

Marc Russo, MBBS, DA*
 Charles Brooker, MBChB^{‡§}
 Michael J. Cousins, MD,
 DSc^{‡§}
 Nathan Taylor, MBBS^{‡§}
 Tillman Boesel, MBBS[¶]
 Richard Sullivan, MBChB^{||}
 Lewis Holford, MBChB^{‡§}
 Erin Hanson, MPH[#]
 Gerrit Eduard Gmel, PhD[#]
 Nastaran Hesam Shariati,
 PhD[#]
 Lawrence Poree, MD, PhD^{**}
 John Parker, PhD^{##}

*Hunter Pain Clinic, Broadmeadow, Australia; [‡]MJC Pain Management and Research Centre, St. Leonards, Australia; [§]Northern Pain Centre, St. Leonards, Australia; [¶]Inner West Pain Center, Newtown, Australia; ^{||}Precision Brain, Spine, and Pain Centre, Kew, Australia; [#]Saluda Medical Pty Ltd, Artarmon, Australia; ^{**}University of California at San Francisco, California; ^{##}Graduate School of Biomedical Engineering, University of New South Wales, Kensington, Australia

This work has been previously presented as a podium and ePoster at the 22nd Annual Scientific Meeting of the North American Neuromodulation Society on January 17-20, 2019, in Las Vegas, Nevada. Brooker C, Cousins MJ, Russo M, et al. Effective relief of pain and associated symptoms with closed-loop SCS: long-term results.

Correspondence:

Gerrit Eduard Gmel, PhD,
 Saluda Medical Pty Ltd,
 407 Pacific Hwy,
 Artarmon 2064, Australia.
 Email: gerrit.gmel@saludamedical.com

Received, April 22, 2019.

Accepted, November 22, 2019.

Published Online, February 5, 2020.

© Congress of Neurological Surgeons
 2020.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Sustained Long-Term Outcomes With Closed-Loop Spinal Cord Stimulation: 12-Month Results of the Prospective, Multicenter, Open-Label Avalon Study

BACKGROUND: Spinal cord stimulation (SCS) activates the dorsal column fibers using electrical stimuli. Current SCS systems function in fixed-output mode, delivering the same stimulus regardless of spinal cord (SC) activation.

OBJECTIVE: To present long-term outcomes of a novel closed-loop SCS system that aims to maintain the SC activation near a set target level and within a therapeutic window for each patient. SC activation is measured through the evoked compound action potential (ECAP) generated by each stimulus pulse.

METHODS: Fifty patients with lower back and/or leg pain who were successfully trialed received a permanent system (Evoke; Saluda Medical, Sydney, Australia). Ratings of pain (visual analog scale), quality of life, function, sleep, and medication use were collected at baseline and at each visit. SC activation levels were reported in summary statistics. The therapeutic window for each individual patient was defined as the range of ECAP amplitudes between sensation threshold and uncomfortably strong stimulation.

RESULTS: At 12 mo, the proportion of patients with $\geq 50\%$ relief was 76.9% (back), 79.3% (leg), and 81.4% (overall), and the proportion with $\geq 80\%$ pain relief was 56.4% (back), 58.6% (leg), and 53.5% (overall). Patients spent a median of 84.9% of their time with stimulation in their therapeutic window, and 68.8% (22/32) eliminated or reduced their opioid intake. Statistically significant improvements in secondary outcomes were observed.

CONCLUSION: The majority of patients experienced more than 80% pain relief with stable SC activation, as measured by ECAP amplitude at 12 mo, providing evidence for the long-term effectiveness of the Evoke closed-loop SCS system.

KEY WORDS: Action potentials, Back pain, Chronic pain, Electric stimulation, Feedback, Pain management, Spinal cord stimulation

Neurosurgery 87:E485–E495, 2020

DOI:10.1093/neuros/nyaa003

www.neurosurgery-online.com

Spinal cord stimulation (SCS) is an established therapy that has been used to provide relief from chronic neuropathic pain for over 50 yr.¹ Although the mechanisms of action of SCS are not fully understood, a vast amount of evidence suggests that it acts by activating the dorsal column fibers, which, in turn, inhibit pain processing in the dorsal horn.²

All currently available commercial SCS systems still operate in a fixed-output stimulation configuration (eg, fixed frequency, fixed pulse width, fixed amplitude, and fixed pulse train) regardless of the neural activation of the spinal cord (SC) fibers. These fixed-output (or open-loop) systems do not account for the large variation of electrical field strength and,

ABBREVIATIONS: BPI, Brief Pain Inventory; CLS, closed-loop stimulator; eCLS, external closed-loop stimulator; ECAP, evoked compound action potential; EQ-5D-5L, EuroQol instrument; FBSS, failed back surgery syndrome; FNSS, failed neck surgery syndrome; MME, morphine milligram equivalents; ODI, Oswestry Disability Index; PSQI, Pittsburgh Sleep Quality Index; SAE, serious adverse event; SC, spinal cord; SCS, spinal cord stimulation; SD, standard deviation; SEM, standard error of the mean; TW, therapeutic window; VAS, visual analog scale

Neurosurgery Speaks! Audio abstracts available for this article at www.neurosurgery-online.com.

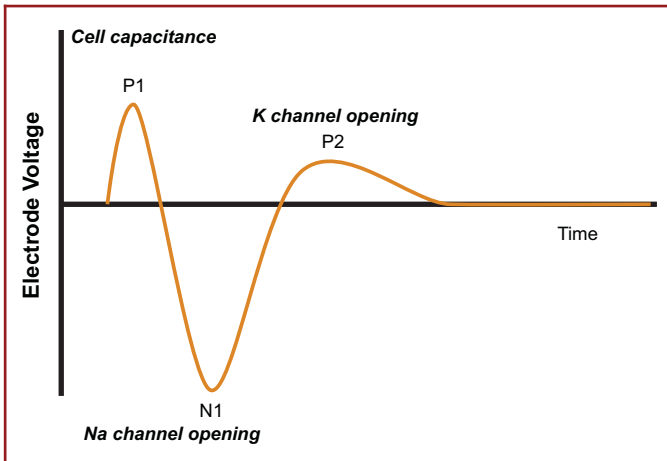


FIGURE 1. Schematic representation of an ECAP. ECAPs have a well-defined shape with 3 peaks: 2 positive and 1 negative, labeled P1, N1, and P2, in order of appearance. In simple terms, they are the combined electrical field generated by the action potentials of stimulated fibers at the recording site. The first P1 peak stems from capacitive coupling between the inside and outside of the fibers and is caused by the incoming action potential. The N1 and P2 peaks result from ionic flow (sodium [Na⁺] and potassium [K⁺]) in and out of the fibers that form the well-known action potential. As the measurement is done outside of the fibers, the polarity of the peaks is reversed compared with intracellular recordings often depicted in textbooks. ECAP, evoked compound action potential.

subsequently, volume of tissue stimulated that occurs because of changes in the distance between the electrode and SC from normal physiological activity (eg, breathing and heartbeat) and movement.³⁻⁵ Changes in stimulation strength lead to variable activation of the SC and, thus, variable inhibition of pain processing pathways.

