Original Research

Spinal Cord Stimulation (SCS) with Anatomically Guided (3D) Neural Targeting Shows Superior Chronic Axial Low Back Pain Relief Compared to Traditional SCS—LUMINA Study

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Abstract

Background. The aim of this study was to determine whether spinal cord stimulation (SCS) using 3D neural targeting provided sustained overall and low back pain relief in a broad routine clinical practice population.

Study Design and Methods. This was a multicenter, open-label observational study with an observational arm and retrospective analysis of a matched cohort. After IPG implantation, programming was done using a patient-specific, model-based algorithm to adjust for lead position (3D neural targeting) or previous generation software (traditional). Demographics, medical histories, SCS parameters, pain locations, pain intensities, disabilities, and safety data were collected for all patients.

Results. A total of 213 patients using 3D neural targeting were included, with a trial-to-implant ratio of 86%. Patients used seven different lead configurations, with 62% receiving 24 to 32 contacts, and a broad range of stimulation parameters utilizing a mean of 14.3 (±6.1) contacts. At 24 months...
intervention, pain intensity decreased significantly from baseline (ΔNRS = 4.2, N = 169, P < 0.0001) and even more in the severe pain subgroup (ΔNRS = 5.3, N = 91, P < 0.0001). Axial low back pain also decreased significantly from baseline to 24 months (ΔNRS = 4.1, N = 70, P < 0.0001, on the overall cohort and ΔNRS = 5.6, N = 38, on the severe subgroup). Matched cohort comparison with 213 patients treated with traditional SCS at the same centers showed overall pain responder rates of 51% (traditional SCS) and 74% (neural targeting SCS) and axial low back pain responder rates of 41% and 71% in the traditional SCS and neural targeting SCS cohorts, respectively. Lastly, complications occurred in a total of 33 of the 213 patients, with a 1.6% lead replacement rate and a 1.6% explant rate.

Conclusions. Our results suggest that 3D neural targeting SCS and its associated hardware flexibility provide effective treatment for both chronic leg and chronic axial low back pain that is significantly superior to traditional SCS.

Key Words. Spinal Cord Stimulation; Chronic Pain; Low Back Pain; Spectra; 3D Neural Targeting SCS

Introduction

Chronic pain, estimated to affect up to 55% of the US population [1–6], has been treated using a variety of approaches. Spinal cord stimulation (SCS) has been used effectively over the past decades to treat chronic neuropathic pain in the trunk and limbs. While treatment of leg pain has been successful, treatment of axial low back pain with traditional SCS has been challenging [7–11]. Anatomical factors are considered to be significant contributors to the complexity in treating low back pain with SCS. In particular, in the lower thoracic spine, the position of the accessible neural fibers innervating the low back area is believed to be in the lateral part of the dorsal columns near the larger and more excitable dorsal roots. The excitation of the dorsal roots in these thoracic spinal regions can contribute to unwanted abdominal stimulation [12]. Further, in the midthoracic spinal regions where back coverage is most likely to be attained, the contacts are separated from the spinal cord by up to several millimeters of highly conductive cerebrospinal fluid [13], making it more difficult to stimulate the back fibers without generating side effects at the dorsal roots [12,14]. Studies of traditional SCS technologies have shown that traditional SCS has difficulties overcoming the challenges in stimulating low back fibers [9]. Recent small studies [15] suggest that technical advancements designed to enable better control of the paresthesia location could yield improvements. Traditionally electrical stimulation of the dorsal columns is associated with paresthesia. Optimal overlap of paresthesia with the area of pain has been a prerequisite for good outcomes and pain-relieving stimulation. Electrical field steering for optimal paresthesia can be challenging due to multiple factors influencing it. Computer modeling taking into account anatomy, neurophysiology, and stimulation-induced electrical fields’ effects on nerve fibers on a three-dimensional volume conductor model provides insight that can potentially lead to improvement of SCS outcomes. Alternative SCS approaches have focused on augmenting the temporal domain, either by increasing the rate of stimulation to very high rates [16,17] or by altering the temporal pattern [18]. However, there are several drawbacks to these approaches. First, these modalities deplete the battery much more rapidly, requiring more frequent recharging. Second, these modalities appear to have significantly longer "wash in" times and require few hours to a couple of days or longer before the patient experiences their benefit [16,17]. As a result, programming optimization may take longer as it is difficult to determine in the clinic whether the lead placement, contact configuration, and stimulation parameters have been optimally selected.

