Prospective Study

The Long-term Outcome of Usual and Unusual Indications for Spinal Cord Stimulation: A Prospective Study

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Background: Evidence of the efficacy of spinal cord stimulation (SCS) has been well demonstrated as a method of pain control for patients who exhibit failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), and inoperable peripheral vascular diseases (PVD) ("usual indications"). However, a long-term study comparing the usual indications for which SCS is employed with those of other intractable painful conditions is still lacking.

Objectives: To assess the long-term effectiveness of SCS treatment for both usual and unusual indications.

Study Design: Observational study and original research.

Setting: This work was conducted at the Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand.

Methods: We recruited patients undergoing SCS treatment for chronic refractory pain caused by various conditions and followed up on those patients for up to 36 months. The patients were divided into usual indications for SCS, including FBSS, CRPS, and PVD; and unusual indications for SCS, including chronic refractory neuropathic pain of various etiologies. Pain intensity, pain-related interference, and health-related quality of life (HRQOL) were collected at the baseline, 6 months, and one, 2, and 3 years after SCS implantation, and the values seen at each time point were compared to the baseline values.

Results: Forty-six patients were recruited, 30 of whom underwent successful SCS implantation (24 usual and 6 unusual indications). The overall pain intensity was significantly lower than it was at the baseline, decreasing from 6 to 3, 5, 4, 4 out of 10 at 6, 12, 24 and 36 months after implantation, respectively ($P < 0.01$). Pain-related interference and HRQOL tended to improve over time after implantation. Patients with usual indications had a significantly higher rate of trial-to-implant ratio than those with unusual indications, with an odd ratio of 5.14 (95% CI 1.36-19.50). Furthermore, patients with usual indications tended to see greater improvement and more constancy in pain intensity, pain-related interference, and HRQOL than those with unusual indications.

Limitations: This analysis was a single-center prospective study with a nonrandomized design and a relatively small sample size.

Conclusions: Overall, SCS is an effective long-term treatment for chronic refractory pain. However, patients with usual indications for SCS have a higher success rate in SCS trials and a trend toward better outcomes after SCS implantation than do patients with unusual indications.

Key words: Spinal cord stimulation, refractory pain, pain intensity, pain-related interference, health-related interference, trial-to-implant ratio, usual indications, unusual indications, Thailand

Registration: This study was registered on thaiclinicaltrials.gov (Identifier number: TCTR20210923001).

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Chronic pain affects an estimated 20% of the adult population in the world, with 10% of the population diagnosed with it annually (1,2). Moreover, chronic pain is associated with physical and psychological comorbidities such as depression and anxiety (3) and has an indirect impact on quality of life, social participation, and the economy (4). Despite advances in medical treatment, many people still experience chronic pain.

Many painful conditions can cause chronic refractory pain, which is commonly found in failed back surgery syndrome (FBSS), complex regional pain (CRPS), peripheral vascular disease (PVD), and other neuropathic pain. These conditions are not uncommon in the general population or in the tertiary care setting (5-7). Furthermore, patients with refractory pain have an extremely low quality of life compared to the general population (8-11).

Spinal cord stimulation (SCS) is a neuromodulative treatment that applies gate control theory and a well-established modality for the treatment of chronic refractory pain from various conditions. SCS is indicated for chronic neuropathic or ischemic pain in patients who have attempted fully conventional treatment or even surgery with limited success and are struggling with the consequences of pain. The efficacy of SCS treatment has been well studied and is evident not only as a method of pain reduction but also a way to improve functioning and quality of life in patients with chronic refractory pain from such conditions as FBSS, CRPS, PVD, and angina pectoris ("usual indications"). However, although many people suffer from refractory pain caused by other conditions, no long-term prospective study that compares other refractory pain conditions with the aforementioned usual indications has been conducted.

The primary goal of this study is to evaluate the overall long-term outcomes of SCS for patients with chronic refractory pain by comparing pain intensity, pain-related interference, and health-related quality of life (HRQOL) before and after treatment in our setting. The secondary objectives are to assess the effectiveness of SCS for different subgroups of patients with chronic refractory pain, one with usual indications and another with unusual indications, and to identify the predictive factors for successful SCS trials.

