clinical experience. *Pain Physician* 2016;19:267–280.
33. Cleeland.pdf [Internet]. http://www.immpact.org/static/meetings/Immpact4/background/Cleeland.pdf. Accessed 10 February 2017.
34. Clemens S, Begum N, Harper C, Whitty JA, Scuffham PA. A comparison of EQ-5D-3L population norms in Queensland, Australia, estimated using utility value sets from Australia, the UK and USA. *Qual Life Res* 2014;23:2375–2381.

COMMENTS

Closed loop amplitude adjustment based upon evoked potentials is an exciting addition to the technology available clinically for spinal cord stimulation; the authors are to be congratulated for developing it. They point out correctly that the present study, a case series that lacks controls, does not provide high-level evidence; a randomized, controlled trial (RCT) of open vs. closed loop stimulation is forthcoming. The impressive results reported here, particularly for axial low back pain, deserve to be reproduced in a controlled setting.

Implicit in this methodology is the titration of stimulation amplitude along the scale from perceptual to discomfort (or even motor) threshold, which is well established for paresthesia-based stimulation (1). Perhaps it also will be applicable, if only indirectly, to paresthesia free stimulation, for which scaling amplitude is surely of some importance, even if therapeutic ranges are different.

Automatic amplitude adjustment has been available for several years using acceleration (and thus body position) rather than an evoked neural response (2). It would be interesting to compare the performance of these two approaches. The forthcoming RCT will compare automatic adjustment with conventional adjustment by the patient, who can close the loop manually (and by changing posture). Although some patients may prefer manual mode as an option, no patient can respond rapidly enough to compensate for all perturbations (heartbeat, unexpected movement, etc.), and so a significant clinical role is foreseeable for this new technology.

Richard B. North, MD
Baltimore, MD, USA

REFERENCES

1. Law JD, Miller LV. Importance and documentation of an epidural stimulating position. *Appl Neurophysiol* 1982;45(4–5):461–464.
2. Schade CM, Schultz DM, Tamayo N, Iyer S, Panken E. Automatic adaptation of neurostimulation therapy in response to changes in patient position: results of the Posture Responsive Spinal Cord Stimulation (PRS) research study. *Pain Physician* 2011;14(5):407–417.

***

This interesting study is another step towards development of a SCS system with self-control based on feedback from the CNS. It is too early to proclaim success but with the early results from the new closed-loop system we are moving in the right direction.

Y. Eugene Mironer, MD
Spartanburg, SC, USA

***

The article is a company driven research paper produced by consultants and employees of a company. There is nothing wrong with that but it needs extra attention.

A closed loop spinal cord stimulation system is tested in a not very well selected group of patients with some form of low back pain and sciatica. The closed loop system is supposed to keep the stimulation within a theoretical therapeutic range by adjusting the current amplitude. Some information is give about the mode of stimulation (frequency, pulse wave, average amplitude) produced by the Evoke pulse generator. Two 12 electrode leads should be implanted. One lead is implanted only to record the evoked compound action potentials; this is a disadvantage of this system.

The primary purpose of this clinical study was to show the feasibility of using a closed-loop SCS system for the treatment of back and/or leg pain. The results of this study demonstrate that closed-loop SCS system might be one of the treatment options in selected patients in the future. However, we have to wait for long-term observation with this system.

Maarten van Kleef, MD, PhD
Maastricht, The Netherlands

Comments not included in the Early View version of this paper.

