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Neurophysiological outcomes that sustained clinically significant improvements over 3 years of physiologic ECAP-controlled closed-loop spinal cord stimulation for the treatment of chronic pain

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ABSTRACT

Introduction A novel, spinal cord stimulation (SCS) system with a physiologic closed-loop (CL) feedback mechanism controlled by evoked compound action potentials (ECAPs) enables the optimization of physiologic neural dose and the accuracy of the stimulation, not possible with any other commercially available SCS systems. The report of objective spinal cord measurements is essential to increase the transparency and reproducibility of SCS therapy. Here, we report a cohort of the EVOKE double-blind randomized controlled trial treated with CL-SCS for 36 months to evaluate the ECAP dose and accuracy that sustained the durability of clinical improvements.

Methods 41 patients randomized to CL-SCS remained in their treatment allocation and were followed up through 36 months. Objective neurophysiological data, including measures of spinal cord activation, were analyzed. Pain relief was assessed by determining the proportion of patients with ≥50% and ≥80% reduction in overall back and leg pain.

Results The performance of the feedback loop resulted in high-dose accuracy by keeping the elicited ECAP within 4µV of the target ECAP set on the system across all timepoints. Percent time stimulating above the ECAP threshold was >98%, and the ECAP dose was ≥19.3µV. Most patients obtained ≥50% reduction (83%) and ≥80% reduction (59%) in overall back and leg pain with a sustained response observed in the rates between 3-month and 36-month follow-up (p=0.083 and p=0.405, respectively).

Conclusion The results suggest that a physiological adherence to supra-ECAP threshold therapy that generates pain inhibition provided by ECAP-controlled CL-SCS leads to durable improvements in pain intensity with no evidence of loss of therapeutic effect through 36-month follow-up.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Spinal cord stimulation (SCS) can provide long-term benefits to patients with chronic pain; however, patients may experience a loss of therapeutic effect over time.

WHAT THIS STUDY ADDS

⇒ Evoked compound action potential (ECAP)-controlled closed-loop (CL) SCS enables the collection of objective neurophysiological measurements that can be used to confirm continuous therapy delivery over time.

⇒ This study represents one of the longest assessments of efficacy in the SCS literature and the longest for ECAP-controlled CL-SCS.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ An objective physiologic approach to SCS is essential to enable a reproducible therapy and outcomes.

⇒ Patients who received ECAP-controlled CL-SCS obtained durable improvements in chronic pain with no evidence of loss of therapeutic effect to 3 years.

INTRODUCTION

Spinal cord stimulation (SCS) using a closed-loop (CL) system informed by the elicited neural response as measured by evoked compound action potentials (ECAPs) represents a novel paradigm in the field of neuromodulation.[1 2] ECAP-controlled CL-SCS enables continuous and automatic real-time adjustment of the output of each electrical pulse to optimize the ECAP dose and accuracy of the stimulation. The dynamic environment between the electrodes and spinal cord requires real-time physiologic assessment via ECAPs and stimulation adjustments to ensure that the dose accuracy is maintained despite continuous variation in the

distance between the electrodes and the spinal cord. The SCS system used in the current study is the only FDA-approved system for chronic pain that meets the FDA definition of a physiologic CL control system.[3 4] Fixed-output, open-loop SCS (OL-SCS) systems deliver a constant electrical output without consideration of these dynamic changes, which can result in variations in spinal cord activation.

The loss of the therapeutic effect over time has been a major limitation of SCS therapy. While often described in the SCS literature as tolerance or habituation, these pharmacodynamic mechanisms[5] do not accurately describe the loss of therapeutic effect observed with SCS. ECAP-controlled CL-SCS enables the collection of objective neurophysiological measurements which can be assessed over time to detect signs of the loss of therapeutic effect. We operationally define the loss of therapeutic effect as the deterioration over time in pain relief or other biopsychosocial components contributing to a patient's chronic pain experience with the same neural dose of stimulation delivered.

The effects of OL-SCS for chronic pain have been evaluated in randomized controlled trials (RCTs), systematic reviews, and numerous observational studies.[6–15] Most OL-SCS data derived from RCTs are limited to 6 months before patients in the comparator arm are allowed to cross over to the intervention arm.[6–8 11 16] In these RCTs, the data analysis at later timepoints considered only those patients that completed the last follow-up assessment.