Each suprathreshold stimulus elicits an evoked compound action potential (ECAP), which represents the sum of all single-fiber action potentials generated by the stimulus. The ECAP is therefore a direct measure of SC activation and provides information on the fibers elicited by SCS, contributing to the therapeutic effect of stimulation.⁶⁻⁸

In order to determine whether maintaining stable SC activation has a beneficial outcome on pain relief, a prospective, multicenter, single-arm study was designed to demonstrate the safety and performance of a new closed-loop SCS system that maintains stable SC activation via continuous ECAP measurement. This closed-loop system adjusts the stimulus current after each pulse to maintain the resulting ECAP amplitude near a target amplitude.

Details regarding the patients, study design, device, and results through 6 mo have been previously published.⁹ Here, the evidence for closed-loop SCS is expanded upon by including results through the 12-mo follow-up and additional patients enrolled in the study. An elective extension of follow-up to 24 mo was offered to all patients; these results will be published once all patients have completed the study.

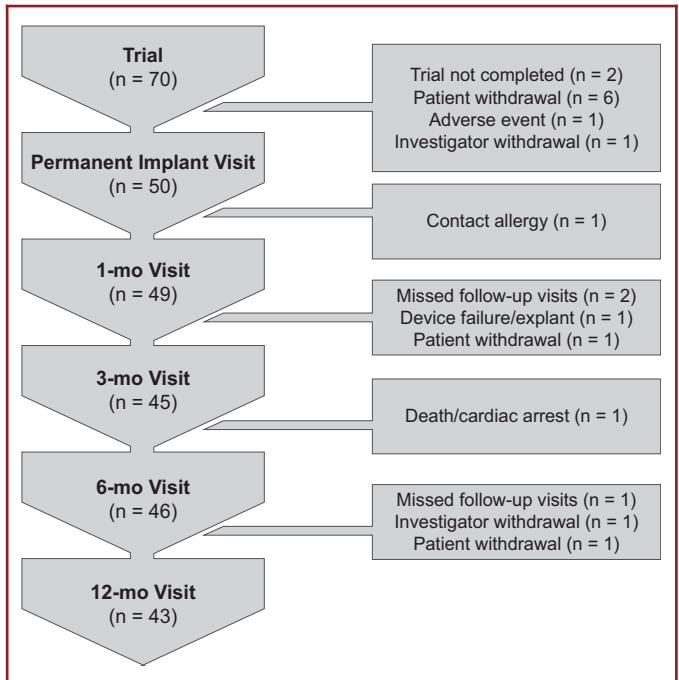


FIGURE 2. Patient progression through the study.

METHODS

Patients

Patients were consented at 5 clinical sites in Australia from August 2015 to April 2017. Key inclusion criteria included the following: patients diagnosed with chronic, intractable pain (visual analog scale [VAS] ≥ 6 cm for the past week) that was refractory to conservative therapy for at least 3 mo and having maintained their prescription pain medication dosage stable for at least 1 mo. Key exclusion criteria included the following: having a contraindication to SCS, a condition that was likely to interfere with study conduct or treatment outcome evaluation, and involvement in litigation involving their pain condition. The study was limited to patients with chronic back and/or leg pain but not restricted to patients with previous back surgery. The study was designed to show that at least 90% of patients could be programmed with closed-loop stimulation with a power of 0.85.

Study Design and Data Collection

The Avalon study was a prospective, multicenter, single-arm study approved by local ethics committees prior to patient enrollment. All patients provided written consent to participate in the study. The protocol was publicly registered at Australian New Zealand Clinical Trials Registry.

Baseline assessments included ratings of pain (100-mm VAS),¹⁰ impact of pain (Brief Pain Inventory [BPI])¹¹ function (Oswestry Disability Index [ODI]),¹² sleep (Pittsburgh Sleep Quality Index [PSQI]),¹³ quality of life (EuroQol instrument [EQ-5D-5L]),¹⁴ and medication usage. Assessments were repeated at the end of the trial period and at 1 (data not shown), 3, 6, and 12 mo postimplantation. Adverse events were assessed throughout the study.

TABLE 1. Baseline Demographics and Characteristics for Permanently Implanted Patients

Implanted patients N = 50	
Age (yr) at enrollment	
Mean (SD)	56.7 (12.2)
Gender, n (%)	
Male	23 (46.0)
Female	27 (54.0)
Primary diagnosis, n (%)	
FBSS/FNSS	28 (56.0)
Radiculopathy	9 (18.0)
Other ^a	13 (26.0)
Primary region of pain, n (%)	
Lower back	39 (78.0)
Leg	8 (16.0)
Foot	3 (6.0)
Prior history of SCS, n (%)	
Yes	3 (6.0)
No	47 (94.0)
Duration (yr) of pain	
Mean (SD)	15.0 (11.0)

FBSS, failed back surgery syndrome; FNSS, failed neck surgery syndrome; SCS, spinal cord stimulation; SD, standard deviation.

^aOther diagnoses: discogenic back (or lower back) pain/internal disc disruption (n = 5), lumbar spondylosis (n = 4), lumbar degenerative disease (n = 1), neuropathic pain/neuropathic low back pain post trauma (n = 1), peripheral neuropathy (n = 1), and sciatica and gluteal tendinopathy (n = 1).

Device and Implantation

The Evoke SCS system (Saluda Medical, Sydney, Australia) consists of a rechargeable external closed-loop stimulator (eCLS), implantable closed-loop stimulator (CLS), two 12-contact percutaneous leads, and all necessary surgical and supporting tools. For the trial procedure, patients were implanted with trial leads in the epidural space over the dorsal columns at the thoracic vertebral level associated with pain for an average of 7 d to evaluate its effect. If the trial was deemed successful ($\geq 40\%$ reduction in pain in any segmental VAS score with baseline VAS ≥ 6 cm), patients were given the option to receive the implanted system.

Evoke is the first closed-loop SCS system to have the ability to measure human SC activation in real time. The recording electrodes for measuring the ECAP can be any 2 nonstimulating electrodes on either lead, and either or both leads may be used for stimulation. The ECAP elicited by the stimulation is sensed, sampled, and processed by the stimulator to measure its amplitude (Figure 1). The amplitude is then used to drive a feedback loop that adjusts the stimulus current at each stimulus pulse to maintain near-constant SC activation. For each patient, programming involved first optimizing the stimulation location and then identifying appropriate electrodes to optimize ECAP measurement to assess SC activation. The level of SC activation, in other words the ECAP amplitude, is obtained by filtering the measured response resulting in a single value measured in microvolts.⁹

Prior work established that ECAP amplitude correlates with stimulation sensation intensity in a linear fashion.¹⁵ In other words, a higher ECAP amplitude results in an equal or stronger perceived stimulus sensation (never weaker). Therefore, the patient’s therapeutic window is defined as the range of ECAP amplitudes lying between the stimulus perception threshold and the maximum level of stimulation (discomfort threshold). This definition is consistent with the literature,^{16,17} but creates a relationship between SC activation and stimulation perception.

