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Original Research Article

Long-Term Improvements in Chronic Axial Low Back Pain Patients Without Previous Spinal Surgery: A Cohort Analysis of 10-kHz High-Frequency Spinal Cord Stimulation over 36 Months

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Abstract

Objective. This prospective, open-label study was designed to evaluate the long-term effectiveness of 10-kHz high-frequency spinal cord stimulation (SCS) in the treatment of chronic axial low back pain with no history of spinal surgery.

Methods. Patients with chronic low back pain without previous spinal surgery underwent assessment by a multidisciplinary pain and surgical team to confirm eligibility. After a successful temporary trial of 10-kHz HF-SCS therapy, defined by ≥50% back pain reduction, enrolled subjects underwent permanent system implantation and were followed up for 36 months. Outcome measures consisted of a 100-mm visual analog scale (VAS) for pain intensity, the Oswestry Disability Index (ODI), and a standard measure of health-related quality of life.

Results. Twenty-one patients satisfied the inclusion/exclusion criteria. Following a temporary trial, 20 of 21 (95%) subjects were implanted with a pulse generator, and 17 of 20 reached the 36-month time point. From baseline to 36 months, the average VAS pain intensity decreased from 79 ± 12 mm to 10 ± 12 mm, the average ODI score decreased from 53 ± 13 to 19.8 ± 13, and use of opioids decreased from 18 subjects to two subjects. One subject was deceased, unrelated to the study, one subject was explanted due to loss of effectiveness, and one subject was lost to follow-up.

Conclusions. These results suggest that 10-kHz high-frequency SCS may provide significant, long-term back pain relief, improvement in disability and quality of life, and reduction in opioids for nonsurgical refractory back pain.

Key Words. Spinal Cord Stimulation; SCS; High-Frequency Stimulation; 10 kHz; Chronic Back Pain; Discogenic Pain; Neuromodulation

Introduction

Traditional spinal cord stimulation (SCS) is an established therapy for treating neuropathic pain. Electrodes in the epidural space stimulate targeted zones of the spinal cord dorsal columns at frequencies of 40–70 Hz, producing paresthesia. Pain relief has been thought to result from overlapping paresthesia with the area of pain [1].

Randomized trials of traditional low-frequency SCS compared with conservative management or repeat spinal surgery showed benefits for leg but not back pain [2,3]. Obtaining paresthesia over the lower back is difficult due to the topographical organization of the lumbar neural pathways. Therefore, current use traditional low-frequency SCS in spinal pain has largely been limited to treating leg pain as a result of the failed back surgery syndrome.

A novel form or SCS, using a frequency of 10 kHz (10,000 Hz), extends the efficacy of SCS to include the axial low back component of chronic spinal pain. A European multicenter cohort study of subjects with predominant axial back pain demonstrated that 10-kHz SCS appears to produce safe and effective pain relief sustained for 24 months [4]. Subsequently, a US multicenter prospective randomized controlled trial in a similar population confirmed superior low back pain relief with 10-kHz therapy compared with conventional low-frequency SCS, again sustained through 24 months [5]; 10-kHz stimulation is also better tolerated by patients due to a lack of paresthesia [5]. A further advantage is that electrode placement is performed anatomically without time-consuming intra-operative testing that traditional low-frequency SCS requires.

Traditional SCS has been used as a "salvage" therapy for patients who have had unsuccessful spinal surgery and back pain for many years. Kumar et al. demonstrated that the quality of outcomes in SCS therapy is inversely related to duration of pain [6]. Spinal surgery can result in mechanical and neuropathic changes that may lead to more complex and refractory back pain. SCS is a minimally invasive and reversible therapy. Early use of 10-kHz SCS and use in patients who have not had spinal surgery might produce better outcomes for patients.

This study examines long-term outcomes from 10-kHz SCS in people suffering from chronic low back pain (CLBP) who have not had prior spinal surgery. The data examined here are extended follow-up results from a previously reported "proof of concept" cohort study [7]. In the previous study, significant improvements were seen at 12 months in both pain and pain-related disability. Axial low back pain was reduced by 72.6% from baseline, and ODI was reduced by 47.6%. Here we examine follow-up results at 36 months postimplant to scrutinize whether the long-term efficacy and safety of 10-kHz high-frequency SCS is sustained.