Methods

Study Population

Patients with chronic refractory pain who underwent SCS implantation at Siriraj Hospital between April 2015 and March 2021 were enrolled in the study, which was followed until December 2021. The inclusion criteria were as follows: 1) an age of more than 7 years, 2) having been offered an SCS trial due to chronic refractory pain from any condition, and 3) reporting an unsatisfactory level of chronic refractory pain (at least 5 out of 10 on a numerical rating scale of pain intensity) despite appropriate conventional treatment (physical therapy, appropriate regimen of pain medications, pain interventions or surgery).

The patients were divided into 2 groups according to their pain conditions, based on the level of evidence support from the Neuromodulation Appropriateness Consensus Committee (13). One group collected patients who had "usual indications" for SCS, and the other included only patients who had "unusual indications" for SCS. Usual indications for SCS consisted of the group of conditions for which SCS had strong evidence of effectiveness, including FBSS, CRPS, and PVD. The unusual indications were other conditions, such as neuropathic pain from brachial plexus avulsion, brachial plexitis, residual limb pain, phantom limb pain, spinal cord tumors, and central neuropathic pain.

Patients who underwent a successful SCS trial and were subsequently implanted were followed for data collection. Patients who were unable to assess their pain or complete the questionnaires were excluded from the study.

All the spinal cord stimulation costs were either reimbursed through the patient's healthcare coverage or sponsored by the Siriraj Foundation, a charitable organization contributing to the medical expenses of underprivileged patients. There was no industrial support for devices in this study.

Sample Size Calculation and Ethics Committee Approval

Based on the decrease in pain intensity after spinal stimulation in the study by Zucco et al (5), it was 2.45 out of 10 (SD = 2.80). Using the paired t-test formula, a significance level of 0.05, and 90% power, we found that the complete data, up to 3-years follow-up, of 16 patients were required. We assumed that we might lose up to 50% of our patients to follow-up, so we figured that a successful implantation rate at the beginning would consist of at least 32 patients. Because we also assumed that the overall trial to implant ratio (number of implanted patients divided by number of trials) in our study would be approximately 0.7, we decided to recruit an initial 46 patients.

The study was approved by the Institutional Review Board of Siriraj Hospital (certificate of approval: Si 441/2019). All patients received information about the study, and informed consent sheets were signed before the data collection process.

Procedure

The patients were recruited and selected for the SCS trial on the consensus of pain physicians, neurosurgeons, and pain psychiatrists. The SCS trial procedure was performed in the operating theater on patients under light sedation. Patients were discharged and followed 3-10 days after the trial to determine the result of the trial, and trial leads were subsequently removed. SCS implantation was considered if the patient experienced at least 50% pain reduction during the trial period. If the patient reported pain reduction of less than 50%, SCS implantation was not offered, and conventional treatment continued. SCS implantations were performed in the operating theater, under general anesthesia, and patients were admitted for 3-4 days. Patients were followed up at one, 3, and 6 months and then once a year after implantation.

Data Collection

The demographic and clinical data of the patients were collected during the outpatient department (OPD) visit at the enrollment of both groups. After successful SCS trials, patients were assessed by questionnaires in the OPD or preoperative admission before SCS implantation. Follow-up visits, conducted at the sixth and twelfth month after the implantation and every year afterward, involved assessment through additional questionnaires. The data for nonimplanted patients were collected only once, during enrollment in the OPD.

Demographic data consisted of age, body weight, and gender. Clinical data consisted of diagnosis, locations of pain, comorbidities, duration, current medication, previous treatments, pain intensity, interference related to pain, and HRQOL. Pain intensity was measured on a numerical rating scale (0-10). Pain-related interference was measured using the Brief Pain Inventory (BPI) (Thai version) (18), consisting of 7 categories of scores: general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. The total score was the sum of the scores for each category (0-10), based on the severity of the interference, ranging from 0-70. Worldwide HRQOL was evaluated by EQ-5D-5L health questionnaires (19), including a Thai version (11). The questionnaires were divided into 5 categories—mobility, self-care, usual activities, pain/discomfort, and anxiety/depression—each of which could be ranked from one to 5 based on severity. The data obtained from the questionnaire were applied to calculate the utility score using a Thailand-specific program developed by the Health Intervention and Technology Assessment Program (HITAP) (20). The utility score ranges from 0 to one, zero meaning death and one meaning complete health.