A new method to improve SCS outcome for axial low back pain transforms how the desired neural targets are selected. The approach, called Anatomically Guided Neural Targeted, uses a combination of independent current control with up to 32 contacts and a three-dimensional programming algorithm that calculates precisely how much current is needed at each contact. The algorithm is based on a 3D anatomical model that takes into account the electrical conductivity of spinal column structures—including dorsal CSF depth, relative lead location, and vertebral level of the leads. This system was developed to supplant an already advanced traditional SCS system (PRECISION) that had the ability to fractionate current by 1% increments between contacts. These advances have allowed specific steering to the stimulation to target locations and, with the use of Anatomically Guided 3D Neural Targeting, rely at the outset on model-based calculation of how to optimally position the central points of stimulation. When stimulation is turned on, a central point of stimulation (CPS) is generated, enabling precise real-time targeting of the stimulation field to the nerve fibers needed to recruit. By stimulating the right nerve fibers, the objective is to achieve consistent axial low back pain relief compared with traditional SCS. Unlike traditional SCS, which utilizes a trial-and-error method of turning on and off contact electrodes in a trial-and-error fashion in order to achieve desired paresthesia, the novel anatomically guided 3D neural targeting relies on a priori calculations in order to target the "sweet spot" of stimulation.

To test the hypothesis that neural targeting can provide effective low back pain relief, we performed a multicenter, long-term pragmatic clinical study of over 200 patients. We examined the improvement in pain scores observed in real-world clinical practice, which would indicate the effectiveness of SCS therapy and would support the decision-making process on specific chronic pain clinical phenotypes best treated by neuromodulation. Real world refers to the concept of "real world
Study Cohorts

3D Neural Targeting SCS Cohort. Two hundred thirteen patients consecutively trialed with 3D neural targeting SCS who met the inclusion criteria were enrolled in the study. This cohort was treated with the Precision Spectra SCS System, which supports up to 32 contacts and has multiple current sources and a three-dimensional model-based algorithm that takes into account multiple anatomical variables along the vertebral spine that affect SCS current delivery (Precision Spectra, Boston Scientific Corporation, Valencia, CA, USA).

Traditional SCS Cohort. All consecutive patients treated at the participating study center with the prior generation Precision SCS System (Precision, Boston Scientific Corporation, Valencia, CA, USA) were considered for inclusion in the study. This system has been commercially available since 2004 and supports up to 16 contacts with multiple current sources, but without the model-based algorithm. Propensity score matching (PSM) was used for inclusion of 213 patients trialed/implanted with traditional SCS (see Data Collection and Statistical Analysis).

Device Description

The 3D neural targeting SCS cohort in this study was treated with the Precision Spectra SCS System (Boston Scientific Corporation, Valencia, CA, USA). The system delivers stimulation from an implantable pulse generator (IPG) with up to 32 contacts on leads that are implanted in the epidural space of the spinal canal. The device can deliver different amounts of current to each of the 32 contacts assigned by the Illumina 3D programming algorithm. The algorithm uses a patient-specific, model-based method designed to enable particularly efficient programming by allowing the clinician to specify the central point of stimulation (CPS) in high resolution using real time up/down/left/right adjustment (e.g., 300 microns in the rostral-caudal direction) with intuitive high-level controls (Figure 1). The algorithm automatically assigns anode/cathode/off and percentage (%) current for each contact, accounting for lead positions. Current fractionation is possible down to 1 percentile increments. Furthermore, the algorithm allows the user to adjust anode-cathode spacing, or Focus, a parameter theorized to be important in adjusting the ratio of the dorsal root threshold-to-dorsal column threshold [19,20]. The model employed is a finite-element model of the spinal canal that accounts for relative lead positions, distance between leads, CSF thickness, and electrical conductivities of several tissue domains and uses an inverse solution method (minimization of squared differences between the modeled desired field and the field that the model predicts to be achievable with the physical contacts) (Figure 1). The algorithm relies on the system’s ability to assign both polarity and percentage of total current (resolution = 1%) using the multiple current source architecture.
The traditional SCS cohort was treated with the Precision SCS System (Boston Scientific Corporation, Valencia, CA, USA). Like Precision Spectra, Precision can control the amount of current delivered to each and every contact, that is, multiple independent current control (MICC). It supports up to 16 contacts and two lead ports. Device parameters are optimized manually, generating the stimulation field by assigning individual contacts.

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Figure 1 3D neural targeting programming algorithm. The programming algorithm (A) is shown with inputs and outputs. The core of the algorithm is a well-posed least-squares matrix equation that relies on the finite element model of spinal cord stimulation (SCS) shown in panel (B) [20]. The stimulation field model includes distinct electrical properties for several tissue domains and incorporates estimates of the lead positions in three dimensions based on inputs from the user in a lead configuration screen (not shown). In the equation, the electrical behavior of the model is encapsulated in the transformation matrix $A$, and the desired stimulation field input by the user as a central point of stimulation (CPS) is represented as $\varphi$. Given the model $A$ and the desired stimulation $\varphi$, the distribution of currents for each electrode to best approximate $\varphi$ can be calculated as $J$. When the CPS is incrementally steered by the user, the algorithm also modulates the amplitude to attempt to keep the stimulation intensity constant. An example is shown in panels (C) and (D). In this example, the color map in panel (C) represents a desired stimulation field (scalar potential, $u$) generated by a simple bipole from two imaginary contacts (dotted white rectangles). The algorithm outputs the polarity and percent current (integers in (D)) on each of the available physical contacts (rectangles, representing two eight-contact leads that are staggered) such that the color map of panel (D) best mimics that of (C) in a least-squares sense. Note the similarity of the color maps. Also note the complexity of the current distribution that is automated by the algorithm. The solution afforded by the algorithm allows the clinician greater flexibility in choosing the desired stimulation field.
anode and cathode locations along the leads by trial and error based on patients’ feedback regarding paresthesia location.

