Prospective Study

Successful Long-term Nerve Root Stimulation for Chronic Neuropathic Pain: A Real World, Single Center Canadian Experience

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Background: Spinal cord stimulation (SCS) is a well-established treatment for chronic neuropathic pain in the lower limbs. However, some patients have pain in distributions that are difficult to target specifically and consistently with SCS. This often involves pain in the groin or upper limbs, or pain limited to a specific dermatome. We hypothesized that dorsal nerve root stimulation (DNRS) would provide similar pain relief for these patients, compared to our results using SCS.

Objectives: In this study we report our experience treating patients with chronic neuropathic pain using SCS and DNRS.

Study Design: Open label, prospective study that includes all patients treated with a new trial stimulator system at a single center between July 1, 2011, and October 31, 2013.

Setting: Academic university neurosurgical pain center.

Methods: One hundred thirty-two consecutive patients had trials of spinal stimulation. Seventy-six patients went on to permanent implants, of which 26 received only DNRS, 47 only SCS, and 3 both. The technique was selected based on clinical assessment and intraoperative test stimulation. Other than pain location and diagnosis, the DNRS and SCS groups had similar baseline characteristics. Follow-up is reported at 12 months. Patients were assessed using a visual analogue scale (VAS) for pain, the SF-36 for quality of life, and the morphine equivalent daily dose (MEDD).

Results: At 12 months, the average VAS score for the DNRS group had decreased from 7.5 (SD 1.4) to 4.4 (SD 2.6) and 47% of patients with permanent implants achieved > 50% pain reduction. There were improvements in all subscores and component summary scores of the SF-36. The MEDD had been reduced in 55% of the patients with available data. There was no significant difference in complication or revision rates between the 2 groups.

Limitations: Patients were not randomized to treatment groups, and instead were assigned to SCS or DNRS based on what was expected to provide superior pain coverage. There is incomplete follow-up data for some patients due to missed clinic visits.

Conclusion: In our study, DNRS provided excellent pain reduction, quality of life improvement, and opioid medication use decreases. We conclude that it is an effective long-term treatment for chronic neuropathic pain.

Key words: Spinal cord stimulation, dorsal nerve root stimulation, lumbar, thoracic, cervical, neuropathic pain, neuromodulation, clinical effectiveness, chronic pain, visual analogue scale

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The use of electrical stimulation for the treatment of pain was first documented almost 2000 years ago (1), but began in its modern sense following the publication of the gate theory of pain by Melzack and Wall in 1965 (2). In a remarkable example of translational research, spinal cord stimulation (SCS) was first trialed in 1967 (3,4) and since then has obtained widespread use to treat chronic pain syndromes such as complex regional pain syndrome (CRPS) (5-9) and failed back surgery syndrome (FBSS) (9-11). The majority of the evidence for SCS studied its use for lower limb pain, which is generally targeted through electrode placement on the thoracic spinal cord. This technique has been found in randomized controlled trials to have superior results to conventional medical management (10), repeat spinal surgeries (11), and physical therapy alone (5).

The limitations of SCS include incomplete or inconsistent coverage for certain areas of the body (such as the groin, upper limbs, and torso), and excessively broad areas of coverage for some patients (12,13). Peripheral nerve stimulation (PNS) has been used to provide focused coverage of areas difficult to reach with SCS, however PNS is limited by its need for surgical access to the affected nerve and a lack of selectivity for stimulating sensory over motor fibers (14). Nerve root stimulation (NRS) has been theorized to address these issues by providing more specific paresthesias in cases where the pain is limited to one or a small number of dermatomal segments without stimulating adjacent areas, while maintaining the durability and accessibility of SCS compared to PNS. The dorsal nerve roots have a lower stimulation threshold than the dorsal column, which extends the battery life of the device and may reduce the chance of unwanted motor or sensory side effects from stimulation. This is due to several physical properties of the nerve roots and their interface with the spinal cord that have been elucidated through computer modeling studies (15). In addition, we have observed that dorsal nerve root stimulation (DNRS) is less positional than SCS, especially in the cervical spine.

While SCS has been used for decades, successful DNRS was first accomplished much more recently (16,17). To date there is no level I or II evidence as to the long-term effectiveness of DNRS in treating chronic pain (18). A recent prospective case series of 3 patients concluded that DNRS is ineffective in providing relief at 3 months after implant (19); however, we believe that the small sample size in this study precludes significant conclusions. Conversely, case reports have been published describing its successful use in the treatment of diabetic neuropathy (20), interstitial cystitis (21), and postherpetic neuralgia (22). A recent trial found excellent results from stimulation of the dorsal root ganglion (23). We believe DNRS has certain advantages over dorsal root ganglion stimulation technique, as it offers similar dermatomal specificity, but does not require specialized electrodes, allows for one electrode to cover multiple nerve roots, and can be easily converted to and from a spinal cord stimulator intra-operatively. In this paper we report our experience with 132 consecutive patients treated at our center with a new trial of spinal stimulation between July 1, 2011, and October 31, 2013. We plan to publish additional updates as more long-term data become available for our patients.