Methods

This is a 36-month follow-up of a preliminary single-center, prospective, proof-of-concept study designed to explore the safety and effectiveness of 10-kHz high-frequency SCS

in patients with predominant axial low back pain without previous spinal surgery. This study was conducted in accordance with local regulations, good clinical practice guidelines (ISO 14155), and the declaration of Helsinki. Ethical committee approval was granted (NRES Committee North East – Northern & Yorkshire, REC reference 11/NE/0047, April 2011), and the study was registered with a clinical trials database (ISRCTN96424062). Written informed consent was obtained from all the study subjects prior to their enrollment.

Study Participants

All subjects screened for this trial were assessed by a multidisciplinary team consisting of an experienced pain physician, nurse, physiotherapist, and psychologist to determine the appropriateness of spinal cord stimulation therapy. In addition, all subjects were reviewed by an experienced spinal surgeon to exclude spinal pathology that may be suitable for spinal surgery.

Inclusion criteria were 1) age between 18 and 65 years; 2) symptoms of axial low back pain for at least six months, with a minimum intensity of 50/100 mm on VAS; 3) predominant low back pain (VAS back pain score at least 20 mm greater than leg pain VAS score); 4) failure to respond to conventional medical management, including, where appropriate, an intensive physical rehabilitation program and facet joint or medial branch local anesthetic infiltrations; 5) no history of previous spinal surgery; 6) cleared of any spinal pathology that would lead to recommendation for any evidence-based surgical intervention; 7) degenerative disc disease confirmed by MRI and/or by discography; 8) on stable dose (six months or longer) of analgesic medications, including opioids and antineuropathic drugs.

The main exclusion criteria are listed in Table 1.

Study Intervention

All enrolled subjects were required to undergo a temporary trial of 10-kHz stimulation in accordance with standard clinical practice. This trial was for 10 to 14 days, and its purpose was to assess both tolerability and effectiveness. Only subjects reporting greater than 50% reduction in low back pain intensity were then subsequently implanted with a permanent implanted pulse generator (Senza system, Nevro Corp., Redwood City, CA, USA).

Table 1 Key exclusion criteria

Not able to comply with study-related requirements, procedures, and visits
Low back pain for less than 6 months or not having tried conservative treatment (e.g., physical therapy, multiple facet joint injections)
Active alcohol, marijuana, recreational or prescription drug abuse or dependence or unwillingness to stop/reduce excessive inappropriate medication
Had previous spinal fusion surgery or spinal cord stimulation
Evidence of an active disruptive psychological or psychiatric disorder or other known condition significant enough to impact perception of pain, compliance of intervention, and/or ability to evaluate treatment outcome
Mechanical spine instability on clinical and radiological assessment

Electrode placement was performed under fluoroscopic guidance, and two cylindrical leads were placed in the posterior epidural space in the anatomical midline with the tip at the level of T8 and T9 (Figure 1). This was to ensure that electrodes were able to stimulate at the level of the T9/10 disc and a small adjacent area above and below to account for patient variation. The leads were either externalized to an outside battery for the trial or connected to a subcutaneously placed IPG for the permanent implant. Intraoperative testing was not required.

Bipolar stimulation programs (10 kHz, 30 μs, 1–5 mA) were provided to initially target the spinal cord in the area corresponding to T9-T10 vertebral bodies and were subsequently optimized for significant pain relief through an algorithmic bipole searching strategy [7].

Data Collection

Primary Outcome

Standardized outcomes were measured at study visits at baseline, end of trial, and one, three, six, 12, 24, and 36 months after permanent implantation. The analyses in the present study focus on results at 36 months. Baseline characteristics are presented in Table 2. In addition to the predetermined scheduled visits, subjects were able to attend for reprogramming if required.

The primary outcome was a reduction in pain intensity in the low back greater than 50% from baseline, measured using a 0–100 mm visual analog scale.

Secondary Outcomes

The Oswestry Disability Index [8] was used as a measure of disability, with a range 0–100. The EuroQol five Dimensional Questionnaire (EQ-5 D) was used to measure health-related quality of life [9], and the MOS 36 Item Short Form Health Survey v. 2 (SF-36) was used to measure general, physical, and mental health [10]. Patients' experience (global impression of change, satisfaction, recommendation to others), opioid use, sleep quality (average sleep hours per night, average pain-induced sleep disturbances per night), and work status were also collected.