Previous publications of the EVOKE participant, investigator, and outcome assessor-blinded, parallel-arm RCT have reported the efficacy and safety of CL-SCS compared with OL-SCS for the full cohort through 36 months of follow-up.[17–19] The 36-month analysis of the EVOKE RCT comparing CL-SCS to OL-SCS that followed best practices using the intention-to-treat (ITT) principle with imputation for missing data has been previously published.[19] Presented here is the analysis of the subjects who were randomized to CL-SCS and chose to remain in CL-SCS following the self-selected crossover through 36 months to elucidate the neurophysiological data that sustained the durability of physiologic CL-SCS therapy when received, as intended, over the long-term. The analysis in the current study of patients who completed the follow-up is consistent with other previous reports of SCS.[20–24]

MATERIALS AND METHODS

Study design, participants, trial procedure, and SCS system

Study design, participants, and trial procedure to 36 months of follow-up are reported in detail elsewhere[19] and presented in online supplemental material 1 for completion. The neuromodulation system, physiologic CL controller (Evoke System, Saluda Medical, Artarmon, Australia), provided ECAP-controlled CL-SCS and the ability to measure neural activation. All patients included in the current analysis were initially randomized to and completed the 36-month follow-up visit in the CL-SCS arm.

Outcomes

Objective device data

Objective device data collected provide information on device settings, system utilization, dose, and system performance.

Device settings (stimulation frequency and pulse width)

Programming parameters including frequency (Hz) and pulse width (µs) were collected.

System utilization

System utilization was defined as the proportion of time the system was on for the week prior to the scheduled visit.

Dose (ECAP dose, electrical dose, dose ratio, dose-response, and dose sensitivity)

The time period for these data includes the out-of-clinic neural activation for the week leading up to the scheduled visit that produced the clinical outcomes reported.

ECAP dose or neural dose is defined by the median ECAP level (normalized ECAP amplitude (µV)). The electrical dose is defined by the charge (µC/pulse), the product of pulse width(µs), and the current amplitude (mA) (µC=current amplitude (mA) × pulse width (µs) × 1A/1000mA). Dose-response and dose sensitivity were defined as the relationship between electrical dose (ie, charge) and neural activation levels (ECAPs (µV)) at perception threshold, comfort, and maximum (ie, discomfort threshold). Dose sensitivity is the slope of the dose-response curve (µV/µC).

The dose ratio is determined by the estimated current (mA) at the median ECAP level divided by the current (mA) at the ECAP threshold. The dose ratio allows individualization of a patient's neural dose using their spinal cord sensitivity (slope of the ECAP amplitude to current curve) and their ECAP threshold, such that it is transferable across patients. This metric normalizes for electrode-cord distance and distances between stimulation and recording electrodes.

Dose accuracy

The ability of the system to minimize the error between the ECAP target and measured ECAP was assessed in clinic. The dose accuracy is defined by the root mean square error of recorded ECAPs compared with the ECAP target and is based on µV of deviation from the ECAP target.

Holistic treatment response

The assessment of pain relief and patient-reported outcome measures used are reported elsewhere[19] and presented in online supplemental material 1 for completion. The treatment response was assessed by attaining minimal clinically important differences (MCIDs) for the visual analog scale (VAS), Oswestry Disability Index (ODI), Profile of Mood States (POMS), Pittsburgh Sleep Quality Index (PSQI), and generic health-related quality of life (HRQoL, EuroQol 5-Dimension 5-level (EQ-5D-5L)). The breadth of treatment response refers to the number of domains in which at least one MCID was achieved while the depth of treatment response refers to the number of MCIDs obtained in each domain. Holistic treatment response was determined for each patient based on attaining at least one MCID improvement in all domains that were impaired at baseline when compared with normative US values.[25 26] In addition, the total amount of MCIDs achieved was calculated for each domain and pooled for all domains to derive a cumulative responder score. The holistic MCID considered the cumulative responder score adjusted for the number of impaired domains at baseline for each patient.

Adverse events

All adverse events (AEs) were reported by the investigators throughout the study and reviewed and adjudicated by a blinded, independent clinical events committee.