Statistical Analysis

Data were analyzed using SPSS version 24 (SPSS Inc.). Continuous data such as NRS, BPI, and EQ-5D-5L were presented as mean + standard deviation (SD) or median (IQR1, IQR3) and compared using the Student's t-test or Mann-Whitney U test. Categorical data, such as gender and incidence of side effects, were presented as number (percentage) and compared using Pearson's chi-squared test. A *P*-value under 0.05 was considered statistically significant. Missing outcome data were not imputed.

Results

Forty-six patients were recruited for this study. Demographic data of the patients at enrollment—diagnosis, pain score, location of pain, location of SCS leads, BPI, and EQ-5D-5L score—are shown in Table 1. Sixteen patients did not show adequate response to the SCS trial, and only 30 patients subsequently underwent SCS implantation. The total trial-to-implant ratio was 0.65. FBSS and central neuropathic pain were the most common diagnoses in implanted and nonimplanted patients, respectively. There was no significant difference in age, weight, gender, location of pain, baseline intensity of pain, duration of pain, BPI, or EQ-5D-5L score between implanted and nonimplanted patients (Table 1 and Supplemental Table 1). Whether a diagnosis was classified as a usual indication was the only factor that showed a statistically significant difference (Table 1).

The chance that a patient underwent implantation was shown by the trial-to-implant and odds ratios (Table 2). The odds ratio in the usual-indications group was 5.14 (95% confidence interval 1.36-19.50) compared to the unusual-conditions group. Further subgroup analysis of the trial-to-implant ratio showed no significant differences among the groups' odds and trial-to-implant ratios, location of pain, or level of SCS trial. However, when the second subgroup of FBSS patients was examined, patients with predominantly

Table 1. *Characteristics of the patients at the time of study enrollment.*

Characteristics	Implantation (n = 30)	Non-implantation (n = 16)	*P*-value
Age (years)	47.47 ± 16.22	50.25 ± 13.85	0.564
Body weight (kg)	65.70 ± 14.18	63.25 ± 10.81	0.550
Gender			
• Male	16 (53.33%)	7 (43.75%)	0.536
• Female	14 (46.67%)	9 (56.25%)	
Diagnosis			
• Usual indications	24 (80.00%)	7 (43.75%)	0.012
• FBSS	17	5	
• Somatic pain predominates	2	3	
• Radicular pain predominates	15	2	
• CRPS	3	2	
• Peripheral vascular disease	4	-	
• Unusual indications	6 (20.00%)	9 (56.25%)	0.012
• Central neuropathic pain	3	7	
• Spinal cord tumor	3	1	
• Spinal cord injury	-	3	
• Syringomyelia	-	3	
• Peripheral neuropathic pain	3	2	
• Brachial plexus avulsion/plexitis	2	-	
• Phantom limb pain in the lower extremities	1	1	
• Sciatic nerve tumor	-	1	
Location of pain			
• Axial pain	2 (6.67%)	3 (18.75%)	0.215
• Limb pain	28 (93.33%)	13 (81.25%)	
Duration of pain (years)	4.5 (2-8)	5.00 (4-6)	0.651
NRS, 0-10			
• Maximum	8 (7-10)	8 (7-10)	0.645
• Minimum	5 (2.5-7)	4 (2-6)	0.617
• Average	6 (5-8)	5.5 (5-8)	0.898
Level for the SCS trial (n, %)			
• Cervical	7 (23.33%)	2 (12.50%)	0.570
• Thoracic	22 (73.33%)	12 (75.00%)	
• Lumbosacral	1 (3.33%)	2 (12.5%)	
BPI, 0-70	37.47 ± 17.38	41.55 ± 13.09	0.507
• Activity	5.53 ± 3.12	6.36 ± 2.29	0.444
• Mood	4.84 ± 2.95	4.82 ± 3.31	0.984
• Walk	5.42 ± 3.10	6.55 ± 2.54	0.317
• Work	5.95 ± 2.88	6.73 ±2.49	0.460
• Relation	3.74 ±3.09	4.91 ± 3.59	0.353
• Sleep	6.37 ± 3.35	6.45 ± 2.50	0.942
• Enjoy	5.63 ± 3.25	5.73 ± 2.72	0.935
EQ-5D-5L, 0-1	0.46 ± 0.18	0.41 ± 0.32	0.568