Adverse events (AEs) were recorded as a measure of safety and tolerability. Specifically investigated AEs

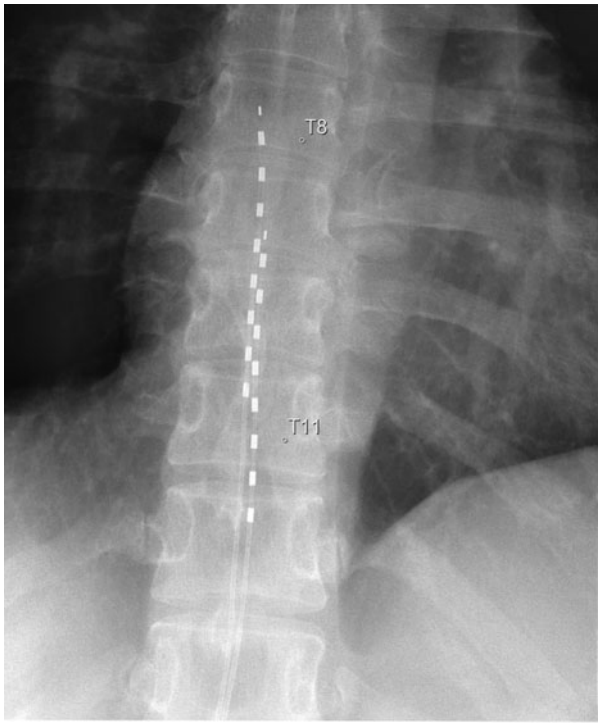

Figure 1 Radiographic position of the 10-kHz spinal cord stimulator electrodes. Electrodes cover the area between T8 and T11. The main area of stimulation is over the disc of T9 and T10.

Table 2 Baseline characteristics of the included patients

Age (mean ± SD), y	43.1 ± 9.6
Female, No. (%)	9 (42.9)
Back VAS score (mean ± SD), mm	79 ± 13
Leg VAS score (mean ± SD), mm	33 ± 21
Oswestry Disability Index (mean ± SD)	53 ± 13
EQ-5D TTO (mean ± SD)	0.17 ± 0.28
SF-36 PCS (mean ± SD)	30.3 ± 8.1
SF-36 MSC (mean ± SD)	42.7 ± 11.2
Time since onset of chronic pain (mean ± SD), y	7.0 ± 5.8