Methods

The study involved a single center, open label design and was approved by the Research Ethics Board at Western University, London, Canada. All patients who had been treated at University Hospital, London, between July 1, 2011, and October 31, 2013 with a new implantation of SCS or DNRS trial system entered the study.

Patient Selection

Patients were 18 years of age or older and had been referred for surgical management of pain that failed to respond to conservative measures including medication, psychological therapy, physical therapy, nerve blocks, and/or pain management programs. Exclusion criteria included another clinically significant or disabling chronic pain condition; an expected inability to manage the SCS system; a history of a coagulation disorder; evidence of an active psychiatric disorder, another condition known to affect the perception of pain, or inability to evaluate treatment outcome; an existing or planned pregnancy; likelihood to undergo magnetic resonance imaging; and/or life expectancy of less than one year.

Procedures

Treatment involved a trial period of 3 weeks with percutaneously implanted electrodes, during which stimulation parameters were adjusted and the response to treatment monitored. After this the trial electrodes were removed and there was a mandatory washout period of at least 2 weeks. Permanent implantation followed successful trials, defined as a visual analogue scale (VAS) decrease of > 50% or a significantly benefi-

cial effect on the patient's quality of life. Other than the electrode location, the trial protocols were the same for both groups of patients. The stimulation technique was based on the surgeon's clinical assessment and intra-operative test stimulation. Figures 1 - 3 shows anterior-posterior and lateral x-rays demonstrating electrode placement in the cervical, thoracic, and lumbar spine.

Data Collection and Analysis

Average pain intensity was assessed on a visual analogue scale from 0 cm (no pain) to 10 cm (worst possible pain). Quality of life was assessed using the Short Form-36 (SF-36) questionnaire. SF-36 component summary scores were calculated using Canadian population norms. Patients were assessed prospectively at

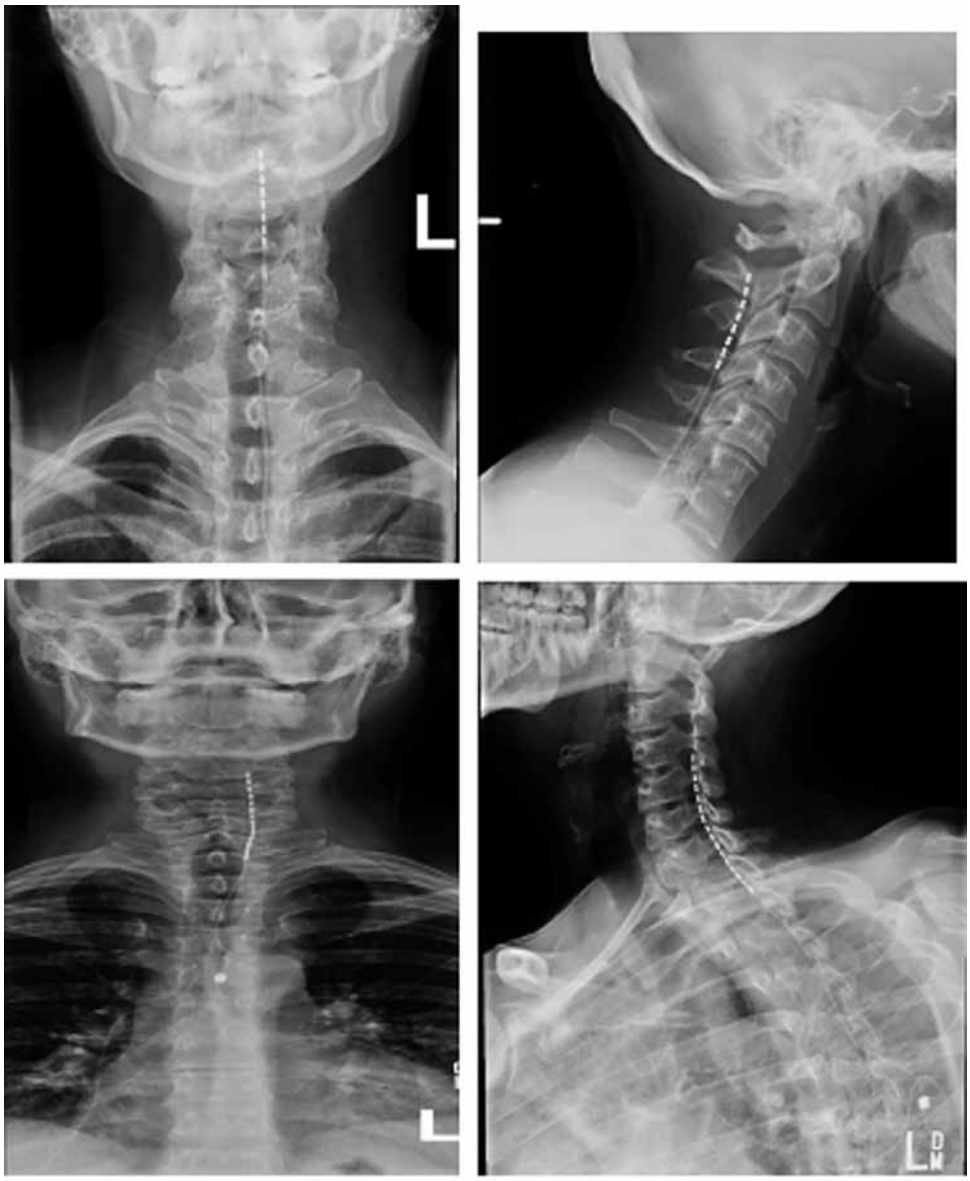

Fig 1. *AP (left) and lateral (right) x rays showing placement of cervical SCS (top) and DNRS (bottom) electrodes.*