FBSS, failed back surgery syndrome; PVD, peripheral vascular disease; CRPS, complex regional pain syndrome; NRS, numeric rating scale; BPI, Brief Pain Inventory. Data presented as n (%), mean ± SD, or median (interquartile range). $P < 0.05$ is considered statistically significant.

radicular pain showed a significantly greater trial-to-implant ratio than did those with predominantly somatic pain, with an odds ratio of 11.25 (95% confidence interval 1.11-114.37).

Table 2. *Trial-to-implant ratio. $P < 0.05$ is statistically significant.*

	Trial to implant ratio	Odd ratio (95% CI)	*P* value
Diagnosis	0.65		0.016
• Unusual indications	0.40	1.00	
• Usual indications	0.77	5.14 (1.36 - 19.50)	
Usual indications			0.362
• CRPS	0.60	1.00	
• FBSS	0.77	2.27 (0.29 - 17.58)	
• Peripheral vascular disease	1.00	N/A	
Unusual indications			0.274
• Central neuropathic pain	0.30	1	
• Peripheral neuropathic pain	0.60	3.50 (0.37 - 32.97)	
FBSS			0.04
• Somatic pain predominates	0.40	1	
• Radicular pain predominates	0.88	11.25 (1.11 - 114.37)	
Location of pain			0.228
• Axial predominates	0.40	1	
• Limb predominates	0.68	3.23 (0.48 - 21.74)	
Level of the SCS trial			0.439
Lumbar	0.50	1.00	
Cervical	0.78	3.50 (0.14 - 84.70)	
Thoracic	0.65	1.83 (0.11-32.00)	

The Efficacy of SCS on Pain Reduction

The number of patients at each follow-up point is shown in Fig. 1. The 3-year follow-up data for NRS, BPI, EQ-5D-5L and the number of patients whose NRS decreased by at least 50% are shown in Figs. 2, 3, 4 and 5, respectively. The overall average NRS score was significantly lower at all time periods than at the baseline. Additionally, overall BPI scores decreased while EQ-5D-5L scores increased through the 3 years of follow-up. For the usual-indications group, the trends seen in the NRS, BPI, and EQ-5D-5L scores compared to the baseline agreed with the overall data. In contrast, there were no significant differences in the NRS, BPI, or EQ-5D-5L scores for the unusual-indications group at any time points compared to the baseline. The percentage of patients who saw a 50% reduction in pain at 3 years was 47% for the usual-indications group and 0% for the unusual-indications group (Fig. 5). The overall number needed to treat (NNT) of patients who saw 50% pain reduction over 3 years ranges from 1.69 to 2.86. The NNT of patients in the usual-indications group ranges from 1.78 to 2.29, whereas the NNT for unusual-indication patients is incalculable (1.5 to infinity).

Pain-Related Interferences and Quality of Life After SCS Implantation

The scores in each category of the BPI and EQ-5D-5L are shown in Figs. 6 and 7. The results of the BPI analysis subscale compared to the baseline showed that patients in the usual-indications group tended toward lower interference on all subscales. Usual-indication patients demonstrated significant differences in activity level, walking, and working at one year and relationships and sleep quality at 6 months and 3 years after SCS implantation. Meanwhile, the results of the EQ-5D-5L analysis subscale compared to the baseline showed that there were significant differences in activity level at 2 years and pain at 6 months and one, 2, and 3 years. As for the unusual-indications group, there were no significant differences in the BPI and EQ-5D-5L subscales compared to the baseline at any time point.