Statistical analysis

Descriptive statistics were provided as mean (SD), median (IQR), or number of observations (percentage), as appropriate.

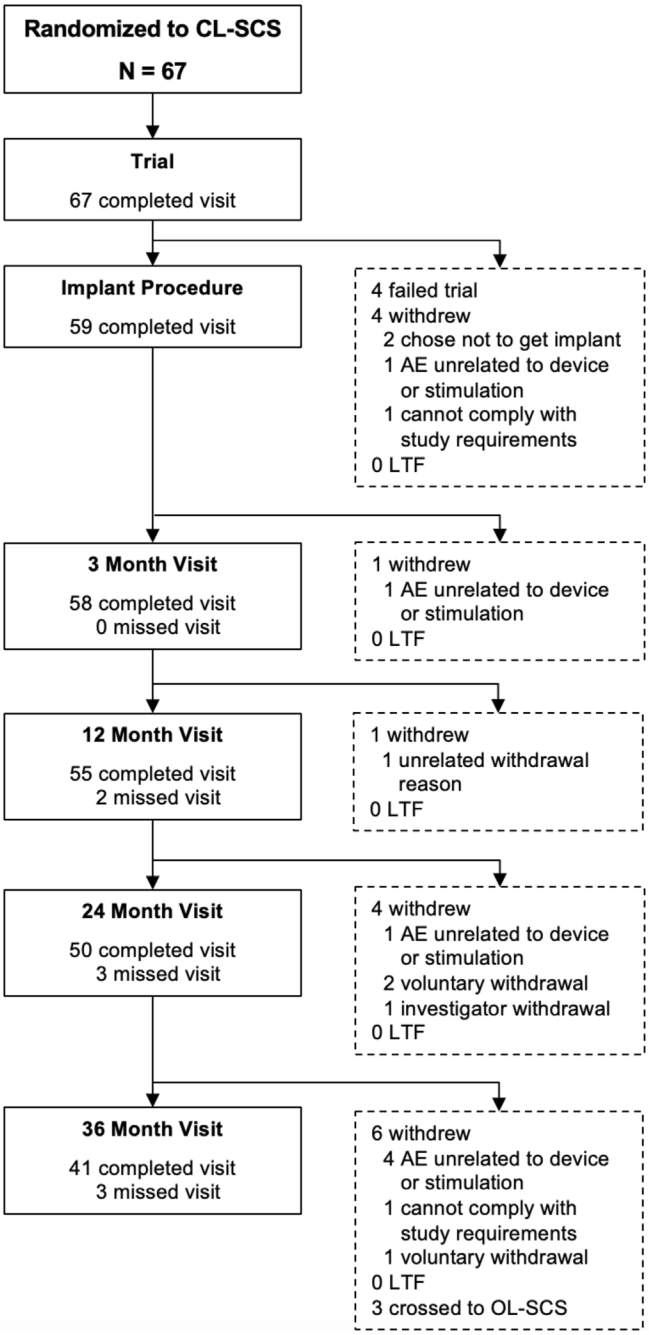

Figure 1 Patient disposition in the ECAP-controlled CL-SCS arm through 36 months.

Paired-sample t-tests were used to compare differences in outcome measures between baseline and follow-up. Mean difference (MD) and 95% CIs were reported. Wilcoxon signed-rank test was used to compare differences between medians. Cochran-Mantel-Haenszel test was used to compare differences in matched categorical data. Additionally, a longitudinal mixed effect quantile regression for electrical dose changes over time was performed.[27] Statistical significance was judged at the 5% level. Statistical analyses were conducted using SAS statistical softwareV.9.4 (SAS Institute) and R V.4.3.1.

RESULTS

67 patients were randomized to CL-SCS and underwent a screening trial procedure (figure 1). 59 patients reported ≥50% reduction in overall back and leg pain VAS score and proceeded to implantation of the SCS leads and pulse generator. Baseline demographics and other characteristics were largely similar between the patients initially randomized to CL-SCS and those that completed 36-month follow-up with this intervention (online supplemental table S1). There was a slightly greater proportion of patients taking opioids at baseline in the initial group randomized to CL-SCS. The most common etiology was radiculopathy both for the patients initially randomized to CL-SCS (61/67, 91%) and those that completed the 36-month follow-up (37/41, 90%).