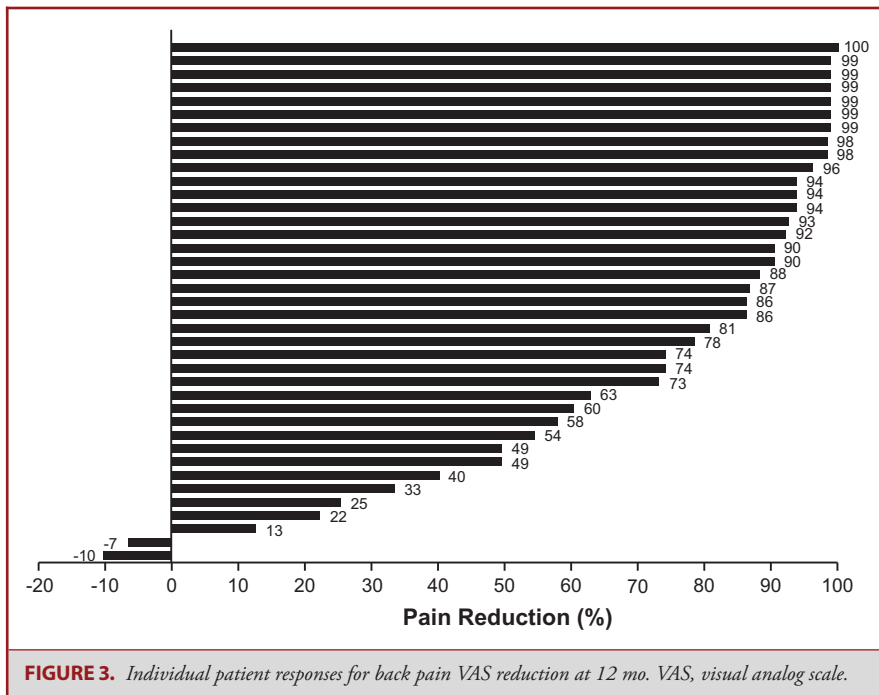


FIGURE 3. Individual patient responses for back pain VAS reduction at 12 mo. VAS, visual analog scale.

TABLE 2. Summary of Back, Leg, and Overall Pain Visual Analog Scale Scores Over Time for Permanently Implanted Patients

	Baseline	3 mo	6 mo	12 mo
Back pain				
N	46	41	42	39
Mean raw VAS score, mm (SEM)	81.3 (1.4)	24.9 (3.4)	22.6 (3.7)	22.7 (4.1)
Mean percent improvement in VAS scores (SEM)	–	69.2 (4.3)	72.6 (4.3)	72.0 (5.0)
Mean improvement in VAS scores, mm (SEM, <i>P</i> value)	–	56.7 (3.7, <i>P</i> < .0001)	58.4 (3.5, <i>P</i> < .0001)	57.9 (4.2, <i>P</i> < .0001)
Proportion of patients responding at ≥ 50% improvement, %	–	75.6	76.2	76.9
Proportion of patients responding at ≥ 80% improvement, %	–	53.7	50.0	56.4
Leg pain				
N	35	32	32	29
Mean raw VAS score, mm (SEM)	77.7 (1.8)	18.6 (3.4)	15.7 (3.2)	21.1 (4.7)
Mean percent improvement in VAS scores (SEM)	–	75.7 (4.3)	78.9 (4.6)	72.1 (6.1)
Mean improvement in VAS scores, mm (SEM, <i>P</i> value)	–	59.6 (3.9, <i>P</i> < .0001)	61.7 (3.9, <i>P</i> < .0001)	56.6 (5.1, <i>P</i> < .0001)
Proportion of patients responding at ≥ 50% improvement, %	–	87.5	84.4	79.3
Proportion of patients responding at ≥ 80% improvement, %	–	53.1	62.5	58.6
Overall pain				
N	50	45	46	43
Mean raw VAS score, mm (SEM)	81.3 (1.6)	22.8 (2.9)	22.6 (3.5)	21.0 (3.4)
Mean percent improvement in VAS scores (SEM)	–	71.2 (4.0)	71.7 (4.5)	73.6 (4.3)
Mean improvement in VAS scores, mm (SEM, <i>P</i> value)	–	58.6 (3.3, <i>P</i> < .0001)	58.7 (3.7, <i>P</i> < .0001)	59.8 (3.8, <i>P</i> < .0001)
Proportion of patients responding at ≥ 50% improvement, %	–	80.0	78.3	81.4
Proportion of patients responding at ≥ 80% improvement, %	–	42.2	52.2	53.5

SEM, standard error of the mean; VAS, visual analog scale.

The change from baseline summary presented in the table is based on subjects providing data both at baseline and at follow-up. All available data at the individual timepoints are presented for completeness.

The implant automatically records and stores the amplitudes of the ECAPs elicited by each stimulus pulse. To investigate the patients’ SC activation patterns and therapy use, the ECAP amplitudes for the patients’ preferred (or most used) program during the 1 wk prior to the scheduled visits were extracted and analyzed.

Data Management and Analysis

Throughout the study, standard data management procedures were observed, and monitoring was carried out periodically by an independent clinical research organization to ensure data quality.

Along with raw scores and percent change from baseline, VAS data were also analyzed as responders (≥50% pain relief) and high responders (≥80% pain relief). Paired *t*-tests with an alpha of 0.05 were used to test that mean change from baseline was different from 0 using SAS Enterprise Guide 7.1. Efficacy, medication, and device data are presented for the permanently implanted patients only; for the sake of transparency, we present safety data for all enrolled patients.