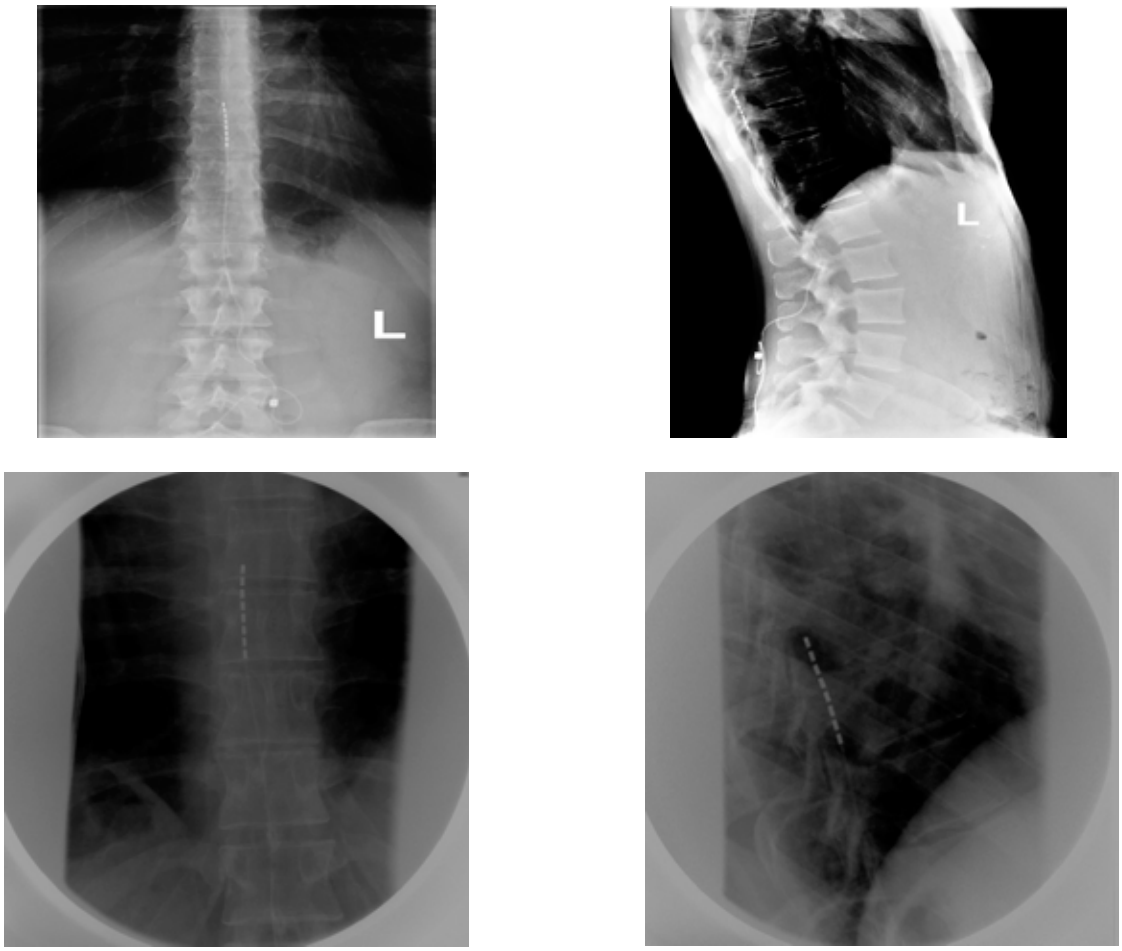

Fig 2. *AP (left) and lateral (right) x rays of thoracic SCS (top) and DNRS (bottom).*