Adverse Outcomes of SCS Implantation

Seventeen patients were implanted with rechargeable spinal cord stimulators and 13 patients with nonrechargeable spinal cord stimulators. Percutaneous leads were used in 29 patients, and a paddle lead was used in one patient. There were 4 reported complications (13%), including 2 premature battery depletions within one year after implantation (FBSS and CRPS1 patient) and 2 implantable pulse generator (IPG) infections (CRPS1 and PVD). One of the IPG infections occurred early after the IPG placement and was successfully treated with debridement and antibiotics. Another infection eventually required explantation a year after implantation. There is no explantation due to inadequate pain relief, no report of neurological complication, and no lead migration needing revision. One patient died from brain stem infarction 8 months after SCS implantation, though the infarction was not related to said SCS implantation.

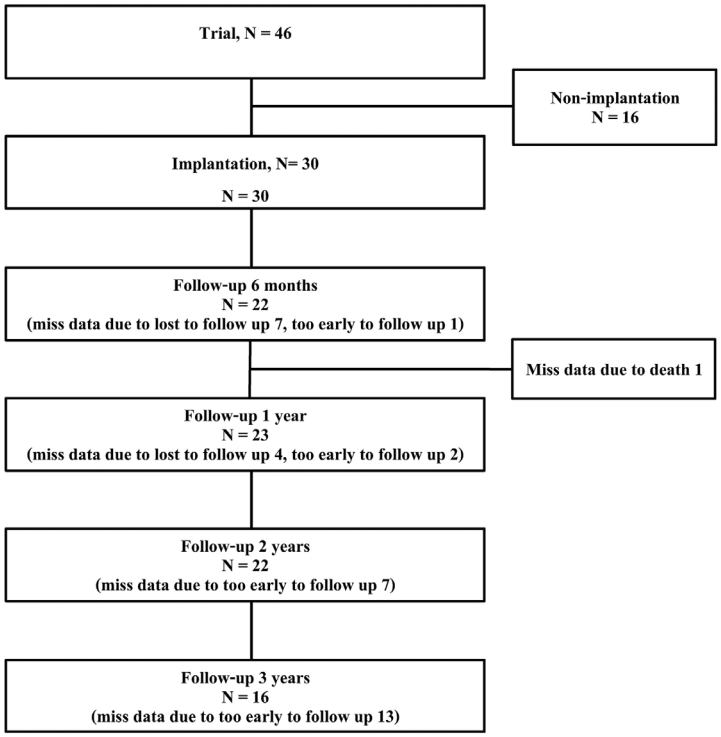

Fig. 1. *Number of patients during follow-up.*

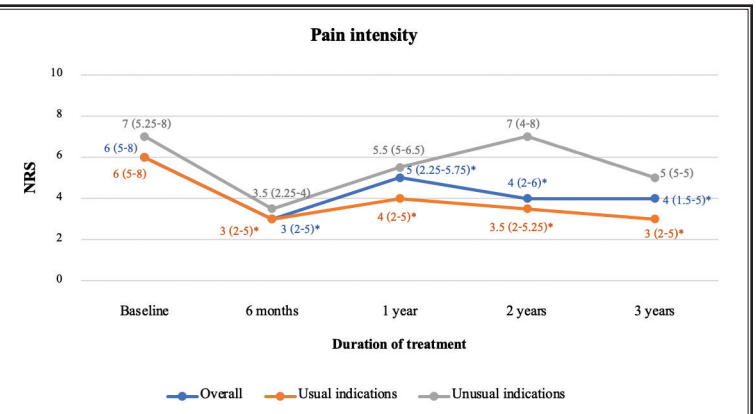

Fig. 2. *Follow-up data on up to 3 years of pain intensity measured by Numeric Rating Scale (NRS) overall and on usual and unusual indications. Data presented as median (interquartile range). *: $P < 0.05$ is statistically significant. (See Supplemental Table 2 for more detail.)*

Discussion

This prospective observational study demonstrated that SCS was a safe and effective treatment for patients suffering from chronic refractory pain. Successful treatment reduced pain intensity and pain-related interference and improved health-related quality of life. Additionally, usual indications for SCS implantation, including FBSS, CRPS, and PVD, were associated with a higher successful trial rate and better short- and long-term results.