RESULTS

Patients, Demographics, and Baseline Characteristics

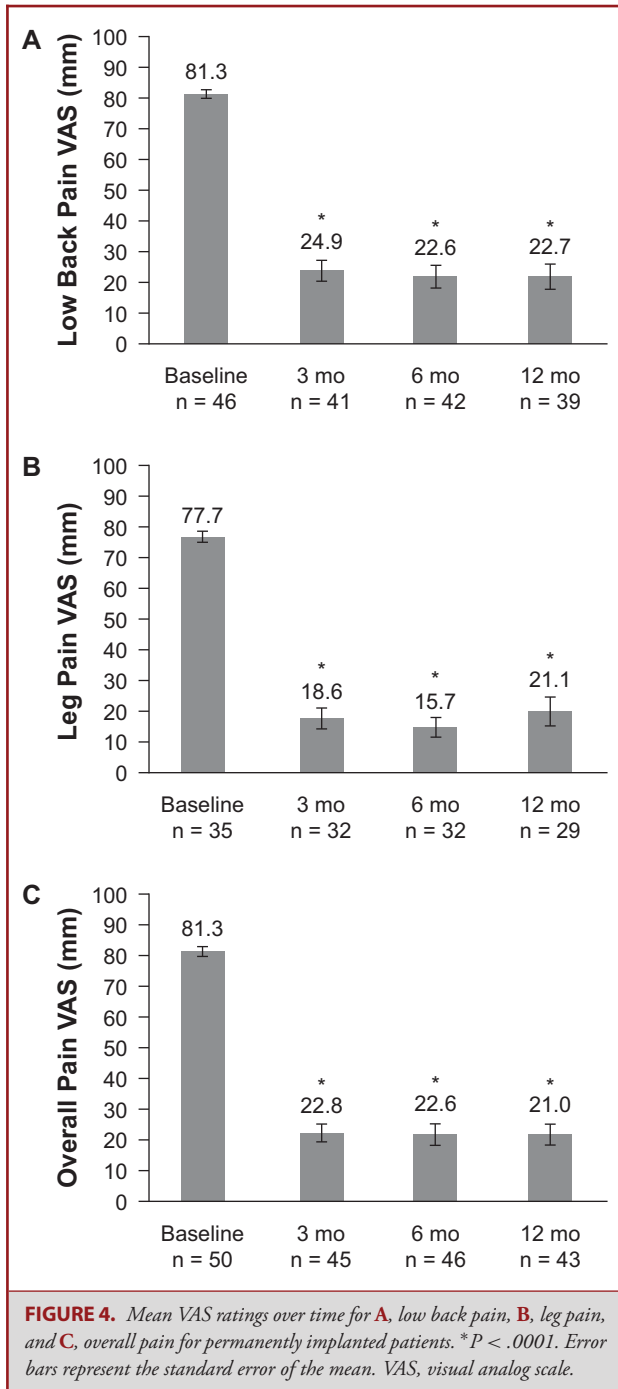
A total of 70 patients underwent a trial procedure. Of these, 68 (97.1%) completed the end-of-trial assessments and were evaluable. Of the 68 patients, 56 (82.4%) with assessment data had a reduction of 40% or more from baseline in their overall VAS rating; of those, 48 patients elected to proceed with a permanent implant. Two additional patients with a segmental VAS reduction

of 40% or more proceeded with a permanent implant as per the protocol inclusion criterion (Figure 2). Fifty subjects were implanted (71.4% of those trialed), which is in line with the literature (reported rates are between 41.4% and 86.4%¹⁸⁻²¹). On average, patients had a permanent implant for 19.8 mo (range, 0.5-25.8 mo) at the time of this report. One subject died of cardiac arrest between the 3- and 6-mo visit, but the occurrence was determined to not be related to the device or procedure. One patient was withdrawn by the investigator for noncompliance with study requirements between the 6- and 12-mo visits. All patients had completed the 12-mo follow-up at the time of this report.

Demographics and baseline characteristics for the cohort of implanted patients are presented in Table 1. Persistent or recurrent pain following spinal surgery was the main diagnosis across the cohort (56.0%), and the lower back was the most commonly reported primary pain area (78.0%). Three patients have had previous experience with SCS.

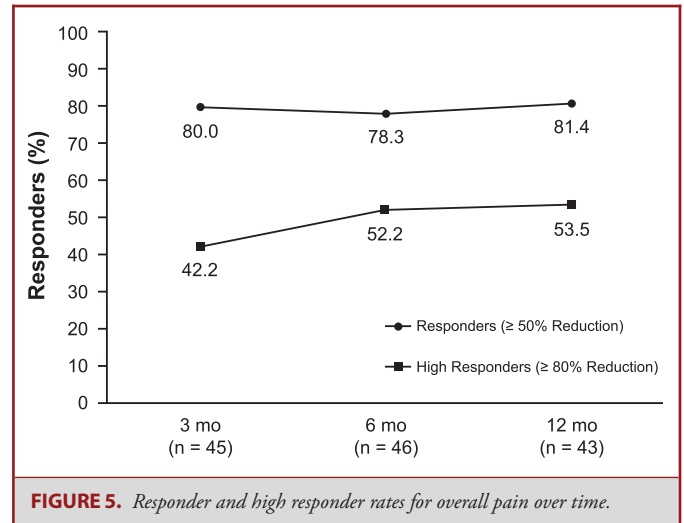
Pain Relief Outcomes

Across all permanently implanted patients, mean rating of back pain was 81.3 mm (±1.4) at baseline (n = 46 patients). After 12 mo of treatment, back pain rating was reduced by 57.9 mm (±4.2, *P* < .0001) to 22.7 (±4.1), a mean percent reduction of 72.0% (±5.0). At 12 mo, 76.9% of patients were back pain



responders ($\geq 50\%$ pain reduction), with 56.4% being classified as high responders ($\geq 80\%$ pain reduction). Individual patient responses for back pain at 12 mo are shown in Figure 3.

Mean rating of leg pain for permanently implanted patients was 77.7 mm (± 1.8) at baseline (n = 35 patients). Leg pain was reduced to 21.1 mm (± 4.7) after 12 mo of treatment, a statistically significant mean reduction of 56.6 mm (± 5.1 , $P < .0001$)



and a mean percent reduction of 72.1% (± 6.1). The proportion of patients who were leg pain responders at 12 mo was 79.3%, and 58.6% of patients were high responders.

Mean rating of overall pain for permanently implanted patients was 81.3 mm (± 1.6) at baseline (n = 50 patients). Overall pain was reduced to 21.0 mm (± 3.4) after 12 mo of treatment, a statistically significant mean reduction of 59.8 mm (± 3.8 , $P < .001$) and a mean percent reduction of 73.6% (± 4.3). The proportion of patients who were overall pain responders at 12 mo was 81.4%, and 53.5% of patients were high responders. Back, leg, and overall pain outcomes are presented in Table 2 and Figures 4 and 5.

Secondary Outcomes

BPI, EQ-5D-5 L, ODI, and PSQI for permanently implanted patients all showed statistically significant improvements at 12 mo compared with baseline. Outcomes at 12 mo are described below, and outcomes at other timepoints can be found in Table 3 and Figures 6 and 7.

The mean BPI severity score was more than halved over the 12-mo follow-up period, with a mean change of 3.6 (± 0.3 , $P < .0001$). The mean BPI interference score decreased by 3.8 (± 0.4 , $P < .0001$) from a baseline of 7.1 (± 0.2).