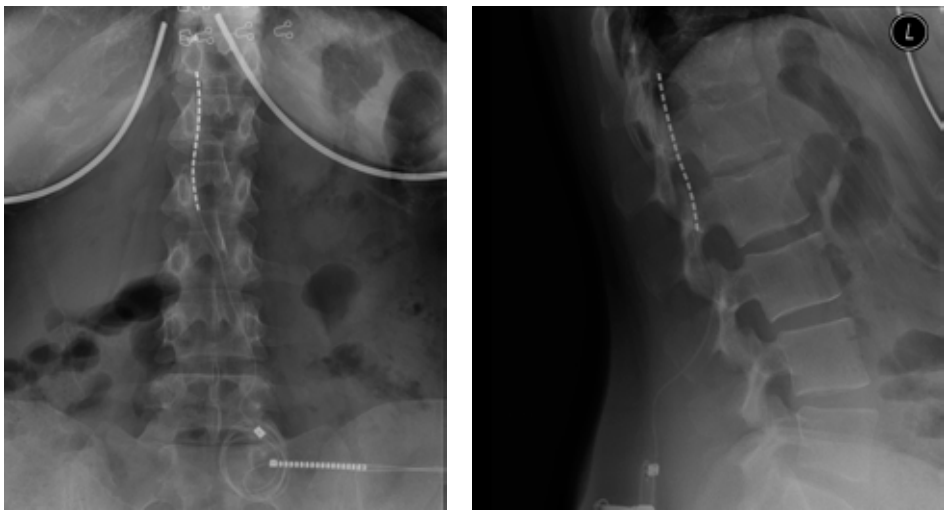

Fig 3. *AP (left) and lateral (right) x rays of lumbar DNRS.*

the following time points: before trial stimulation, 3 weekly trial visits, before permanent implantation, at 3, 6, and 12 month follow-up, and annually thereafter. Evaluations were performed by the neurosurgeon, a nurse trained in neuromodulation, or a research student. Results are reported at 12 months, with the exception of average VAS scores, which are plotted over the full 24 month follow-up.

A univariate analysis was carried out for each variable to test its association with the type of stimulation. The unpaired Student's t-test was used for the continuous variables and a Pearson $\chi 2$ statistic was used for the categorical variables. Wilcoxon rank sum test was used for non-parametric variables. For the categorical variables, if at least one cell on a 2x2 table had an expected value of less than 5, Fisher's exact test was used to obtain *P*-values. The unadjusted odds ratio and 95% confidence intervals (CI) were obtained for each of the categorical variables. A significance level of $\alpha = 0.05$ was chosen for all statistical tests and all *P*-values in this report are 2-tailed. All statistical analysis was completed with SAS® 9.2 (SAS Institute, Cary, NC).

Results

Patient Population and Trial Results

Of 132 eligible patients, 41 had trials of only DNRS, 82 of only SCS, and 9 of both techniques. Seventy-six patients went on to permanent implants, of whom 26 received only DNRS, 47 only SCS, and 3 both. Some patients had trials of concurrent peripheral field nerve stimulation; in this case, the trial results were reported based on the main stimulation method used. Three patients in the SCS group and one in the SCS + DNRS group have had their permanent devices removed. Due to the small size of the group with both SCS and DNRS, it was excluded from further analysis. Table 1 shows a breakdown of baseline characteristics for all patients receiving trials, divided into SCS and DNRS groups. The 2 groups did not differ significantly in age at implant, time since pain onset, gender proportions (52% of SCS patients and 59% of DNRS patients were women), baseline pain score, or employment status.

Pain location was classified as upper limb, lower limb, groin (includes abdomen), and other (includes back, thorax, and multiple primary sites). Pain diagnosis was classified as CRPS, FBSS, neuropathic pain not otherwise specified (NOS), central neuropathic pain, and other (includes postherpetic neuralgia, interstitial cystitis, pudendal neuralgia, and loin pain hematuria syndrome). Table 2 shows the pain locations, pain diagnoses, and electrode locations for the 2 groups of patients. The DNRS patients predominantly had pain in the upper limbs and groin, with the majority having a diagnosis of neuropathic pain NOS. In contrast, most (65%) SCS patients had pain in the lower limbs and there were similar numbers diagnosed with CRPS, FBSS, and neuropathic pain NOS. Accordingly, the SCS patients had their leads placed mainly in the region of the thoracic vertebrae, while the DNRS patients had a significant number in the cervical and lumbar spine.

Pain Reduction

Figure 4 shows the average VAS scores for all patients with available data in each group over the 24 months of follow-up. The baseline VAS scores for all patients trialed

Table 1. *Baseline patient characteristics*.

		SCS		DNRS	
Total patients trialled		82		41	
Age in years - mean (SD)		47.9	(11.5)	46.0	(12.0)
Years since pain onset - mean (SD)		7.4	(6.1)	5.6	(3.3)
Gender female - n (%)		43	(52)	24	(59)
Currently employed - n (%)		18	(23)	11	(28)
Visual analogue scale - mean (SD)		7.6	(1.2)	7.5	(1.4)
MEDD - mean (SD)		300	(449)	158	(258)
Short-form 36 - mean (SD)	N	50		28	
Physical functioning		24.1	(22.7)	42.9	(30.1)
Role-physical		4.1	(14.7)	13.8	(30.3)
Bodily pain		15.6	(15.0)	20.4	(17.2)
General health		58.7	(23.3)	50.2	(27.7)
Vitality		25.9	(18.5)	30.1	(19.7)
Social functioning		33.7	(23.7)	39.6	(23.8)
Role-emotional		22.2	(33.9)	22.4	(34.0)
Mental health		53.0	(20.6)	52.8	(22.5)
Health transition		38.8	(24.9)	40.0	(21.7)
Physical component summary**		24.9	(7.7)	29.0	(10.7)
Mental component summary**		34.1	(12.5)	33.2	(13.4)