Procedures

The SCS trial and permanent implantation procedures were performed per each center’s standard practice. No lead location or lead type was mandated. Trial duration was between three and seven days, based on individual patient requirements. Trial success was assessed by percent pain relief (PPR), where a successful trial was defined as a PPR of 50% or greater. At permanent implant, the IPG was placed in either the buttock or abdominal area, per the directions for use. During the implantation procedure, fluoroscopic imaging was used to guide the leads within the epidural space of the spinal canal. In the 3D neural targeting group, up to four leads and 32 contacts could be used, and programming was done with the patient-specific, model-based algorithm that accounted for lead position (Table 2; Figures 3 and 4). In the control group, up to two leads and 16 contacts could be used, and programming was done with previous generation (traditional) software that does not have the model-based algorithm that automatically accounted for lead position. In both groups, reprogramming could be done as needed per standard of care.

Data Collection and Statistical Analysis

To minimize potential bias, data collection from patients was performed directly by clinical site personnel, without Sponsor involvement, for baseline (pre-SCS trial), trial, implant, three months, six months, 12 months, and 24 months post–implant procedure. Demographic information, medical history, stimulation parameters, pain locations, pain intensity, and safety data were collected for all patients. The primary outcome measure of pain intensity was collected on a 0–10 NRS where 0 = no pain and 10 = the worst pain imaginable. Responder rate analysis was performed in the 3D neural targeting SCS cohort to control for the difference between a statistically significant and a clinically significant change. It is acceptable to define a responder to be between 30–50% [21]. In this analysis, a responder was defined as any patient showing 50% or greater reduction from baseline in NRS score.

Data were summarized using descriptive statistics for continuous variables (e.g., mean, standard deviation, N, minimum, maximum), frequency tables or proportions for discrete variables, and 95% confidence intervals. Statistical significance was tested using analysis of variance (ANOVA) for repeated measures. In this analysis, responder rate was based on the proportion of patients showing a 50% or greater reduction in their reported NRS pain score between baseline and follow-up (it is clinically acceptable to define responder to be between 30–50% [21]). Statistical analysis was performed using SAS version 9.3 (SAS, Cary, NC, USA).

Comparison between the 3D neural targeting and the traditional SCS cohorts was performed using propensity score matching (PSM). Statistical matching is an increasingly popular method for removing imbalance in the empirical distribution of the pretreatment confounders between the treatment and control groups [22,23]. PSM is a statistical matching technique for unbiased comparison of a treatment effect estimate between two groups of patients in a nonrandomized study by accounting for the covariates that predict whether the treatment was received instead of randomizing patients to treatment or control. The propensity score matching algorithm was implemented following Dehejia and Wahba 2002 [24]. Accordingly:

\[
\tilde{\tau}_{iT} = 1 - \frac{1}{|N|} \sum_{i=1}^{N} \left( \frac{1}{|J_i|} \sum_{j=1}^{|J_i|} Y_j \right)
\]

where \( N \) is the treatment group, \(|N|\) is the number of units in the treatment group, \( J_i \) is the set of comparison units matched to treatment unit \( i \), and \(|J_i|\) is the number of comparison units in \( J_i \). Single nearest-neighbor matching without replacement was applied to include 213 propensity score–matched patients from the full consecutively trialed traditional SCS patients. Nearest-neighbor ties were adjudicated by the treated-first rule to replicate consecutive enrollment. Confounders in the model included site, gender, age, diagnosis, pain location, and pain severity.