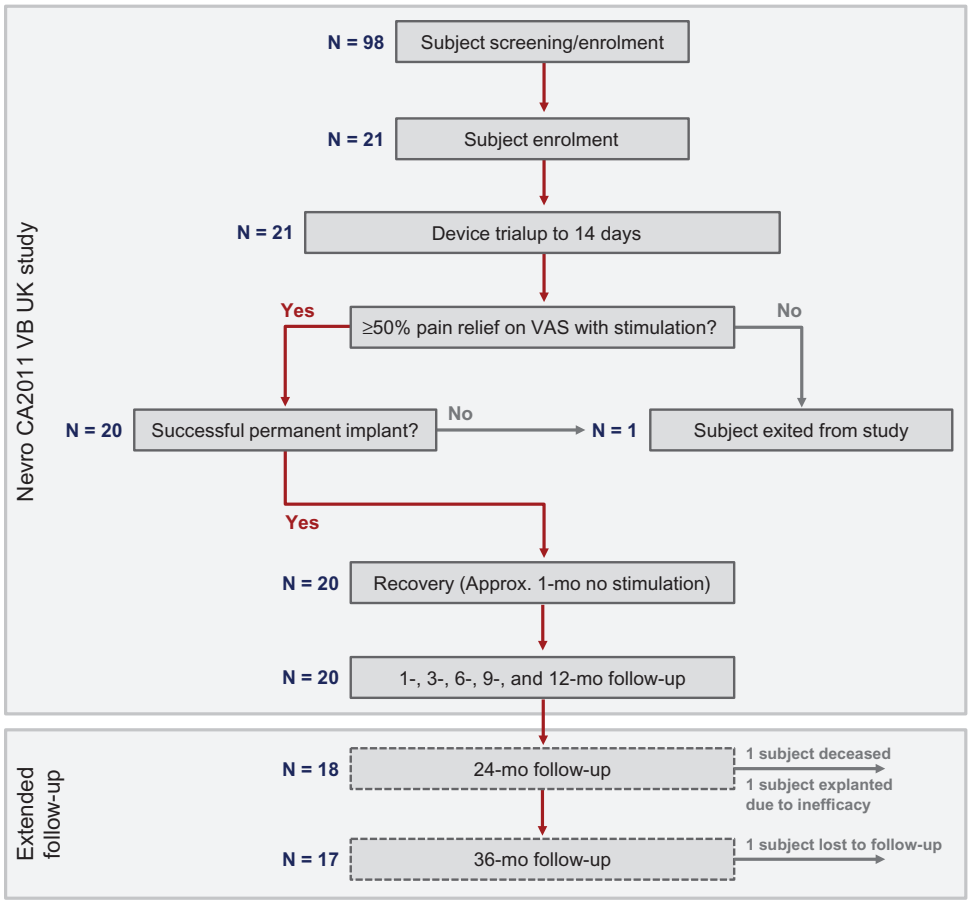

Figure 2 Study flowchart. Top area shows screening, recruitment to 12-month follow-up. The lower area shows follow-up at 24 and 36 months. VAS = visual analog scale.

included lead migration, fracture, and disconnection, infections, painful implantable pulse generator (IPG) pocket, and new neurological symptoms.

Analysis of Magnetic Resonance Imaging Data

A single experienced radiologist assessed MRI scans of the lumbar spine from all participants. A radiological diagnosis of intervertebral disc degeneration at each vertebral level was made if at least one of the following was present: Pfirrmann grade 4 or 5, Modic I or II changes, or the presence of a high intensity zone [11].

Statistical Analysis

This study was an extended follow-up analysis from a preliminary proof-of-concept study and, as such, the sample size was not determined around a target effect size. Statistical analyses were conducted using SAS v. 9.1 (SAS Institute, Inc., USA), and statistical significance was accepted at the $P < 0.05$ level. Continuous data were expressed as mean ± standard deviation, or median and range. Frequency and percentage are reported for ordinal and categorical variables. An analysis of variance including the period (baseline vs follow-up) as a repeated factor was applied to each of the analyzed variables; pairwise comparisons of periods were also performed within the same model. Quality-adjusted life-year (QALY) gain was estimated following the multiplicative model by subtracting from each three-month utility value the baseline value.

Results

Over a period between April 2012 and October 2013, 21 patients were eligible for study inclusion out of a total of 98 potential patients screened (Figure 2).

Baseline imaging data and patient demographics are described in Table 2.

Twenty out of 21 patients had a successful trial of temporary stimulation and proceeded to permanent implantation. A study flowchart is shown in Figure 2. All implanted patients were followed up at 36 months, but three were lost to follow-up. The reasons for this were loss of efficacy (one), death unrelated to study (one),

and development of new leg pain (one). MRI findings are shown in Table 3.

Primary Outcome: Back Pain Reduction

Pain intensity measured on an average VAS decreased from a baseline of 79 ± 12 mm to 10 ± 12 mm at 36 months ($P < 0.0001$) (Figure 3). Sixteen (80%) patients reported a greater than 50% reduction in pain VAS from baseline at 36 months (Figure 4).

Leg Pain Reduction

Subjects were specifically selected to have back pain greater than leg pain, so the average baseline VAS for leg pain was low at 33 ± 21 mm. Nonetheless, subjects also experienced significant reductions in leg pain, with an average VAS score of 9 ± 13 mm at 36 months (Figure 3).

Functional Improvement

Baseline ODI scores were 53 ± 13, and this was reduced to 19.8 ± 13 at 36 months ($P < 0.0001$). At 36 months, 10 subjects (50%) were in the "minimal disability" category, double the number at baseline, when only five subjects (25%) were classified as "minimally disabled." Overall, 14 subjects experienced a reduction of greater than 15 points on the ODI (Figure 3).

Medication Intake

At 36 months, 88% of all subjects were not using any opioids compared with 10% at baseline (Table 4).

Overall Subject Impression and Satisfaction

Eighty-five percent of subjects were satisfied (4/20) or very satisfied (13/20) at 36 months. All subjects would recommend this therapy to others with chronic low back pain.