The mean EQ-5D-5L index score increased significantly from baseline to 12 mo by 0.214 (± 0.032 , $P < .0001$); similarly, the EQ-5D-5L Health VAS score increased significantly by 17.4 (± 4.1 , $P = .0001$). At 12 mo, 88.4% of patients experienced at least a minimally important difference (≥ 0.074) in EQ-5D-5L.²²

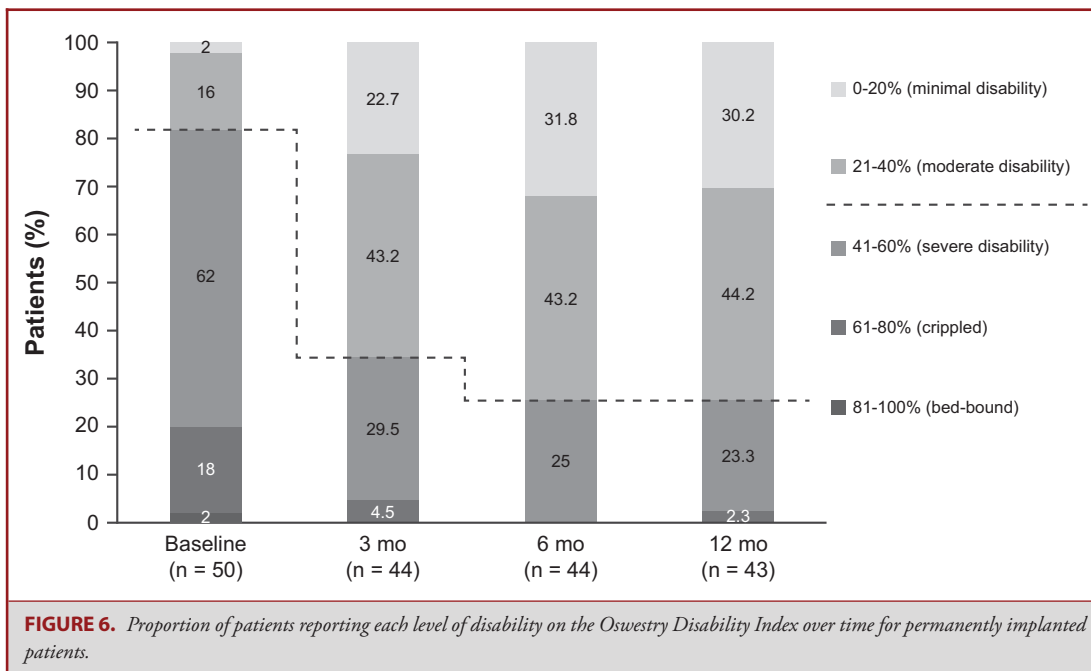
The mean ODI score decreased by 20.3 (± 2.1 , $P < .0001$). This resulted in a large shift of the patient population toward lower disability, with 74.4% of implanted patients being only minimally or moderately disabled at 12 mo, compared with 18.0% at baseline (Figure 6).

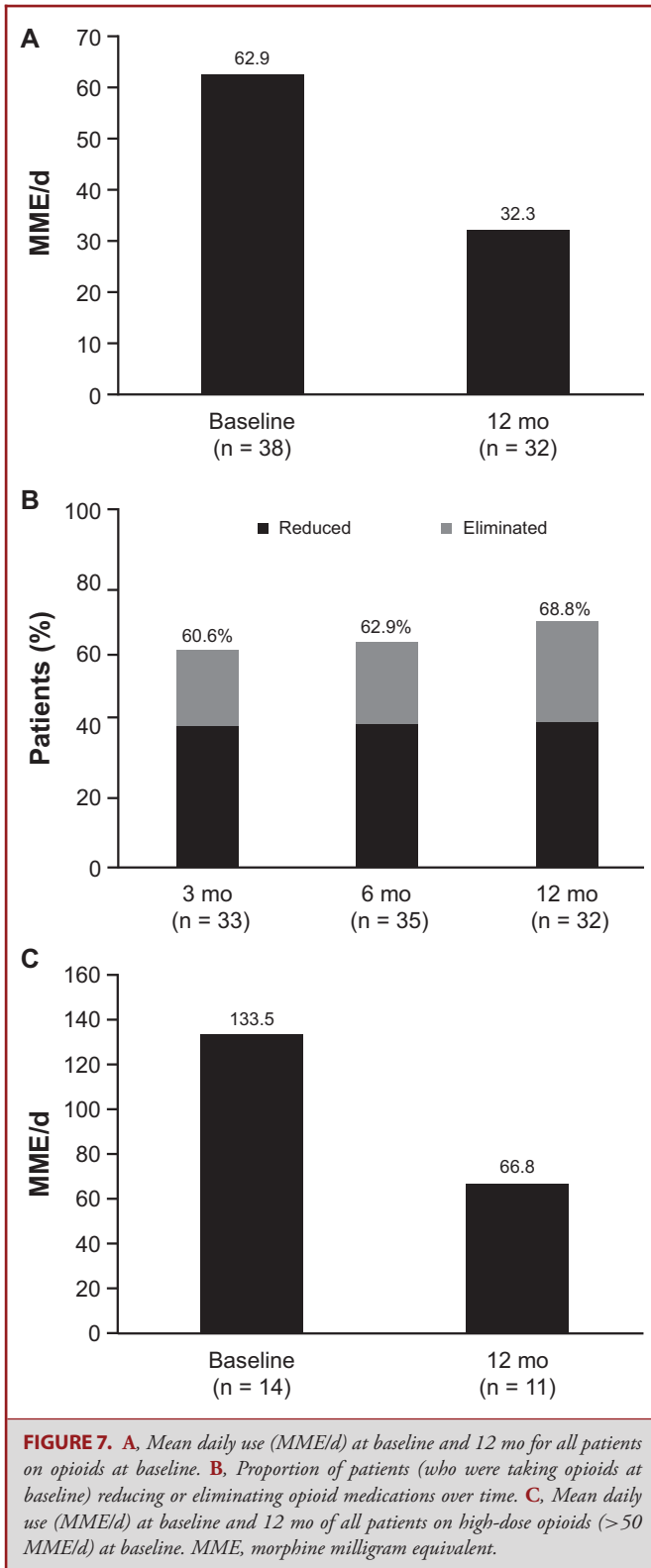
Sleep quality, as measured by the mean PSQI score, was also improved from 12 (± 0.6) at baseline to 8.6 (± 0.8) at 12 mo, with 22 patients (54.2%) having a clinically meaningful

TABLE 3. Summary of Secondary Outcomes Over Time for Permanently Implanted Patients