Results

Patient Enrollment and Baseline Characteristics

A total of 213 patients were included in the 3D neural targeting SCS cohort with fully consecutive inclusion at the 11 participating centers during the enrollment period. Baseline and trial data were available for all 213 patients. Table 1 displays the characteristics of the study population. Both cohorts appear similar in baseline characteristics. No statistically significant differences in baseline characteristics were found between the two cohorts, indicating a successful PSM procedure. The three-month follow-up data were available for all patients who received a permanent implant (N = 184). Data from the six-month, 12-month, and 24-month follow-up visits were available from 181, 178, and 169 patients, respectively, reflecting minimal loss to follow-up or early attrition during the study period (92% data completeness at 24 months). At baseline, the mean (±SD) patient age was 56.8 (±14.39) years and 63% of the patients were female. The most common primary diagnosis for receiving SCS was failed back surgery syndrome (36%). Patients with chronic axial low back pain (no radicular component to their pain) comprised 42% of the cohort (N = 89), while patients with both leg and low back
pain comprised 38% (N = 80) and patients with only leg pain comprised 21% (N = 44). The distribution of pain scores (0–10 scale) at baseline is shown in Figure 2. Mean baseline pain intensity score [NRS] was 7.2 ± 2.06, and median baseline pain was 8 (N = 213). Nearly 90% of patients reported either moderate or severe pain at baseline, with over half reporting severe pain (N = 108 with baseline NRS pain scores of 8–10) (Figure 2). Apart from improving pain scores, the decision to proceed with SCS was mutual between patient and clinician and was based on desire to improve function and sleep and reduce analgesic medication use.

### Table 1 Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>3D neural targeting SCS</th>
<th>Traditional SCS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>56.8 (±14.39)</td>
<td>59.2 (±11.21)</td>
</tr>
<tr>
<td><strong>Gender [N (%)]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>135 (63.4)</td>
<td>144 (67.6)</td>
</tr>
<tr>
<td>Male</td>
<td>78 (36.6)</td>
<td>69 (32.4)</td>
</tr>
<tr>
<td><strong>Primary diagnosis [N (%)]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failed back surgery syndrome</td>
<td>76 (35.7)</td>
<td>81 (38.0)</td>
</tr>
<tr>
<td>Chronic spinal pain</td>
<td>73 (34.3)</td>
<td>65 (30.5)</td>
</tr>
<tr>
<td>Radiculopathies</td>
<td>23 (10.8)</td>
<td>27 (12.7)</td>
</tr>
<tr>
<td>Degenerative disc disease</td>
<td>15 (7.0)</td>
<td>19 (8.9)</td>
</tr>
<tr>
<td>Complex regional pain</td>
<td>10 (4.7)</td>
<td>13 (6.1)</td>
</tr>
<tr>
<td>Other*</td>
<td>16 (7.5)</td>
<td>8 (3.8)</td>
</tr>
<tr>
<td><strong>Pain distribution [N (%)]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low back only†</td>
<td>89 (41.8)</td>
<td>67 (31.5)</td>
</tr>
<tr>
<td>Legs and low back</td>
<td>80 (37.6)</td>
<td>95 (44.6)</td>
</tr>
<tr>
<td>Legs only</td>
<td>44 (20.7)</td>
<td>51 (23.9)</td>
</tr>
<tr>
<td><strong>Pain severity [mean SD, n]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall pain</td>
<td>7.17 ± 2.06 (213)</td>
<td>7.09 ± 2.60 (213)</td>
</tr>
<tr>
<td>Low back pain</td>
<td>7.21 ± 1.96 (89)</td>
<td>7.32 ± 2.24 (67)</td>
</tr>
</tbody>
</table>

*The Other category includes diagnoses found in three patients or fewer (e.g., neuropathies, spinal deformities).
†Low back only pain distribution reflects axial low back pain.

**Figure 2** Distribution of baseline pain intensities (3D neural targeting spinal cord stimulation [SCS] cohort). Majority of patients reported either moderate or severe pain at baseline, with half of all patients reporting severe pain.
SCS Trial and Implant

A total of 213 consecutive patients underwent percutaneous SCS epidural lead placement for SCS trial, which lasted three to seven days. The trial success rate was 94% (N = 200/213), with 200 patients proceeding to SCS implant. Additionally, two patients who had a 40% PPR were identified by the clinicians as appropriate for receiving a permanent SCS implant due to marked improvement in self-reported quality of life and a strong desire to continue with SCS treatment. Due to insurance restrictions and other external constraints, the final number of patients who moved on to receive permanent SCS implant was 184, corresponding to an 86.4% trial-to-perm rate. During the implantation procedure of the 3D neural targeting cohort, SCS leads were placed primarily between the T6 and T9 vertebral levels, based on the location of the rostral lead tip (Figure 3). The majority of patients were implanted with leads placed at the T8 vertebral level (42%), followed by T7 (30%). There was a variety of different lead configurations across the 184 implanted patients, as shown in Table 2. The predominant lead configurations were two 16-contact percutaneous leads (37%), two eight-contact percutaneous leads (35%), and four percutaneous eight-contact linear leads (12%). These configurations correspond to a variable number of total contacts between 16 and 32. This variation is shown further in Figure 4 with the percent of patients implanted with one, two, three, and four leads and the percent of patients implanted with eight, 16, 24, and 32 contacts (electrodes). The predominant number of leads implanted was two leads (72%), and the predominant number of contacts implanted was 32 (52%), followed by 16 (37%).