Table 3 MRI findings

	No. (%)
Facet joint arthropathy/hypertrophy	5 (25)
Lateral recess stenosis	8 (40)
Foraminal stenosis	4 (20)
Nerve impingement	3 (15)
High intensity zone	10 (50)
Modic changes	12 (60)
Pfirrman grade 4 or 5	18 (90)
Schizas grade > B	6 (30)

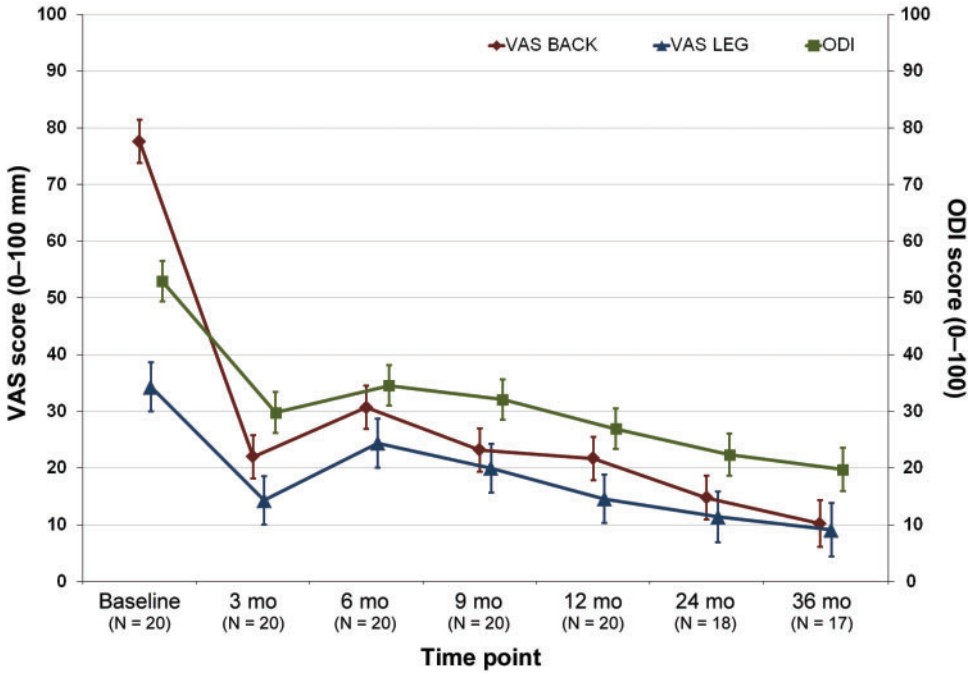

Figure 3 Pain intensity measured by a visual analog scale and Oswestry Disability Index. ODI = Oswestry Disability Index; VAS = visual analog scale.

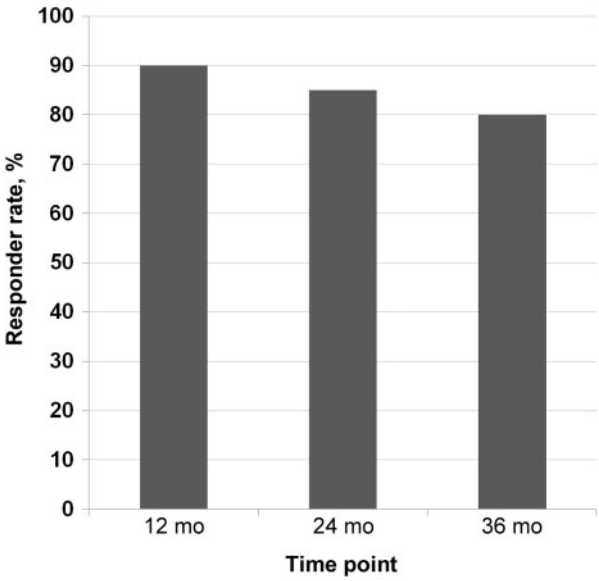

Figure 4 Responder rate (>50% pain reduction) for low back pain at 12, 24, and 36 months using ITT model (n=20). VAS = visual analog scale.

Table 4 Frequency of opioid intake at 12, 24 and 36 months

Opioid Intake Frequency	Baseline (N = 20)	12 Months (N = 20)	24 Months (N = 18)	36 Months (N = 17)
Regularly	17	7	4	2
As needed	1	7	5	0
Never	2	6	9	15

Health, Employment, and Quality of Life Status

Among the working age (18–65 years), 11 subjects were working at baseline and 15 at 36 months. Over the 36-month time span, EQ5D TTO improved from 0.17 to 0.84 ($P < 0.0001$), the SF-36 Physical component improved from from 30.3 to 48.2 ($P < 0.0001$), and the SF-36 Mental component improved from 42.7 to 56.8 ($P < 0.0001$).