**component summary scores were calculated using Canadian population norms

Table 2. *Pain characteristics and electrode placement.*

	SCS		DNRS	
	n	(%)	n	(%)
Pain location				
Upper limb	15	(18)	18	(44)
Lower limb	53	(65)	2	(5)
Groin	8	(10)	18	(44)
Other	6	(7)	3	(7)
Pain diagnosis				
CRPS	26	(32)	9	(22)
FBS	26	(32)	0	(0)
Neuropathic NOS	24	(29)	27	(66)
Central neuropathic	4	(5)	0	(0)
Other	2	(2)	5	(12)
Trial electrode location*				
Total patients	82		41	
Cervical	16	(20)	18	(44)
Thoracic	67	(82)	12	(29)
Lumbar	1	(1)	12	(29)
Sacral	0	(0)	3	(7)
Permanent electrode location*				
Total patients	47		26	
Cervical	12	(26)	12	(46)
Thoracic	37	(79)	9	(35)
Lumbar	0	(0)	8	(31)
Sacral	0	(0)	0	(0)

*Sum of 4 locations may add up to > 100% because some patients had electrodes at multiple locations.

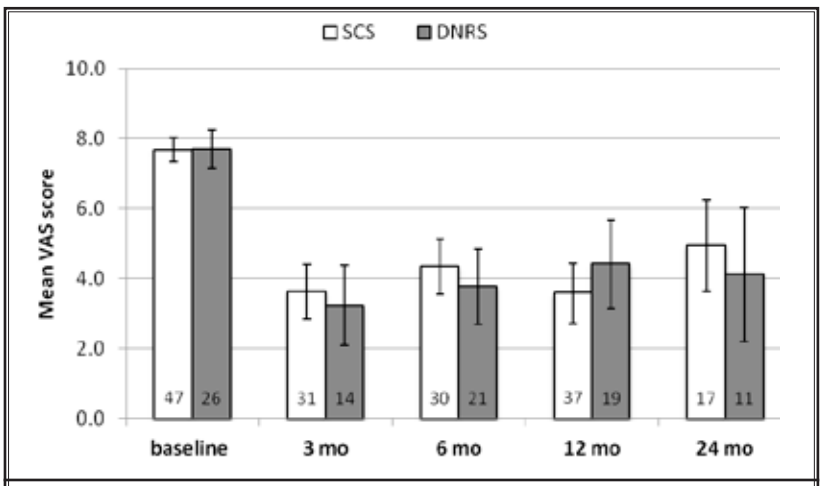

Fig. 4. *Aggregated average VAS pain score for implanted patients over 24 months follow-up (N shown within bars).*

were 7.5 (SD 1.4) and 7.6 (SD 1.2) for the DNRS and SCS groups, respectively. Among patients who progressed to permanent implant, the baseline scores were 7.7 (95% CI 7.2 – 8.2, SD 1.4) for DNRS patients and 7.7 (7.3 – 8.0, SD 1.2) for SCS patients. At 12 months the average VAS score had decreased to 4.4 (3.1 – 5.7, SD 2.6) for DNRS patients and 3.6 (2.7 – 4.4, SD 2.6) for SCS patients. Across all time points in the post-operative period, there were statistically significant decreases in average pain scores for both groups and no significant differences between the 2 groups.

Figure 5 is a breakdown of the pain responses for each group. Patients with > 50% VAS reduction were considered responders, 30% – 50% reduction partial-responders, and < 30% reduction non-responders. Both groups had close to half the patients achieving 50% pain reduction (47% of DNRS patients and 51% of SCS patients) and there was no statistically significant difference between the groups.

Secondary Endpoints

At baseline, both groups had large impairments in all subscores of the SF-36 quality of life survey. Figure 6 shows the difference between 12 months follow-up and the initial baseline score. Both groups had improvements in all subscores, with an average increase across all subscores of 33.9 for DNRS patients and 15.4 for SCS patients. There was statistically more improvement in DNRS patients in the mental health (P = 0.048), role emotional (P = 0.04), and vitality (P = 0.04) subscores. Table 3 shows the SF-36 mental component summary (MCS) and physical component summary (PCS) scores for patients who received permanent implants, taken at baseline and 12 month postoperative. There was a significant baseline difference between the PCS scores of the DNRS group and the SCS group (P = 0.02), and at 12 months both groups had improved a similar amount. The MCS scores were not significantly different at baseline, but by 12 months the DNRS group had improved by 17.1, while the SCS group had only improved by 1.5 (P = 0.01).

The average MEDD (morphine equivalent daily dose) at baseline assessment was 158 (SD 258) for DNRS patients and 300 (SD 449) for SCS patients. At 12 months, the average MEDD was 137 (SD 234) for DNRS

patients and 259 (SD 482) for SCS patients. There were 7 patients using methadone for pain relief during this study (6 in SCS group and one in the DNRS group) who had an average MEDD of 1317 (SD 715). Due to the wide range in opioid doses and resulting potential for outliers to skew average baseline values, it was better represented by dividing follow-

Table 3. *SF-36 component summary scores for patients with permanent implants.*

	SCS	DNRS	
Physical component summary			
Baseline	24.6	32.1	($P = 0.02$)
12 month	34.5	42.3	
Improvement	10.0	10.3	
Mental component summary			
Baseline	37.6	28.2	
12 month	39.2	45.6	
Improvement	1.5	17.5	($P = 0.01$)