Patients were treated with a wide range of stimulation parameters, as seen in Table 3, optimized to each patient’s requirements per standard clinical practice. The mean frequency of stimulation was 59.8 Hz (±109.3 Hz) at a 5.64 mA (±3.43 mA) mean amplitude. Notably, the mean number of programs used per patient during the study was 5.9 (±4.0), using, on average, 14.3 contacts (±6.1).
Reduction in Overall Pain (Low Back and Leg Pain)

Mean overall pain prior to treatment for the 3D neural targeting cohort was 7.17 ± 2.06 (N = 213) on a 0–10 scale. The pain intensity score decreased significantly from implant baseline to 3.21 ± 2.20 (N = 184), 2.92 ± 2.07 (N = 181), and 2.94 ± 2.62 (N = 169) at three, six, and 24 months, respectively, a statistically significant long-term difference of 4.23 NRS points (P < 0.0001, ANOVA) (Figure 5).

To examine whether the clinical outcomes of 3D neural targeting SCS were dependent on patients’ baseline pain severity, we also analyzed pain reduction in the cohort of severe pain patients, defined as those patients with a baseline NRS score of 8–10 (N = 108). The overall mean pain of 8.75 ± 0.78 (N = 108) at baseline was reduced to 3.35 ± 2.38 (N = 98) by three months and 3.03 ± 2.23 (N = 96) by six months postimplant. This reduction was sustained out to 24 months postimplant, with an overall mean pain of 3.41 ± 2.33 (N = 91), a statistically significant difference of 5.34 NRS points (P < 0.0001, ANOVA).

Improvement in Axial Low Back Pain

Of the 213 total patients trialed in this study, 89 patients were treated for chronic axial low back pain only (chronic low back pain with no radicular component). Mean low back pain prior to treatment was 7.21 ± 1.96 (N = 89). At three months postimplant, the mean low back pain was 3.51 ± 2.02 (N = 76), and by six months it reached 3.1 ± 1.95 (N = 74) and was sustained through 24 months with a mean NRS score of 3.1 ± 2.6 (N = 70) (Figure 6). This corresponds to a statistically significant difference of 4.1 NRS points (P < 0.0001, ANOVA). The severe axial low back pain patients started with a baseline mean of 8.6 ± 0.7 (N = 49) and reported a mean low back pain of 3.5 ± 2.2 (N = 43) at three months postimplant. At six months postimplant, this was reduced to a mean of 3.1 ± 2.0 (N = 42) and remained below three through 24 months postimplant at 3 ± 2.4 (N = 38), a statistically significant long-term difference of 5.6 points (P < 0.0001, ANOVA).

Responder Rate Analysis

At three months postimplant, 64% of patients were responders to 3D neural targeting SCS, with 50% or more

Table 3  Device stimulation parameters during 24-month study period (3D neural targeting SCS cohort)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulation amplitude</td>
<td>5.64 ± 3.43 mA</td>
</tr>
<tr>
<td>Pulse width</td>
<td>392 ± 232 µsec</td>
</tr>
<tr>
<td>Stimulation frequency</td>
<td>59.8 ± 109.3 Hz</td>
</tr>
<tr>
<td>Number of programs per patient</td>
<td>5.9 ± 4.0</td>
</tr>
<tr>
<td>Number of anodes per patient</td>
<td>9.3 ± 5.2</td>
</tr>
<tr>
<td>Number of cathodes per patient</td>
<td>9.0 ± 5.0</td>
</tr>
<tr>
<td>Number of electrodes per patient</td>
<td>14.3 ± 6.1</td>
</tr>
</tbody>
</table>
reduction in overall pain from baseline. By six months postimplant, the responder rate reached 73% and remained stable long-term through the entire duration of the study, reaching 74% at 24 months post–implant procedure (see Figure 7). Responder rate analysis of the axial low back pain cohort showed very similar results.

Figure 5 Mean overall pain from baseline to 24 months postimplant procedure (3D neural targeting spinal cord stimulation cohort). All patients are shown in the full cohort, and severe patients refers to the patient subgroup with baseline numeric rating scale score of 8–10. Statistical significance reflects results of repeated measures analysis of variance.

Figure 6 Mean axial low back pain from baseline to 24 months postimplant procedure (3D neural targeting spinal cord stimulation cohort). The graph to the left reflects full axial low back pain cohort, and severe patients in the graph to the right reflects the patient subgroup with baseline numeric rating scale score of 8–10. Statistical significance reflects results of repeated measures analysis of variance.
While at three months postimplant 58% of patients were responders, by six months the responder rate was at 72% and remained stable long term, with 71% of axial low back pain patients showing 50% or more reduction in low back pain (Figure 7).