	Baseline	3 mo	6 mo	12 mo
BPI				
N	50	45	46	43
Mean severity score (SEM)	6.8 (0.2)	3.3 (0.3)	3.2 (0.3)	3.1 (0.3)
Mean change from baseline, severity score (SEM, <i>P</i> value)	–	3.5 (0.3, <i>P</i> < .0001)	3.6 (0.3, <i>P</i> < .0001)	3.6 (0.3, <i>P</i> < .0001)
Mean interference score (SEM)	7.1 (0.2)	3.5 (0.4)	3.4 (0.4)	3.2 (0.4)
Mean change from baseline, interference score (SEM, <i>P</i> value)	–	3.5 (0.4, <i>P</i> < .0001)	3.6 (0.4, <i>P</i> < .0001)	3.8 (0.4, <i>P</i> < .0001)
EQ-5D-5L				
N	50	45	46	43
Mean EQ index score (SEM)	0.404 (0.030)	0.637 (0.029)	0.688 (0.029)	0.633 (0.034)
Mean change from baseline – EQ index score (SEM, <i>P</i> value)	–	0.233 (0.036, <i>P</i> < .0001)	0.278 (0.034, <i>P</i> < .0001)	0.214 (0.032, <i>P</i> < .0001)
Minimally important difference from baseline (≥0.074)	–	80.0% (36/45)	87.0% (40/46)	88.4% (38/43)
Mean EQ Health VAS score (SEM)	53.3 (2.9)	73.2 (2.5)	75.2 (3.0)	71.4 (3.3)
Mean change from baseline – EQ Health VAS (SEM, <i>P</i> value)	–	18.4 (3.7, <i>P</i> < .0001)	20.7 (4.1, <i>P</i> < .0001)	17.4 (4.1, <i>P</i> = .0001)
ODI				
N	50	44	44	43
Mean ODI score (SEM)	52.3 (1.7)	34.6 (2.1)	31.7 (2.3)	31.2 (2.5)
Mean change from baseline – final score (SEM, <i>P</i> value)	–	17.1 (1.8, <i>P</i> < .0001)	20.1 (2.1, <i>P</i> < .0001)	20.3 (2.1, <i>P</i> < .0001)
Minimum detectable change from baseline (≥10%)	–	70.5% (31/44)	70.5% (31/44)	76.7% (33/43)
PSQI				
N	50	45	46	42
Mean PSQI score (SEM)	12.0 (0.6)	8.4 (0.7)	8.3 (0.7)	8.6 (0.8)
Mean change from baseline – global score (SEM, <i>P</i> value)	–	3.5 (0.7, <i>P</i> < .0001)	3.6 (0.7, <i>P</i> < .0001)	3.1 (0.7, <i>P</i> < .0001)

BPI, Brief Pain Inventory; EQ-5D-5 L, EuroQol instrument; PSQI, Pittsburgh Sleep Quality Index; ODI, Oswestry Disability; SEM, standard error of the mean; VAS, visual analog scale. The change from baseline summary presented in the table is based on patients providing data both at baseline and at follow-up. All available data at the individual timepoints are presented for completeness.





PSQI change at 12 mo (≥ 3 point reduction) compared with baseline.²³

Remarkably, opioid use was almost halved over the course of the study. At baseline, 76.0% (38/50) of permanently implanted patients were on opioids with an average daily dose of 62.9 morphine milligram equivalents ([MME]/d), which decreased throughout the study to 32.3 MME/d after 12 mo of treatment (Figure 7A showing actual mg vs time). In addition, 68.8% (22/32) of permanently implanted patients who were on opioids at baseline eliminated or reduced MMEs at the 12-mo visit (Figure 7B). More notably, 14 patients on high-dose opioid therapy (>50 MME) at baseline had a significant decrease in opioid usage from 133.5 MME/d down to 66.8 MME/d at 12 mo (Figure 7C).

Finally, patients were asked to rate their overall satisfaction with the stimulator using a 5-point scale (with options ranging from “very unsatisfied” to “very satisfied”). At 12 mo, 88.4% of patients reported they were “satisfied” or “very satisfied” with their treatment.

ECAP Amplitude Data

Closed-loop stimulation was programmable in all patients at 12 mo. For each patient, we calculated the most frequent ECAP amplitudes for their preferred program; the median value across patients ranged from 20.3 to 28.5 μV across the 3-, 6-, and 12-mo visits without clear upward or downward trend. Time spent within and below the therapeutic window across scheduled visits is displayed in Figure 8. At the 3-, 6-, and 12-mo follow-up visits, patients were in the therapeutic window a median of between 83.1% and 96.7% of the time. Patients spent a median of 2.9% to 6.8% of the total time below the therapeutic window and a median of 0% to 0.1% of the time above the therapeutic window across 3-, 6-, and 12-mo visits. Because of the non-normal distribution of the population, median values were used to present the therapeutic window and ECAP amplitude data.

Safety Outcomes

At the time of writing, 3 (4.3%) study/device-related serious adverse events (SAEs) have been reported (see Table 4). One patient developed an allergic reaction to titanium after the implant, another patient experienced severe new low back pain during the trial period, and the third experienced postoperative wound dehiscence following the implant procedure because of poor skin integrity. All 3 SAEs resolved with treatment.

No unanticipated adverse events were recorded, and the type, rate, nature, and severity of adverse events that have occurred in the Avalon study were consistent and comparable with other SCS device studies and to reported adverse events in the literature.²⁴

Programming Burden

During the course of the study, patients could return to the clinic at any time to get support with the device or ask for reprogramming. These visits were unscheduled programming visits and showed a clear downward trend as seen in Figure 9. After an

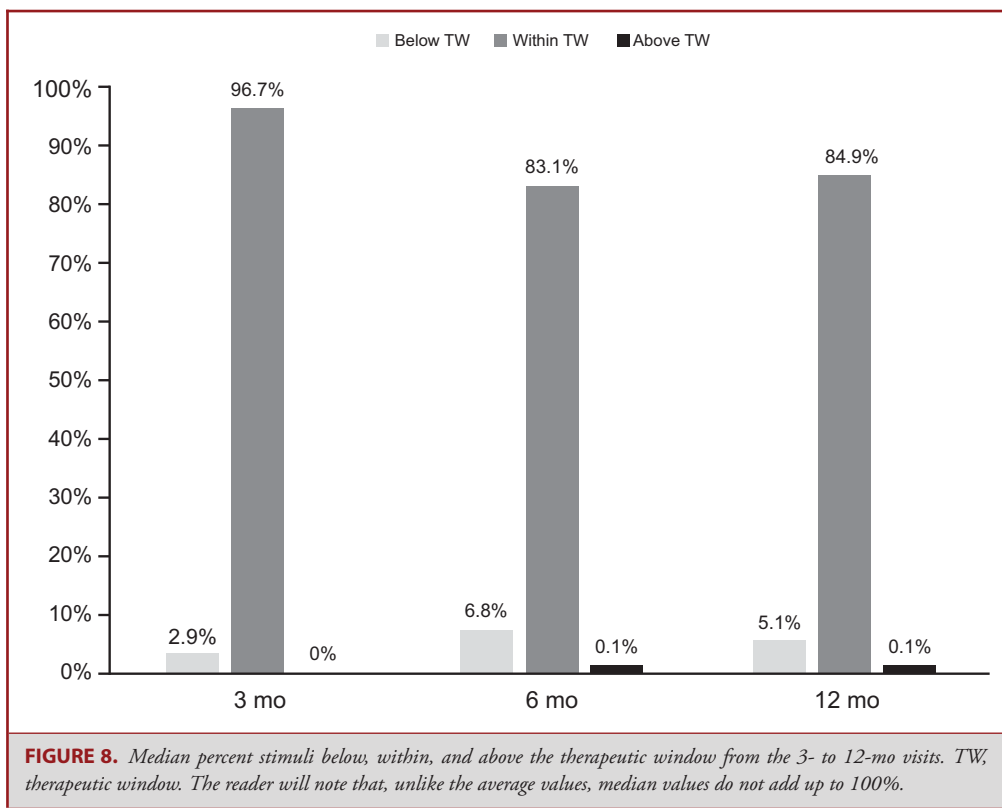


TABLE 4. Serious Adverse Event Rates

Serious adverse event rates	Events N	Patients n/N (%)
Study-related SAEs	3	3/70 (4.2)
Unanticipated adverse device effects	0	0/70 (0)

SAE, serious adverse event.

initial optimization period, reprogramming was necessary only in a subset of patients and became increasingly rare. These data suggest that, in the long term, patients may need no more than 1 programming session per year on average.