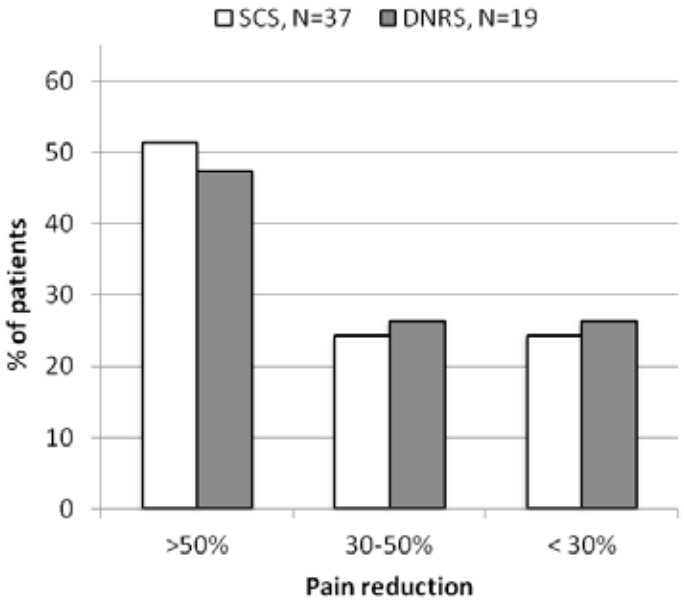

Fig. 5. VAS reduction at 12 mo., categorized as responders, partial responders, and non-responders by % pain reducation from baseline value.

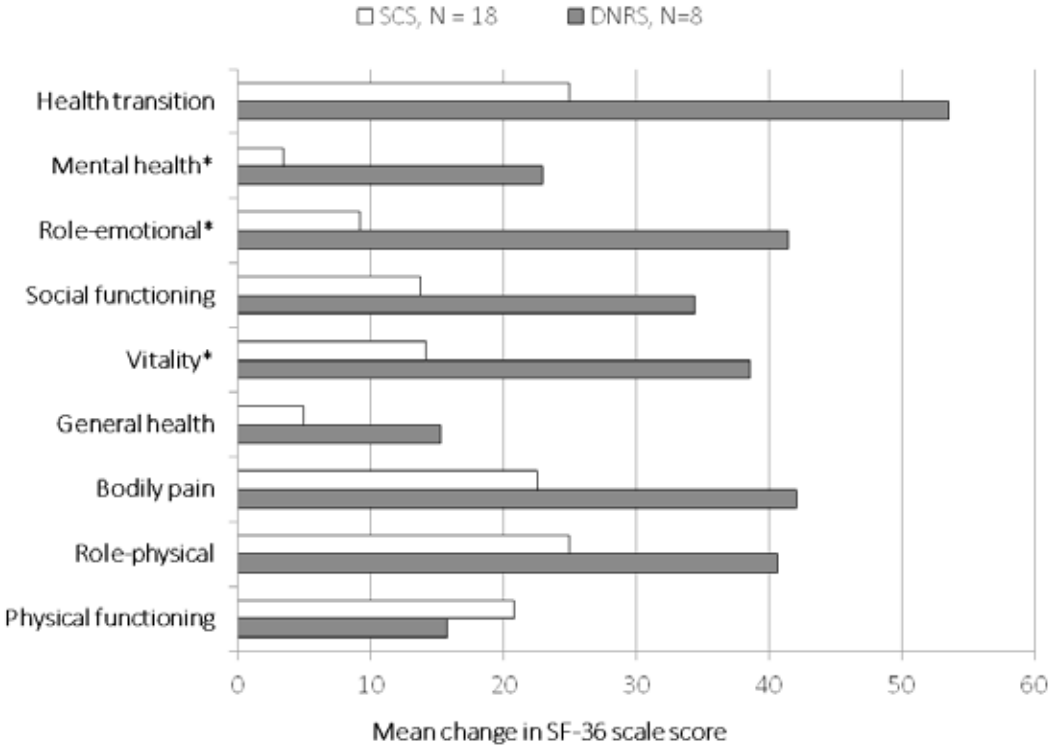

Fig. 6. *Short-form 36, change from baseline at 12 months (*between group P value < 0.05).*