16 of 50 (32%) CL-SCS patients self-selected to cross over to OL-SCS at the 24-month timepoint. The most common reason to try the other stimulation mode was curiosity of experiencing the other mode of therapy (13/16 (81%)). 13 of the 16 patients who chose to try the other stimulation mode returned to CL-SCS (7 patients after 1 month and 6 patients after 3 months). 41 CL-SCS patients, including the patients who did not cross over and those who crossed and returned to CL-SCS, completed the 36-month follow-up visit. None of the reasons for withdrawal were due to a lack of therapeutic effect or an AE that was related to the device or stimulation (a study flow diagram with detailed reasons for withdrawals is presented in online supplemental figure S1). All patients were blinded to the mode of stimulation administered from randomization through to the last assessment at 36 months.

Neural activation

The performance of the feedback loop resulted in high dose accuracy by keeping the elicited ECAP within 4μV of the target ECAP set on the system across all timepoints (table 1). The median stimulation frequency was 40 Hz (IQR 30–50 Hz) across all timepoints. SCS system utilization was >77%, percent time stimulating above ECAP threshold was >98%, ECAP dose was ≥19.3μV, and the dose ratio was >1.3 (ie, 30% above ECAP threshold) on average at all timepoints. While the clinical effect was maintained through 36 months, there was a gradual decrease in the dose requirements over time, with less system utilization ($p<0.001$), percent time stimulating above ECAP threshold, and ECAP dose observed at 36 months compared with 3 months. Additionally, there was a significant left shift in the dose-response curves at perception, comfort, and maximum (discomfort) threshold from 3 months to 36 months (figure 2). A longitudinal mixed effect quantile regression for electrical dose changes over time demonstrated a statistically significant left shift in the dose-response curve (ie, a reduction in median stimulation dose) from 3-month to 12-month, 24-month, and 36-month follow-up at perception and comfort dose and from 3-month to 36-month follow-up at a maximum dose (online supplemental table S2). Spinal cord sensitivity values (μV/μC), the slope of the dose-response curve which describes the sensitivity of the spinal cord to stimulation, did not significantly change over time from 3 months to 36 months.

Holistic treatment assessment

Overall back and leg pain intensity reduction, additional patient-reported outcomes collected including ODI, POMS, EQ-5D-5L, and PSQI and treatment response for individual domains are presented in online supplemental material 5 and 6.

The average improvement in each domain was greater than the clinically meaningful threshold (ie, 1 MCID) at all timepoints through 36 months (online supplemental figure S5). For VAS, ODI, and POMS, >2 MCIDs were reported, and for

Table 1 Objective measures of program parameters and neural activation with CL-SCS through 36 months

		3 months	12 months	24 months	36 months	Difference between 3 months and 36 months*
Stimulation frequency (Hz)		40 (40–50)	40 (30–40)	40 (30–40)	40 (30–40)	0.090
Pulse width (µs)		320 (240–360)	285 (240–350)	310 (255–355)	320 (270–360)	0.448
Dose accuracy (in-clinic RMSE, µV)		3.1 (1.8–4.6)	3.9 (2.4–5.8)	3.2 (2.2–5.1)	3.7 (2.7–5.4)	0.400
System utilization (% time on)		90.0 (76.9–97.0)	88.4 (65.6–9.5)	88.0 (46.1–96.7)	77.6 (0.9–95.9)	<0.001
Percent time stimulating above ECAP threshold (%, out of time on)		99.9 (95.6–100.0)	100.0 (94.7–100.0)	99.2 (65.7–100.0)	97.9 (50.7–100.0)	0.009
ECAP dose (normalized median ECAP amplitude, µV)		31.1 (16.9–67.6)	29.7 (11.7–67.6)	22.7 (5.5–47.2)	19.3 (3.1–34.8)	0.005
Dose ratio (estimated current at median ECAP amplitude/current at ECAP threshold)		1.42 (1.24–1.56)	1.42 (1.31–1.53)	1.34 (1.17–1.50)	1.34 (1.17–1.42)	0.071
Dose-response curve	Perception threshold charge (µC/pulse)	1.7 (1.0–2.6)	1.4 (0.9–2.4)	1.4 (1.0–2.3)	1.2 (0.9–1.9)	0.024
	Perception threshold ECAP (µV)	6.0 (2.0–14.5)	4.5 (1.0–14.0)	6.0 (1.0–15.0)	4.0 (1.5–9.0)	0.390
	Comfort threshold charge (µC/pulse)	2.3 (1.5–3.3)	1.7 (1.3–2.9)	1.7 (1.2–2.8)	1.7 (1.1–2.7)	0.013
	Comfort threshold ECAP (mv)	31.5 (12.5–62.0)	26.5 (18.0–62.0)	25.0 (10.0–49.0)	21.5 (11.0–45.0)	0.135
	Maximum Threshold Charge (µC/pulse)	3.1 (1.8–4.2)	2.2 (1.6–3.6)	2.1 (1.6–3.4)	2.2 (15–3.0)	0.018
	Maximum Threshold ECAP (µV)	97.0 (69.0–219.5)	110.0 (72.0–170.0)	95.0 (52.0–154.0)	95.0 (58.5–132.5)	0.081
Dose sensitivity (µV/µC)		131.4 (50.4–216.9)	112.1 (63.4–243.4)	149.0 (60.8–219.7)	159.0 (49.6–223.9)	0.593