Comparison of 3D Neural Targeting SCS over Traditional SCS

A cohort of 213 propensity score–matched patients trialed and implanted with traditional SCS without the 3D neural targeting algorithm was analyzed retrospectively for direct comparison with the 3D neural targeting SCS patients. Table 1 shows the baseline characteristics of this cohort. At baseline, the mean (±SD) patient age was 59.2 years (± 11.21 years) and 68% of the patients were female. As in the 3D neural targeting cohort, the most common primary diagnosis for receiving SCS was failed back surgery syndrome (38%). Patients with chronic axial low back pain (no radicular component to their pain) comprised 32% of the cohort (N = 67), while patients with both leg and low back pain comprised 45% (N = 95) and patients with only leg pain comprised 24% (N = 51). Overall pain and low back pain did improve significantly to 24 months in this cohort (Figure 8). The overall mean pain of 7.1 ± 2.6 (N = 213) at baseline was reduced at 24 months postimplant to an NRS of 4.1 ± 2.9 (N = 141), a statistically significant difference of 2.97 NRS points (P < 0.001, ANOVA). The mean low back pain of 7.32 ± 2.2 (N = 67) at baseline was reduced at 24 months postimplant to a mean low back pain of 5.5 ± 2.5 (N = 45), a statistically significant difference of 1.81 NRS points (P = 0.01, ANOVA). The percentage of patients with 50% or greater reduction in NRS pain scores from baseline (responders) after 24 months of treatment with either neural targeting SCS or a previous-generation device not employing neural targeting stimulation (Figure 9). This long-term responder rate was approximately 1.5 times greater with 3D neural targeting SCS than with the previous-generation system in the overall patient cohort (P < 0.01). This difference was driven primarily by the statistically significant superiority of the 3D neural targeting SCS treatment in the chronic axial low back pain patients, with a 71% responder rate compared with 41% (P < 0.001). The responder rate in the leg pain–only patients was significantly higher in the 3D neural targeting SCS cohort as well (P < 0.05).

Complications

Among the 213 patients in the 3D neural targeting SCS cohort, there were a total of 43 complications across 33 patients throughout the course of the 24-month follow-up period (Table 4). The SCS system was explanted in 1.6% of patients (N = 3). Approximately 3% of patients (N = 5) had a lead revision, while 1.6% (N = 3) had a lead replaced. During the course of the study, 3.8% of patients reported inadequate stimulation (N = 8) and less than 1% reported overstimulation (N = 2). IPG site pain was reported in 3.8% of patients (N = 7), and high impedance across one or more contacts was reported in 2.8% of patients (N = 6). Finally, only one patient (0.5%) reported stimulation in a nontarget area. Two patient deaths were reported, both unrelated to SCS treatment.

The complication rate reflects the number of patients presenting with complications (N) over the total number of patients with potential for complications (213 trialed patients, 184 IPG implanted patients). Overstimulation occurred in less than 1% of patients, and stimulation in
Figure 9  Long-term responder rates of 3D neural targeting spinal cord stimulation (SCS) compared with traditional SCS with a previous generation system. At 24 months postprocedure, responder rate for SCS with 3D neural targeting was superior to traditional SCS without 3D neural targeting for overall pain, leg pain only, and axial back pain patients. In particular, the responder rate is approximately 1.5 times and 1.7 times higher for overall pain and axial back pain, respectively. (3D neural targeting cohort patients were implanted with Precision Spectra System, while previous generation cohort patients were implanted with Precision System.) Superiority of anatomically guided 3D neural targeting SCS was most statistically significant in the axial low back pain cohort.
Table 4  Complications during 24-month study period (3D neural targeting SCS cohort)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Complication rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate stimulation</td>
<td>3.8% (N = 8)*</td>
</tr>
<tr>
<td>IPG site pain</td>
<td>3.8% (N = 7)†</td>
</tr>
<tr>
<td>High impedance</td>
<td>2.8% (N = 6)†</td>
</tr>
<tr>
<td>Lead revision</td>
<td>2.7% (N = 5)†</td>
</tr>
<tr>
<td>System explant</td>
<td>1.6% (N = 3)†</td>
</tr>
<tr>
<td>Lead replacement</td>
<td>1.6% (N = 3)†</td>
</tr>
<tr>
<td>Overstimulation</td>
<td>&lt;1.0% (N = 2)*</td>
</tr>
<tr>
<td>Unwanted stimulation</td>
<td>&lt;1.0% (N = 1)*</td>
</tr>
<tr>
<td>Death</td>
<td>1.0% (N = 2)*</td>
</tr>
<tr>
<td>Other</td>
<td>2.8% (N = 6)*</td>
</tr>
</tbody>
</table>

A total of 43 complications across 33 patients. Complication rate reflects number of patients with presenting with complication (N) over total number of patients with potential for complication (‡ = 213 trialed patients, † = 184 IPG implanted patients). Overstimulation occurred in <1% of patients, and stimulation in an unwanted region occurred in only 0.5% of patients. The two deaths in this study were not related to the SCS device or procedure.