According to the recommendation of the Committee for the Appropriateness of Neuromodulation, the evidence of the effectiveness of SCS was well established for chronic refractory pain in certain conditions such as FBSS (25-26), CRPS, PVD, and refractory angina (13). Our study found consistently that for patients who had moderate to high pain intensity despite having received appropriate conventional treatment for so-called "usual" indications, SCS could reduce pain intensity in the short and long term at all times for up to 3 years of follow-up. The lowest average pain score and the highest proportion of 50% pain reduction within the usual-indications group in our study was at 6 months of follow-up. The pain slightly increased later but was still significantly improved compared to the baseline. This trend showed a similar result to Zucco's FBSS study (5), in which the lowest intensity of pain also occurred 6 months after implantation then increased slightly but still remained lower than the baseline. The reduction in pain intensity at the end of the long-term follow-up in our study was 50% (3 years), comparable to the 43% figure at the 4-year point among patients with FBSS and CRPS seen in the Thomson study (25) and the 32% figure at the 2-year point among patients with FBSS in the Zucco study (5). Furthermore, the proportion of patients who reported more than 50% pain reduction in this study ranged from 44-56%, comparable with the range of 47-50% seen in the studies by Kemler (21) and Kumar et al (22,23), which observed patients suffering from CRPS and FBSS. The proportion of 50% pain reduction over the 3-year follow-up in our study can be converted to a number needed to treat (NNT) ranging from 1.78 to 2.29, which is even lower than the NNT

associated with all first-line medication for neuropathic pain (gabapentinoids, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors) (27).

Our study also revealed that for patients in the usual-indications group, pain-related interference and health-related quality of life tended to improve over time after SCS implantation, correlating with the findings of previous high-quality studies (5,25). Our study's figure of 45% reduction in pain-related interference is comparable to the 42% figure found by Thomson SJ et al (25), and the increase in EQ-5D-5L utility scores in our study was 0.24, also quite similar to the results found by Thomson SJ et al (25) and Zucco et al (5), which were 0.24 and 0.22, respectively. Although our clinical setting is in the context of a low- and middle-income country, our outcomes are still aligned with the aforementioned high-quality research in developed countries. Furthermore, the general complication in our study is 14% and nonlethal, comparable to 24-32% in the PROCESS study (28). This fact implies that if the appropriate selection criteria and international standard practices are applied, the effectiveness and safety of SCS are still universal.

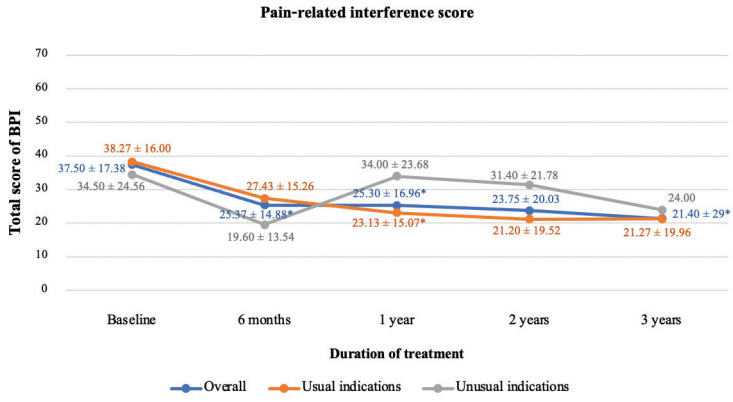

Fig. 3. *Follow-up data on up to 3 years of pain-related interference measured by BPI overall and on usual and unusual indications. BPI, Brief Pain Inventory. Data are presented as mean ± SD. *: P < 0.05 is statistically significant. (See Supplemental Table 3 for more detail.)*