Adverse Events

During the 36 months, there were no serious adverse events. Two subjects experienced pain over the IPG site, one of which required surgical revision. No subject required revision of the leads while three needed reprogramming to account for minor lead migration.

Discussion

The continuing beneficial effects of 10-kHz high-frequency SCS on pain intensity and disability at 36 months suggests that this therapy should be considered as a potential treatment in the long-term management of axial low back pain. Although long-term studies on SCS have been published elsewhere [12], the main difference in our study is that the patient cohort suffers from axial low back pain that is not the result of previous spine surgery.

This challenges the established view that SCS is effective mainly for radicular pain caused by spine surgery. SCS has never been recommended to treat axial low back pain as it can be technically difficult to stimulate back pain pathways [12,13]. In addition, even successful paresthesia-based stimulation of the low back does not always result in pain relief. Thus, SCS presently remains a rescue therapy for ongoing pain resulting from previous spinal surgery. If further appropriately designed RCT studies verify that 10-kHz high-frequency SCS is effective for treating low back pain, this will create entirely new therapeutic opportunities.

Our results mirror those seen in previous long-term studies on 10-kHz high-frequency SCS therapy, with similar pain relief, functional improvements, and increased health-related quality of life [4,5], despite the patient population being different. The present results are also consistent with previous results from our group, studying the effects of 10-kHz high-frequency SCS for chronic low back pain in FBSS [4]. Initial research had shown that the use of such high frequencies results in significant improvements in both radicular and central axial low back pain for FBSS patients [14,15]. These results are also consistent with our earlier results from the same cohort, as studied here at 12 months [7].

The design of this proof-of-concept study was stimulated by the promising results obtained in a subgroup of subjects from the original EU 10-kHz High-Frequency study who suffered from chronic back pain that was not a result of previous spine surgery. The improvement experienced by those "virgin back" patients suggested that 10-kHz high-frequency SCS may be more effective if it was used before spinal surgery. Earlier use of 10-kHz high-frequency SCS in the care continuum could help prevent the development of the negative biopsychosocial sequelae that occur after failed back surgery in a similar pattern seen in conventional SCS, where early therapy is associated with better outcomes [6]. Also, if we only select from patients after failed medical interventions, such a group might have a higher prevalence of psychosocial barriers to therapy, the so-called "yellow flags." Therefore, the use of 10-kHz high-frequency SCS therapy at an earlier stage, before surgery, may maximize the therapeutic effects of neuromodulation, with the potential for even better treatment outcomes.

Study Limitations

One major limitation to our study is that there are no results from a control arm available for comparison as medical devices and surgery carry potentially significant

placebo effects [16] that may influence our outcomes. However, we are encouraged that improvements were sustained at 36 months as we might expect the placebo effect to have diminished earlier in the study. Despite the magnitude and long-term quality of the improvements observed, a randomized controlled trial, preferably using an active placebo control, remains necessary to clearly support the effect of 10-kHz high-frequency SCS in this category of patients. It is worth noting that, as there is no induced paresthesia, it is possible to use a double-blind study design to minimize the bias associated with subjective measurements such as pain and pain-related disability.

The purpose of this study was not to find an alternative to surgery but to investigate a therapy that can be used when surgery is not appropriate. It is not possible to determine if these patients would have benefitted from surgical intervention.

Patient phenotyping was done using a mixture of clinical and radiological measures. Pain has been attributed to disc degeneration, but these findings are common in asymptomatic subjects and a diagnosis of discogenic pain is not made on these criteria alone [17]. Further evaluation on the phenotypic characteristics of axial low back pain may assist in patient selection and help predict successful outcomes.

Conclusion

This preliminary study suggests that HF10 therapy significantly reduces chronic low back pain and associated disability in nonsurgical medically refractory subjects with no past history of surgery. Clinically significant benefits were sustained at 36 months. The orthodoxy that considers SCS for chronic lower back pain as a treatment option only in cases of FBSS should now be challenged with a multicenter randomized controlled trial.

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