Median (IQR).
*Wilcoxon signed-rank test.
ECAP, evoked compound action potential; RMSE, root mean square error.

EQ-5D-5L, >3 MCIDs were observed at all timepoints (online supplemental table S4, figure 3). The cumulative responder score which reflects the total number of MCIDs obtained across all domains was >11 MCIDs at all timepoints (online supplemental table S4, online supplemental figure S6). No differences were observed in the cumulative responder score and components between 3-month and 36-month timepoints (all p≥0.05). The holistic MCID, which adjusts the cumulative responder score by the number of impaired baseline domains, was ≥2.5 at all timepoints (online supplemental table S4, figure 3).

All patients were responders for at least one domain at each timepoint, with 93% and 85% of patients at 36-month follow-up considered responders for ≥2 and ≥3 domains, respectively (online supplemental table S5). Holistic treatment response characterized by the improvement of ≥1 MCID in all domains impaired at baseline was reported by 54% of patients at 36-month follow-up.

Adverse events

Over the course of 36 months, 17 study-related AEs were observed in 11/41 (26.8%) patients (online supplemental table S6). The most common AE was lead migration (four events in four (9.8%) patients) followed by implantable pulse generator pocket pain (three events in three (7.3%) patients). There were no study-related serious AEs in this group through 36-month follow-up.

DISCUSSION

A sustained response to CL-SCS between 3 months and 36 months in the proportion of patients who obtained ≥50% and ≥80% reduction in pain and in the cumulative responder score was observed. Furthermore, the durability of ECAP-controlled CL-SCS over 36 months was evidenced by no degradation of the performance of the physiologic CL controller to maintain dose accuracy. While the clinical effect was maintained at the same level, the ECAP dose requirements were significantly less at 36 months compared with 3 months. The stability of therapeutic effect while requiring reduced ECAP dose discredits the notion previously discussed in SCS publications that consistent activation may lead patients to develop a tolerance to SCS over time and that habituation may explain the loss of therapeutic effect in SCS. Patients received stimulation above ECAP threshold more than 98% of this time with an average frequency of 40 Hz. Therefore, the ECAP-controlled CL-SCS system was activating nerve axons 40 times a second for the majority of the time over 3 years. If a loss of therapeutic effect were an issue for ECAP-controlled CL-SCS, we would expect to see increased usage and/or higher ECAP dosages, but in fact, we found the opposite, that less activation was needed to maintain pain relief over time. Additionally, this phenomenon could manifest itself as a reduced level of neural activation for a given input stimulus over time (other things being equal) which would cause the dose-response curves shown in figure 2 to move to the right over time as more