DISCUSSION

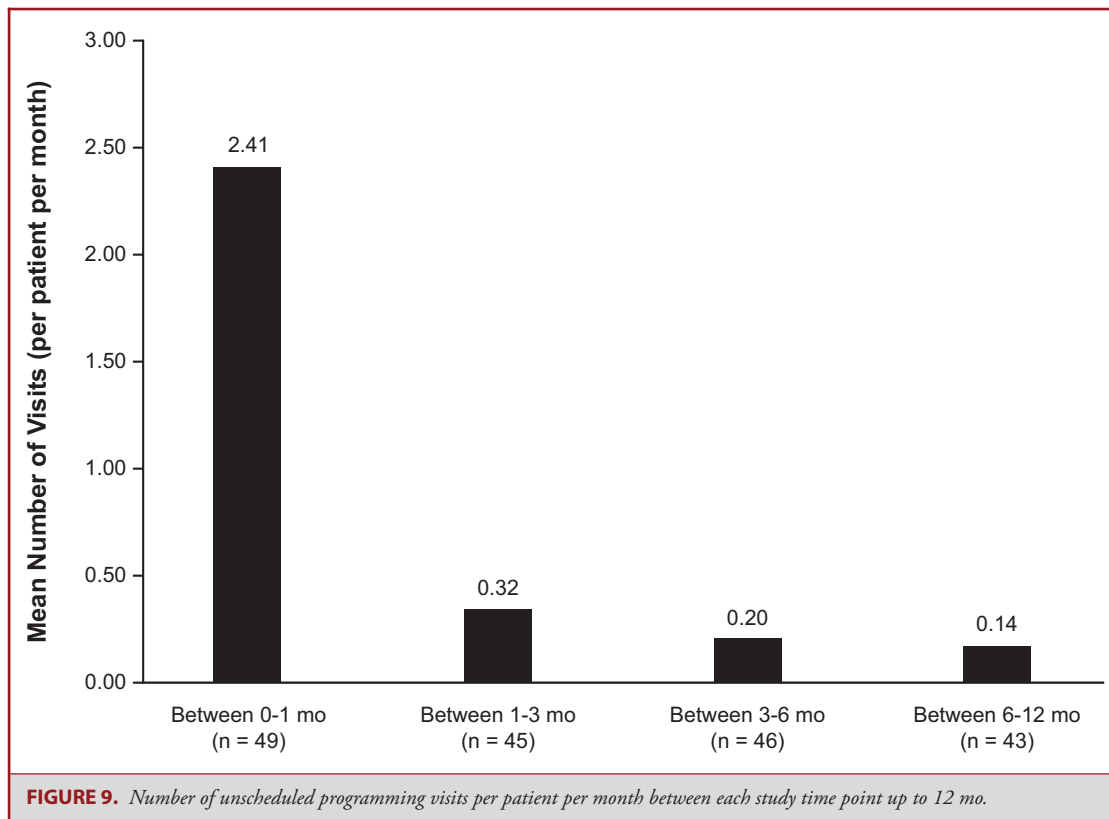
During the development of the Evoke SCS system (Saluda Medical), it was hypothesized that controlling the amount of neural activation and maintaining the SC activation within an individual’s therapeutic range could have profound benefits for long-term efficacy. In this study, we demonstrate that ECAP measurements are possible long term and remain stable over a 12-mo period. Closed-loop SCS is able to maintain SC activation within a therapeutic window for more than 80% of the time. This

helps to avoid discomfort and overstimulation in patients as well as possible understimulation leading to suboptimal therapeutic delivery.^{16,25}

Over the past decade, a large amount of effort has been spent on developing novel waveforms for SCS in an attempt to optimize the therapy.^{20,21} However, no existing device, independent of the waveform, has an objective measure of the effect on the SC. It is likely that stimulation outside the therapeutic window is one cause for loss of efficacy, the main contributor to the 20% to 25% explant rate over a 5-yr period reported in the literature.²⁶⁻²⁹ Although the maintenance of efficacy over several years still needs to be investigated, the stable 12-mo outcome data are promising and could indicate that closed-loop SCS can decrease the explant rate of SCS associated with loss of efficacy.

The study has demonstrated sustained high rates of VAS pain reduction through 12 mo, with mean percent reduction of 72% or greater in back, leg, and overall pain at 12 mo. Responder and high responder rates were profound. More than 76% of patients achieved at least 50% pain relief, and more than 53% of patients achieved at least 80% pain relief in the back, legs, and overall pain at 12 mo. These are the highest levels of pain relief reported at 1-yr follow-up for any SCS system to date.

Functional disability, quality of life, and sleep-related patient-reported outcomes also showed significant improvements over time. After 12 mo of treatment, the proportion of patients



reporting a severe or worse disability on the ODI was reduced by two-thirds (82%-26%). Because it takes time for patients' lives to normalize after improving their pain relief, it is likely that a stable therapy will induce further improvements in quality of life over time. Therefore, these scores will be monitored in this study as the patients progress through their 24-mo visit.

It is well known that excessive opioid use has a wide-ranging impact on both the patient's well-being as well as their family, and the economic burden on the healthcare system is a matter of public health concern.³⁰ The opioid reduction over the course of the study is therefore particularly promising, as finding alternative long-term treatments for pain is a major focus of the international community, and closed-loop SCS could become a valuable tool in helping patients reduce their opioid intake and further improve their quality of life.

In addition to offering an objective measure of SC activation and enabling closed-loop SCS, ECAP measurements have the potential to inform about the health of the SC and the effects of treatment over time. The objective measurements of SC activation and other neurophysiological properties have the potential to hold substantial clinical utility. These data may, in the future, be used to help the diagnosis and treatment of chronic pain and could provide an avenue for more effective, individualized, mechanism-based treatments. This may be extended to other treatments that impact neural activation, such as some types

of pain medications (eg, anticonvulsants and opioids), in which measurement of ECAPs may be used to titrate/optimize dosing and measure the interaction between these medications and SCS. Research is currently underway investigating the mechanisms of action of SCS and the effect of various stimulus paradigms on SC activation.