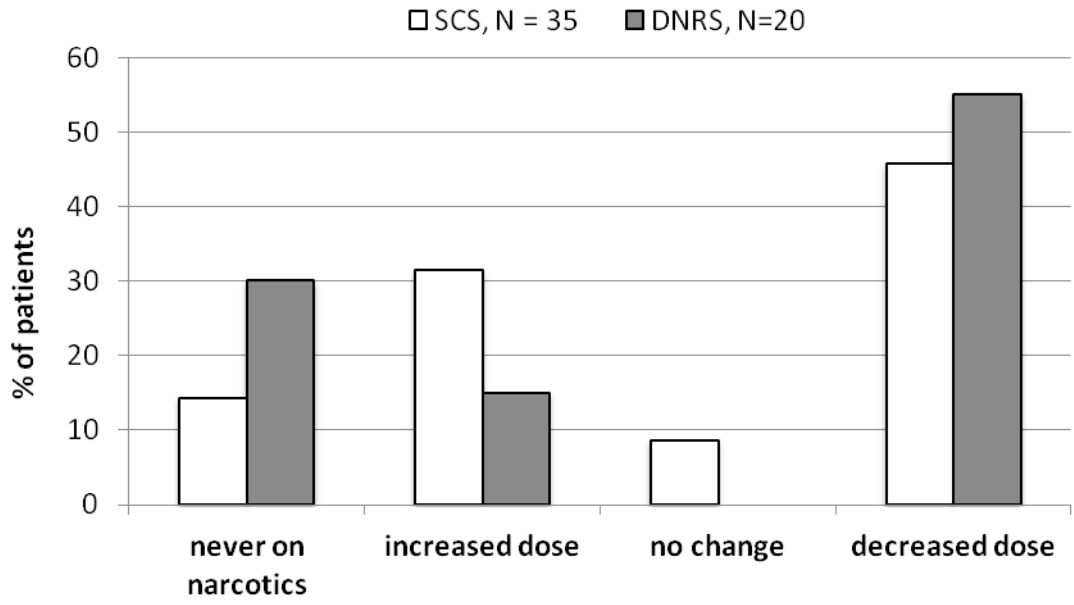

Fig. 7. MEDD change at 12 months compared to initial assessment, categorized as patients who were never on narcotics, increased MEDD, decreased MEDD, or had no change in MEDD.

Table 4. *Complications and revision operations.*

	SCS		DNRS	
	n	(%]	n	(%]
During trial period				
N	82		41	
Infection	7	(9)	5	(12)
Lead migration	8	(10)	6	(15)
CSF leak	6	(7)	0	(0)
During permanent implant				
N	47		26	
CSF leak	7	(15)	3	(12)
Revision operations				
1	11	(23)	5	(19)
>1	10	(21)	3	(12)

up data into 4 categories. These are shown in Fig. 7 as percentages of the total patients with available data. Among 20 DNRS patients with available opioid data at 12 months, 6 had never been on narcotics, 11 had decreased their dose (by an average of 67% compared to baseline), and 3 had increased their dose. Among 35 SCS patients, 5 had never been on opioids, 16 had decreased the dose (by an average of 70%), 11 had increased the dose, and 3 had no change. There was no statistically significant difference between the 2 groups.

At baseline 23% of SCS patients and 28% of DNRS patients were employed. Among patients who were initially unemployed and had data available at 12 months, 1/8 DNRS patients and 2/15 SCS patients had returned to work. Both treatment groups reported excellent patient satisfaction scores. Among DNRS patients, 10/11 (91%) responded yes to "are you satisfied with treatment" and 11/11 to "would you recommend treatment to a friend." Among SCS patients, 20/20 responded yes to both questions. On a clinical global impression scale with one corresponding to "very improved" and 7 corresponding to "very much worse," both groups had average scores slightly greater than 2.

Complications and Revision Operations

A breakdown of the complications during the implant operations and trial period and revisions required during the follow-up period is shown in Table 4. During the trial period the most common complications were skin infection and electrode lead migration. During the permanent implant operation, a cerebrospinal fluid (CSF) leak headache was experienced by 12% of DNRS patients and 15% of SCS patients. Revision operations

were required by 31% of DNRS patients (12% required 2 or more operations) and 45% of SCS patients (21% required 2 or more), which was not a statistically significant difference. The most common reasons for revisions were lead migration, to improve coverage of pain area, and lead fracture or other device malfunction.

Discussion

This study indicates that DNRS relieves pain, improves quality of life and functionality, and allows for medication reduction to a comparable degree as SCS. The positive results from SCS have been previously reported in randomized controlled trials (5,7,10,11), systematic reviews (24), and long-term retrospective studies (25). However, before this study there was minimal evidence supporting the efficacy of DNRS, particularly in the long term. We found similar results in VAS scores for the SCS and DNRS groups at all time points in the study and a similar proportion of DNRS and SCS patients achieved > 50% VAS reduction at 12 months, generally considered the benchmark for a successful response to treatment (26).

A review of 52 studies published in 2007 (27) found that neuropathic pain was associated with impairments in physical, emotional, and social functioning and in global quality of life (QOL), and that the specific pain diagnosis was not related to the severity of its effect on patient functioning. Our patients reported significant impairments in all SF-36 subscores at baseline, with no significant differences in any subscore between the 2 trial groups, although the DNRS group did trend towards higher average values. For patients receiving permanent implants, the DNRS group had a higher baseline physical component summary score. By 12 months, both groups had improvements in all SF-36 subscores and component summary scores, with the DNRS patients having a significantly greater increase in mental component summary than SCS patients.

Opioids have been found to have moderate success reducing neuropathic pain (28), however they are commonly associated with a number of unpleasant side effects (29,30). In our study the analysis of opioid use was complicated by the wide range in doses that patients were taking, as the baseline MEDD ranged from 0 to 2281, and particularly by the complexity in determining equianalgesic dosing for methadone (31,32). The average baseline MEDD was lower in the DNRS group but this was not statistically significant. At 12 months both groups had success in reducing opioid use, with 55% of the DNRS patients having decreased their MEDD.