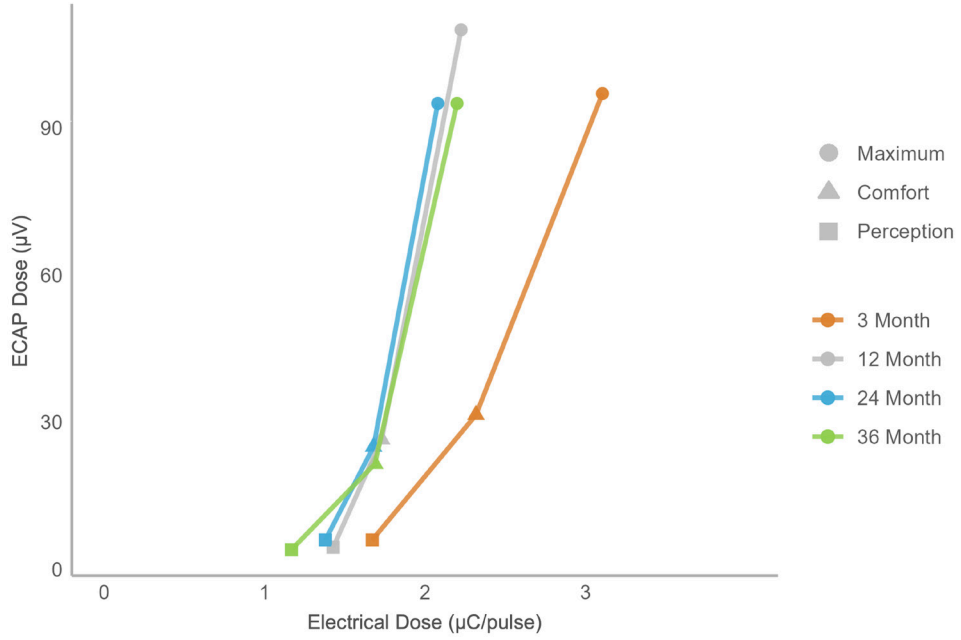

Figure 2 Dose-response curves for CL-SCS through 36 months. The dose-response curves showed a significant left shift from a 3-month to 36-month visit. The dose-response relationship was characterized by assessing the amplitude of the ECAP response in relation to the electrical dose, measured in microcoulombs per pulse (µC/pulse). To illustrate this relationship, median dose values and corresponding responses were plotted at three distinct levels: perception, comfort, and maximum (discomfort threshold). CL-SCS, closed-loop spinal cord stimulation; ECAP, evoked compound action potential.

current would be required to achieve the same degree of activation. In fact, these dose-response curves appear to be remarkably stable between 12 and 36 months and actually moved left between 3 months and 12 months. Some care should be taken when interpreting these data as factors such as programming parameter alterations, and medication usage can affect these curves. These data strongly suggest that if a patient uses their ECAP-controlled CL-SCS system as intended, they may require less therapy over time to achieve the same results, and therefore, the loss of therapeutic effect (usually described as tolerance or habituation) is not a failure mode for ECAP-controlled CL-SCS.

Neurophysiological data may also tell us something about the functioning of the dorsal column fibers. We saw no differences in the sensitivity of the spinal cord to stimulation over time. That is, for a given increase in stimulation (µC), an equivalent increase in the number of fibers activated was seen, manifested by the increasing ECAP size (µV). Furthermore, there were no reports of neurological deficit for ECAP-controlled CL-SCS.