CONCLUSION

The 12-mo results from the Avalon study show the highest degree of pain relief recorded for an SCS system to date. We postulate that the stable level of SC activation is the main factor contributing to achieving this profound level of pain relief. To further test this hypothesis, the Avalon study was extended to a follow-up of 24 mo for consenting patients. Additionally, the Evoke SCS system (Saluda Medical) is currently being evaluated in a randomized, controlled, double-blind study in the United States, comparing the safety and efficacy of open-loop SCS to closed-loop SCS utilizing ECAP measurements.

Disclosures

This study was funded by Saluda Medical Pty Ltd. Dr Russo has served as a consultant for Abbott, Boston Scientific, Mainstay Medical, Medtronic Inc, Nevro Corp, Presidio Medical, Saluda Medical Pty Ltd, and Stimwave. Dr Brooker has

served as a consultant for Sequirus and as an investigator on sponsored research for Abbott, Medtronic Inc, Phosphagenics, RRMedsiences, Saluda Medical Pty Ltd, and Spinal Modulation. Dr Cousins has served as a consultant for Saluda Medical. Mr Sullivan has served as a consultant for Abbott, Medtronic, Nevro, and Sequirus. Ms Hanson, Dr Gmel, Dr Shariati, and Dr Parker are employees of Saluda Medical. Dr Poree has served as a consultant for Medtronic, Sollis, and Circuit Tx; a consultant with stock options for Nalu; a consultant and medical monitor for Saluda Medical; a principal investigator for the Abbott DRG study; a past consultant for StimWave; and a past principal investigator and shareholder for Spinal Modulation.

REFERENCES

1. Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns. *Anesth Analg*. 1967;46(4):489-491.
2. Sdrulla AD, Guan Y, Raja SN. Spinal cord stimulation: clinical efficacy and potential mechanisms. *Pain Pract*. 2018;18(8):1048-1067.
3. Kimura A, Seichi A, Inoue H, et al. Ultrasonographic quantification of spinal cord and dural pulsations during cervical laminoplasty in patients with compressive myelopathy. *Eur Spine J*. 2012;21(12):2450-2455.
4. Ranger MRB, Irwin GJ, Bunbury KM, Peutrell JM. Changing body position alters the location of the spinal cord within the vertebral canal: a magnetic resonance imaging study. *Br J Anaesth*. 2008;101(6):804-809.
5. Ross E, Abejón D. Improving patient experience with spinal cord stimulation: implications of position-related changes in neurostimulation. *Neuromodulation*. 2014;17(S1):36-41.
6. Parker JL, Karantonis DM, Single PS, et al. Electrically evoked compound action potentials recorded from the sheep spinal cord. *Neuromodulation*. 2013;16(4):295-303; discussion 303.
7. Halonen J-P, Jones SJ, Edgar MA, Ransford AO. Conduction properties of epidurally recorded spinal cord potentials following lower limb stimulation in man. *Electroencephalogr Clin Neurophysiol*. 1989;74(3):161-174.
8. Nashmi R, Fehlings MG. Changes in axonal physiology and morphology after chronic compressive injury of the rat thoracic spinal cord. *Neuroscience*. 2001;104(1):235-251.
9. Russo M, Cousins MJ, Brooker C, et al. Effective relief of pain and associated symptoms with closed-loop spinal cord stimulation system: preliminary results of the Avalon study. *Neuromodulation*. 2018;21(1):38-47.
10. 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;17(1):45-56.
11. Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the Brief Pain Inventory for chronic nonmalignant pain. *J Pain*. 2004;5(2):133-137.
12. Fairbank JC, Pynsent PB. The Oswestry Disability Index. *Spine*. 2000;25(22):2940-2953; discussion 2952.
13. 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(2):193-213.
14. EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208.
15. 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(3):593-601.
16. North RB. Neural interface devices: spinal cord stimulation technology. *Proc IEEE*. 2008;96(7):1108-1119.
17. Oakley JC, Prager JP. Spinal cord stimulation. *Spine*. 2002;27(22):2574-2583.
18. Murphy KR, Han JL, Hussaini SMQ, et al. The volume-outcome effect: impact on trial-to-permanent conversion rates in spinal cord stimulation. *Neuromodulation*. 2017;20(3):256-262.
19. Huang KT, Martin J, Marky A, et al. A national survey of spinal cord stimulation trial-to-permanent conversion rates. *Neuromodulation*. 2015;18(2):133-140.
20. 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(4):851-860.
21. 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(1):56-66.
22. 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(6):1523-1532.
23. Buysse DJ, Germain A, Moul DE, et al. Efficacy of brief behavioral treatment for chronic insomnia in older adults. *Arch Intern Med*. 2011;171(10):887-895.
24. 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(4):762-770.
25. Holsheimer J. Effectiveness of spinal cord stimulation in the management of chronic pain: analysis of technical drawbacks and solutions. *Neurosurgery*. 1997;40(5):990-999.
26. Van Buyten J-P, Wille F, Smet I, et al. Therapy-related explants after spinal cord stimulation: results of an international retrospective chart review study. *Neuromodulation*. 2017;20(7):642-649.
27. 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(7):603-609.
28. Dupré DA, Tomyz N, Whiting D, Oh M. Spinal cord stimulator explantation: motives for removal of surgically placed paddle systems. *Pain Pract*. 2018;18(4):500-504.
29. Pope JE, Deer TR, Falowski S, et al. Multicenter retrospective study of neurostimulation with exit of therapy by explant. *Neuromodulation*. 2017;20(6):543-552.
30. Hagemeyer NE. Introduction to the opioid epidemic: the economic burden on the healthcare system and impact on quality of life. *Am J Manag Care*. 2018;24(10 suppl):S200-S206.

Acknowledgments

The authors 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, and Professor Peter Teddy for the contribution to enrollment.

Neurosurgery Speaks! Audio abstracts available for this article at www.neurosurgery-online.com.

COMMENT

The authors present the 12 + month follow-through on the original Avalon study cohort using the ECAP-based Evoke SCS system (Saluda Medical) for back and leg pain. The results overall show sustained benefit to an average of over 19 months per patient to date without any hint that the therapy has started to fail from technical or tolerance issues. In fact, overall functional improvements are all statistically significant and even opioid usage is shown to drop remarkably to where over 60% of patients are off opioids completely. Although one cannot know how aggressive the study practitioners were in decreasing patient dosing, achieving such results by any measure within this context of patients is noteworthy. It will be interesting to see how this new type of

closed-loop system fares when exposed to the competitive marketplace of SCS therapy. Concerns about programming, patient selection, and patient follow-up seem to be attendant to all SCS devices and time will tell whether this ECAP-based approach can dispense with some of these

issues while maintaining the extremely high and prolonged success in pain relief that the field has come to expect.

Jeff Arle
Boston, Massachusetts