Extracranial neuromodulation is generally a very safe treatment, with the most commonly cited complications being lead migration (13.2% incidence), lead breakage (9.1%), and infection (3.4%) (33-35). Less common complications include battery failure, CSF leakage related headache, pain over implant, allergic reaction, and spinal epidural hematoma. We did not observe any significant differences between the SCS and DNRS groups with respect to rates of infection, CSF leak, or need for revision operations.

Proposed Mechanisms

Despite almost 50 years of research, the mechanism of action of spinal stimulation is not completely understood. The paresthesias felt by patients is produced by orthodromic activation of the dorsal column. While this is considered to be a requirement for pain relief with conventional stimulation parameters, it is thought that these sensations are likely epiphenomenal, and the pain relief is due to antidromic dorsal column activation instead (36). There is evidence for an antidromic mechanism from neurophysiology studies showing that SCS produces action potentials in sensory peripheral nerves (37). The gate control theory posits that pain transmission is modulated via interneurons in the substantia gelatinosa (lamina II) of the dorsal horn through the balance of input from small fibers (both unmyelinated C fibers and thinly myelinated Aδ fibers) that "open" the "gate" and large myelinated Aβ fibers that "close" the gate. Antidromic activation of the Aβ fibers in the dorsal column increases input from inhibitory interneurons to second order spinothalamic projection neurons of the wide dynamic range (WDR) type. While this theory is elegant, there are observations of SCS that it does not explain the inability to treat acute nociceptive pain or chronic non-neuropathic pain, and the carryover effect that persists after stimulation is turned off (38,39).

SCS is also hypothesized to affect neurotransmitter levels in the dorsal horn. In rat models of neuropathic pain, SCS was shown to raise levels of gamma-aminobutyric acid (GABA) and decrease levels of excitatory amino acids (EAAs) glutamate and aspartate (40). The changes in neurotransmitter levels correlated with the reduction of allodynia in the models and persisted beyond the stimulation period, which would explain the carryover effect seen clinically. Furthermore, it has been observed that the efficacy of SCS in rats is potentiated by the GABA-B agonist baclofen and inhibited by GABA-B antagonist 5-aminovaleric acid (41).

We see no reason why stimulation of the dorsal

nerve roots would have a significantly different physiologic effect than stimulation of the dorsal column, other than the distribution of coverage. The dorsal column mainly carries Aβ fibers, while the nerve roots also carry Aδ and C fibers that synapse in the dorsal horn and then form the spinothalamic tract. However, given that the stimulation threshold of a nerve fiber is inversely related to its diameter, it is unlikely that the smaller fibers would be activated by a current applied at appropriate parameters to activate Aβ fibers (42). Prior studies on DNRS have identified unpleasant motor effects such as cramping as a significant impediment to its long-term use. In our experience, when the electrode is correctly placed on the dorsal root, these effects occur only with stimulation amplitudes well above what are needed to obtain paresthesias.

Strengths and Limitations

This study has several strengths. It is the first study to follow a large group of DNRS patients for a significant length of time. This is based on a literature review using the US National Library of Medicine PubMed database and Google Scholar with the search term "nerve root stimulation AND pain," and the identification of additional references from the bibliographies of publications, reviews, and textbooks. As endpoints, we have included both aggregated average pain scores as well as the benchmark of 50% pain reduction (26), which is above the estimated minimum clinically important difference of 30% reduction (43). The patients in both groups were referred to us from the same sources and had similar baseline characteristics other than pain location and diagnosis, indicating that the pain is equally severe and chronic in both groups. SCS is a well endorsed and widely used treatment, but the majority of studies on SCS are in patients with lower limb pain. Our results demonstrate that DNRS can provide excellent results for pain in other locations.

The main limitation of our study is due to its nature as a self-funded clinical study that uses data obtained through routine clinical practice. Accordingly, some data is missing due to missed appointments, incomplete surveying at appointments, and complications requiring revision operations. While it would have been ideal to break down the outcomes by specific pain diagnosis (FBSS, CRPS, etc.), unfortunately we did not have sufficient numbers to draw reliable conclusions on this. A potential source of bias is that the majority of the assessments were not done by an independent third party. However, given that the data for our primary and secondary outcomes come from patient surveys, the risk of this bias is small.

This study was not randomized between the 2 treatments and therefore does not provide direct comparison between the techniques. That being said, our objective was not to demonstrate that DNRS is superior to SCS. Rather, contrary to the prevailing view that DNRS does not work, it can be equally effective in appropriately selected patients. Given that the 2 techniques are directed at somewhat different patient groups with respect to pain location and/or diagnosis, it would be difficult to have a randomized study comparing the 2 techniques. The optimal study on DNRS would likely be one randomizing it with best medical management, similarly to what has been done for SCS.

Conclusion

Our findings indicate that at 12 months follow-up, DNRS is effective in producing meaningful pain reduction, improved quality of life, and opioid dose decreases. We believe it is a useful supplementary technique for the treatment of chronic neuropathic pain, particularly for patients with pain in distributions that are difficult to cover with traditional SCS.

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