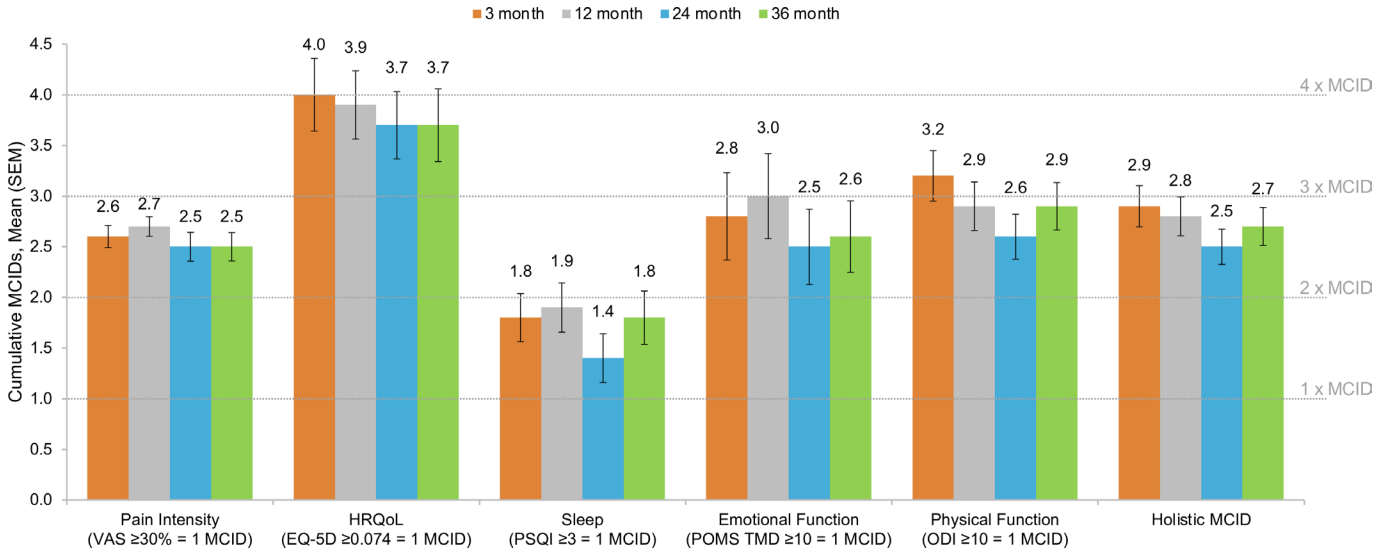

Figure 3 Cumulative MCIDs for each domain and for holistic MCID through 36 months. No significant differences were observed in the number of MCIDs achieved in the holistic domains between the 3-month and 36-month timepoints (p>0.05 for all). ECAP dose requirements were significantly less between the 3-month and 36-month timepoints (3 months (32.3 µV), 12 months (29.7 µV), 24 months (23.9 µV), 36 months (19.3 µV); p=0.001). HRQoL, health-related quality of life; MCID, minimal clinically important difference; ODI, Oswestry Disability Index; POMS, Profile of Mood States; PSQI, Pittsburgh Sleep Quality Index; SEM, SE error of mean; TMD, total mood disorder; VAS, visual analog scale.

Table 2 36-month evidence for SCS

Study (n)	Indication	Pain intensity				Change in HRQoL life		PGIC	System utilization	ECAP dose
		At follow-up	Point reduction	≥50% reduction	≥80% reduction	EQ-5D-5L*	EQ-VAS			
EVOKE CL-SCS (n=41)	CBLP	VAS 2.06†	6.14†	82.9%	58.5%	0.27	34.0	90.2%	80.3%	19.3µV
Kemler *et al* (n=20)[28]	CRPS-T1	VAS 4.1	2.5	NR	NR	NR	NR	NR	NR	NR
Remacle *et al* (n=29)[29]	PSPS-T2	LP NRS Mdn 3 BP NRS Mdn 5	LP Mdn 4 BP Mdn 4	NR	NR	NR	NR	NR	NR	NR
Eldabe *et al* (n=66)[20]‡	Neuropathic pain	NRS 5.03	2.31	31.8%	12.1%	0.21	4.59	NR	NR	NR
Eldabe *et al* PS (n=28)[20]‡		NRS 4.34	2.80	46.4%	17.9%	0.22	9.14	NR	NR	NR
Eldabe *et al* HF (n=23)[20]‡		NRS 5.72	1.87	21.7%	4.3%	0.16	−0.55	NR	NR	NR
Eldabe *et al* Burst (n=14)[20]‡		NRS 5.29	2.04	21.4%	7.1%	0.28	3.57	NR	NR	NR
Van Beek *et al* (n=34)[22]	PDN	NRS Day 3.8 NRS Night 3.9	Day 2.9 Night 2.8	Day 47.1% Night 35.3%	NR	NR	NR	52.9%	NR	NR

*Different tariffs for the EQ-5D (country-specific valuation methods) were used in the studies.
†VAS (0–100 mm) converted to VAS (0–10 cm) by dividing pain scores by 10.[14]
‡Calculated using individual patient data for the TRIAL-STIM overall population, PS, HF, and burst outcomes for ≥50% reduction, ≥80% reduction, and change in EQ-5D-5L. Programming method missing for one patient. Differences in study setting need to be considered when interpreting differences between study results (eg, healthcare system).
BP, back pain; CBLP, chronic back and leg pain; CL-SCS, closed-loop spinal cord stimulation; CRPS-T1, complex regional pain syndrome type 1; HF, high frequency; HRQoL, health-related quality of life; LP, leg pain; Mdn, median; NR, not reported; NRS, numerical rating scale; NTG, no trial group; PDN, painful diabetic neuropathy; PGIC, patient global impression of change; PS, paresthesia-based stimulation; PSPS-T2, persistent spinal pain syndrome type 2; TG, trial group; VAS, visual analog scale.