Discussion

In this multicenter study of 213 patients, we found that 3D neural targeting SCS was capable of providing long-term relief of leg pain, leg pain with low back pain, and exclusive axial low back pain for the entire 24-month study period. Importantly, it provided similar amounts of relief to all subgroups regardless of pain location (low back and leg or low back only) or baseline severity (mild, moderate, or severe), which has traditionally been difficult to achieve, particularly for low back pain [9]. In all of these subgroups, NRS pain scores dropped by more than half at three months postimplantation and were maintained at low levels for at least 24 months postimplantation. In addition, comparison between 3D neural targeting and traditional SCS from a previous-generation system without 3D neural targeting in patients treated at the same clinical sites revealed that the new SCS paradigm was both statistically and clinically superior to traditional SCS in overall pain (51% vs 74%), leg pain (63% vs 81%), and axial low back pain (41% vs 71%). For overall pain, the difference between the mean baseline and mean 24-month pain levels was 1.3 points greater with neural targeting SCS. For axial low back pain, however, this difference was 2.3 points greater with neural targeting SCS than with traditional SCS. Thus, while superiority of neural targeting SCS is observed for all pain areas, it is most pronounced for low back pain. Notably, this is driven by the continuous effectiveness in improving back pain relief at 24 months postimplant. In traditional SCS cohort, while mean low back pain was reduced to 3.9 ± 2.2 at three months, by 24 months postimplant the mean low back pain was back up to 5.5 ± 2.5. In contrast, in the neural targeting SCS cohort, the mean low back pain at 24 months postimplant was maintained at 3.1 ± 2.6.

Unlike traditional SCS modalities used over the past few decades, which optimize their stimulation parameters via trial and error for paresthesia coverage, neural targeting SCS optimizes its parameters by modeling, at the outset, the central points of the stimulation field within the patient’s unique three-dimensional anatomical space and lead location, and then choosing the parameters that best target these central points to the desired neural fibers. Thus, the differentiation from traditional SCS seen in terms of clinical outcomes may be the result of the fundamental approach neural targeting SCS uses to choose the stimulation parameters needed for recruitment of the desired neural fibers, without recruiting extraneous structures.

To date, SCS studies of low back pain have focused on mixed or predominant low back pain, that is, back pain that includes a radicular component. Due to the subjective and dynamic nature of pain, this does not provide a clean signal of the treatment effect as a patient’s ability to distinguish between the effect on the low back vs radicular components of his/her pain is limited. This study, however, includes a large cohort of axial low back pain patients (no radicular component), providing a cleaner signal in determining whether this traditionally difficult-to-treat pain area can be targeted to provide effective and durable long-term relief.

Comparison between two or more treatment groups is often achieved by employing a randomized controlled trial (RCT) design. The RCT design, however, has some important drawbacks, which have been discussed at length in the experimental design literature. Foremost among these is the limited generalizability of the RCT patient population. RCTs include both restrictive patient selection criteria to minimize heterogeneity among patients and highly prescriptive treatment algorithms to minimize heterogeneity among clinicians’ practices. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Real World Data Task Force has noted that many RCTs with extensive inclusion and exclusion criteria may not be generalizable to a real-world patient population, while a well-conducted observational study can often provide more relevant evidence regarding effectiveness in a real-world setting. Consequently, the major health care policy and comparative effectiveness research organizations strongly recommend greater emphasis on observational data. This is not to say that RCTs are not valuable or that observational designs should replace RCT designs. Instead, the two study paradigms address different issues—can it work vs does it work, efficacy vs effectiveness—and should be viewed as complementary. Further, large RCTs in the SCS field have been primarily...
open-label [9,10,17] and could not control for the expectation effect. In fact, previous studies have shown that in open-label RCTs subjects have a higher likelihood of favoring the new treatment [25]. This confounding factor is particularly challenging in SCS studies given the subjective nature of pain and of its methods of measurement.

The primary goal of the Lumina study was to examine whether a new model-based designed algorithm (Anatomically Guided 3D Neural Targeting) when applied clinically results in improved long-term outcomes in treatment of back and leg pain. For that purpose, we selected an observational study design combined with unbiased enrollment of an equivalent treatment group at the same clinical centers and statistical validation of the groups’ comparability. Enrollment was fully consecutive, and site-level sample sizes were matched to the 3D neural targeting treatment group, wherever possible. Selection bias, which is often raised as the key concern with nonrandomized comparisons, was avoided here altogether in that the availability of the two systems at the participating centers did not co-occur. Enrollment of the traditional SCS cohort followed consecutive enrollment during the 24-month period immediately preceding the enrollment of the 3D neural targeting SCS group. External bias was removed by restricting all data collection from patients to clinical site personnel, with no sponsor involvement or presence. Finally, in order to minimize selection bias and ensure comparability between the two treatment groups, propensity score matching was performed for inclusion of the control cohort from the consecutively treated comparison group. Propensity score matching (PSM) [26] is the most commonly used matching method for causal analysis in observational studies [27]. It is used or referenced in over 53,600 scholarly articles [28]. The data collected reflects the true heterogeneity in patients’ etiologies and clinician’s practices that exists with any medical intervention. In doing so, the observed clinical outcomes are reflective of what clinicians and patients can expect in the real world clinical setting.