The type, nature, and rate of AEs for ECAP-controlled CL-SCS were comparable with reports of other SCS modalities. In fact, CL-SCS AE rates even at 36 months were at the low end of the range reported in the literature (online supplemental figure S7). 40 Hz ECAP-controlled CL-SCS does not appear to cause neurophysiological changes that could affect its efficacy or cause patient harm.

The study results show that ECAP-controlled CL-SCS can lead to clinically significant improvements in the long term. At 36 months, a large majority of patients (83%) obtained ≥50% reduction, and 59% obtained a ≥80% reduction in overall back and leg pain. For those patients who obtained ≥50% response at 3 months (88%), there was a >90% chance that they would maintain this response through 36 months. This is an important finding for patient and clinician confidence in the therapy. In addition to pain intensity, statistically and clinically significant improvements were observed in physical function, emotional function, sleep, and HRQoL. All patients obtained a clinically meaningful change in at least one of the five outcome domains at all timepoints through 36-month follow-up, and >50% of patients were holistic treatment responders with a clinically meaningful change in all outcomes assessed. The holistic MCID score was ≥2.5 MCIDs, that is, more than double the threshold for a clinically meaningful response across the individual baseline impaired domains at all timepoints. In parallel with the pain reduction and multimodal improvement observed, voluntary opioid reduction or elimination was observed in 55% of patients at 36 months. Comparative results of ECAP-controlled CL-SCS versus OL-SCS are presented elsewhere.[19]

Reports of SCS outcomes at 36 months or longer show that this therapy can provide long-term benefits to patients with chronic pain.[20 22 28 29] The pain intensity observed in the current study at 36 months was lower (2.06), and the reduction in pain was greater (6.14) than that reported in other studies at the same timepoint (table 2). A greater proportion of patients that received ECAP-controlled CL-SCS obtained ≥50% and ≥80% reduction in pain at 36 months when compared with OL-SCS systems including high-frequency, burst, and paresthesia-based stimulation (online supplemental figure S8, table 2).

Strengths and weaknesses

To the authors' knowledge, the observation that less stimulation therapy may be needed to achieve the same therapeutic effect over time with ECAP-controlled CL-SCS is the first such neurophysiological evidence of this with any SCS therapy. ECAP-controlled CL-SCS enables the measurement of the neural dose from which the dose-response can be observed and understood. Future studies are needed to confirm this finding.

We report the longest follow-up of patients who received ECAP-controlled CL-SCS. Although a single-arm report of an RCT, the outcomes reported by those patients who completed the study receiving the intervention as intended merit consideration. The results of the current report of CL-SCS patients who completed the 36-month follow-up was performed to evaluate the durability of the therapy when received as intended and shows greater improvements for all outcomes for patients who received CL-SCS than those reported in the EVOKE RCT ITT analysis.

CONCLUSIONS

Physiological adherence to the prescribed neural activation level provided by ECAP-controlled CL-SCS demonstrates the potential for sustainable and durable improvements in pain intensity and the multimodal domains impacted by the chronic pain experience. We found no evidence of the loss of therapeutic effect through 36-months of follow-up which suggests that the loss of therapeutic effect (usually described as tolerance or habituation) is not a failure mode for ECAP-controlled CL-SCS. These findings call into question the previously held beliefs that tolerance or habituation occurs with long-term use of SCS. This objective physiologic approach to SCS enables a reproducible therapy that results in long-term improvements in the biopsychosocial aspects of chronic pain as experienced by the individual. At 36-month follow-up, most patients reported high levels of pain relief, more than 50% were holistic treatment responders, and all patients reported at least one clinically meaningful change in an impaired domain at baseline.

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