Technology Considerations

Our findings are consistent with the hypothesis that SCS with 3D neural targeting can address the historical challenges of traditional SCS for axial low back pain and provide highly effective pain relief for both legs and the low back. New technological features incorporated into this form of SCS may contribute to these outcomes. This study is the first to use an SCS system with up to four lead ports and 32 contacts, providing more coverage and flexibility. The 184 patients implanted in this study received seven different lead configurations, spanning all four possible contact numbers (8–32). Theoretical studies examining leads with 20 contacts have suggested that being able to choose from many contacts allows for more specific programming to customize the regions that are stimulated [29]. The broad selection in the stimulation parameters suggests that in real world clinical practice different patients require a wide range of parameters, including stimulation amplitude, frequency, pulse width, and contact configuration. Further, this study is the first to use a 3D neural targeting algorithm incorporating lead position. The algorithm is designed to stimulate desired areas to relieve pain without spilling over into unwanted areas (e.g., abdominal stimulation via dorsal root stimulation). This level of precision is consistent with what was observed in this study, with only one patient (0.5%) reporting stimulation in an area outside the targeted pain regions (i.e., unwanted stimulation). Additionally, the Focus feature (anode-cathode spacing) may further contribute by adjusting the ratio of dorsal root threshold to dorsal column threshold.

Limitations

While careful attention was paid to maximize the interpretability and generalizability of the study outcomes, as with any study, certain limitations exist. The combination of an observational design with statistical cohort matching is a powerful way of achieving valid comparisons between the two treatment groups without compromising the pragmatic generalizability of the study results. Nonetheless, it is important to recognize that unknown confounding variables may exist and this comparison method in this study does not incorporate prospective randomization. Our measurement of low back pain relied only on the axial low back pain patients in our study, not patients with both low back and leg pain. We chose this approach because these patients provide the cleanest signal of low back pain improvement, without the confounding matters of additional pain areas. Additionally, axial low back pain patients have historically been the most challenging [11]. Consequently, measuring low back pain outcomes in these patients is conservative and may mark the minimal expected improvement with this 3D neural targeting for low back pain. The study’s inclusion and exclusion criteria were purposefully left almost entirely open, with the exception of age and on-label treatment, in order to best mirror real world clinical practice. While we believe that this generalizability is critical to the objective of the study, it does inherently result in patient heterogeneity. In fact, it is precisely this heterogeneity that we sought to capture. Nonetheless, a limitation of the study is that the outcomes reflect mean improvements, some of which may be different among different patient subgroups and etiologies. Another limitation relates to the nature of chronic pain. Chronic pain may be nociceptive, neuropathic, or mixed. Our study did not attempt to differentiate the pain types and the phenotype(s) that is (are) responsive to SCS.

Conclusions

The LUMINA Study is the largest multicenter pragmatic SCS cohort results published to date. The study demonstrated the long-term effectiveness of the applied 3D neural targeting algorithm applied for SCS and even its
superiority over traditional SCS in the treatment of overall pain, leg pain, and axial low back pain. The significant improvement with 3D neural targeting SCS was associated with a reduction, on average, from severe pain down to mild pain levels. The precise neural targeting afforded by this new SCS paradigm was associated with minimal unwanted stimulation. The wide selection in lead configuration and stimulation parameters underscores the importance of flexibility and patient-specific customization to achieving these clinical outcomes. To our knowledge, this study presents the largest multicenter chronic axial low back pain SCS cohort published to date, in contrast to recent studies that have excluded axial low back pain with no radicular component [16,17,30]. In light of its overall design, large sample size, and the steps taken to ensure unbiased comparison between its two cohorts, the significant and superior leg and low back pain reduction observed in this study represents evidence that may be generalizable to the broader SCS population. These findings represent an important step forward in the evidence base for SCS treatment of chronic low back pain.

Author Contributions

Protocol was prepared by the Boston Scientific study team with input from investigators. The authors were elected based on their contributions to the study. All investigators were involved in either data collection, execution of the study, or preparation of the manuscript and interpretation of the data.

Dr. Veizi and Dr. Hayek were involved in literature search and preparation of the manuscript. Drs. North, Chafin, Yerwood, Raso, Cairns, Berg, Breiden, Haider, McCarty, and Vucetic were site investigators, provided review for intellectual content, and provided final approval of the manuscript. Mr. Sherman and Drs. Chen and Mekel-Bobrov were part of the sponsor’s study team. Dr. Mekel-Bobrov analyzed the data. The sponsor of the study had full control of the data and performed analysis.

References

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