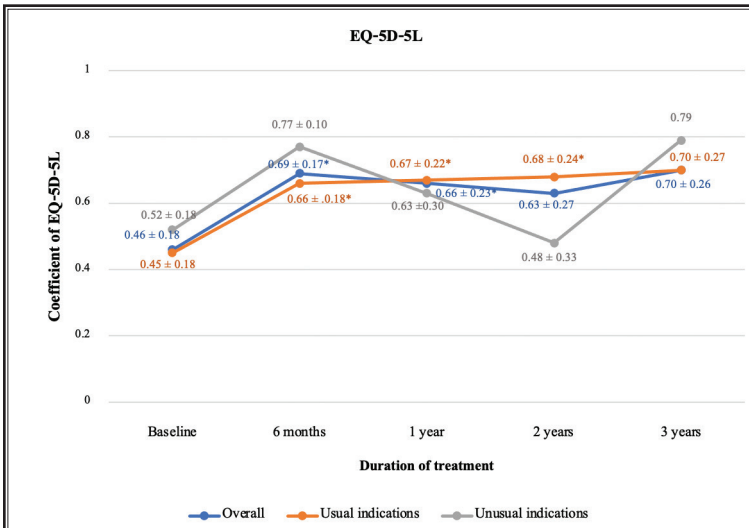

Fig. 4. *Follow-up data on up to 3 years of health-related quality of life measured by EQ-5D-5L overall and on usual and unusual indications. Data are presented as mean ± SD. *: P < 0.05 is statistically significant. (See Supplemental Table 4 for more detail.)*

Although patients with usual indications showed significant and long-term reductions in pain and improved quality of life after their SCS implantations, patients who were not classified into this category saw inconsistent results. At no time did patients in the unusual-indications group show no significant reductions in pain intensity or pain-related inference or improvements in EQ-5D-5L utility scores. Additionally, at some time points, the outcomes for patients in this group tended to be worse than at the baseline. However, since the majority (80%) of our implanted patients were categorized as exhibiting a classic condition, the overall efficacy and improvement of quality of life still showed a trend of improvement over time.

Usual-indication patients were associated not only with better outcomes but also with greater change of implant. The odds ratio of SCS implantation in usual-indication patients was 5.14, compared to unusual-indication patients (trial-to-implant ratios of 0.77 vs. 0.4). Comparing patients within the same group to one another yielded no statistically significant difference between odds ratios and trial-to-implant ratios, except among patients with FBSS. FBSS patients with predominantly radicular pain had a higher chance of

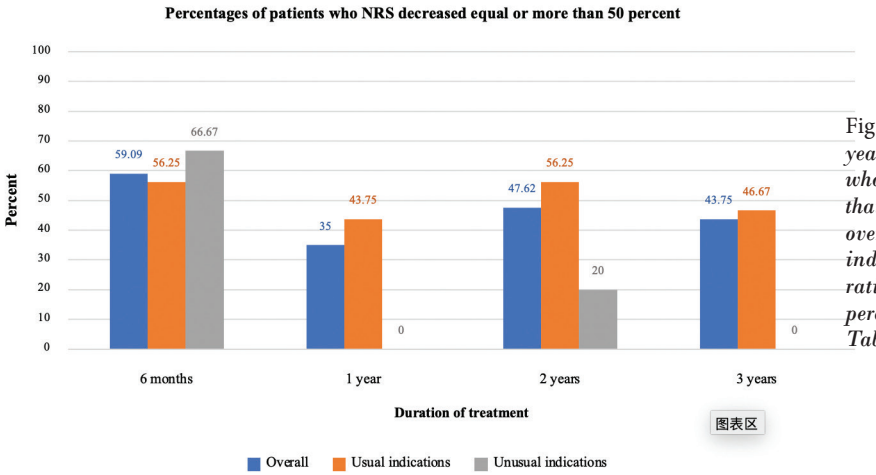

Fig. 5. *Follow-up data on up to 3 years of percentages of patients who reported pain intensity (NRS) that had decreased by 50% or more overall and on usual and unusual indications. NRS, numeric rating scale. Data are presented as percentages. (See Supplemental Table 5 for more detail.)*

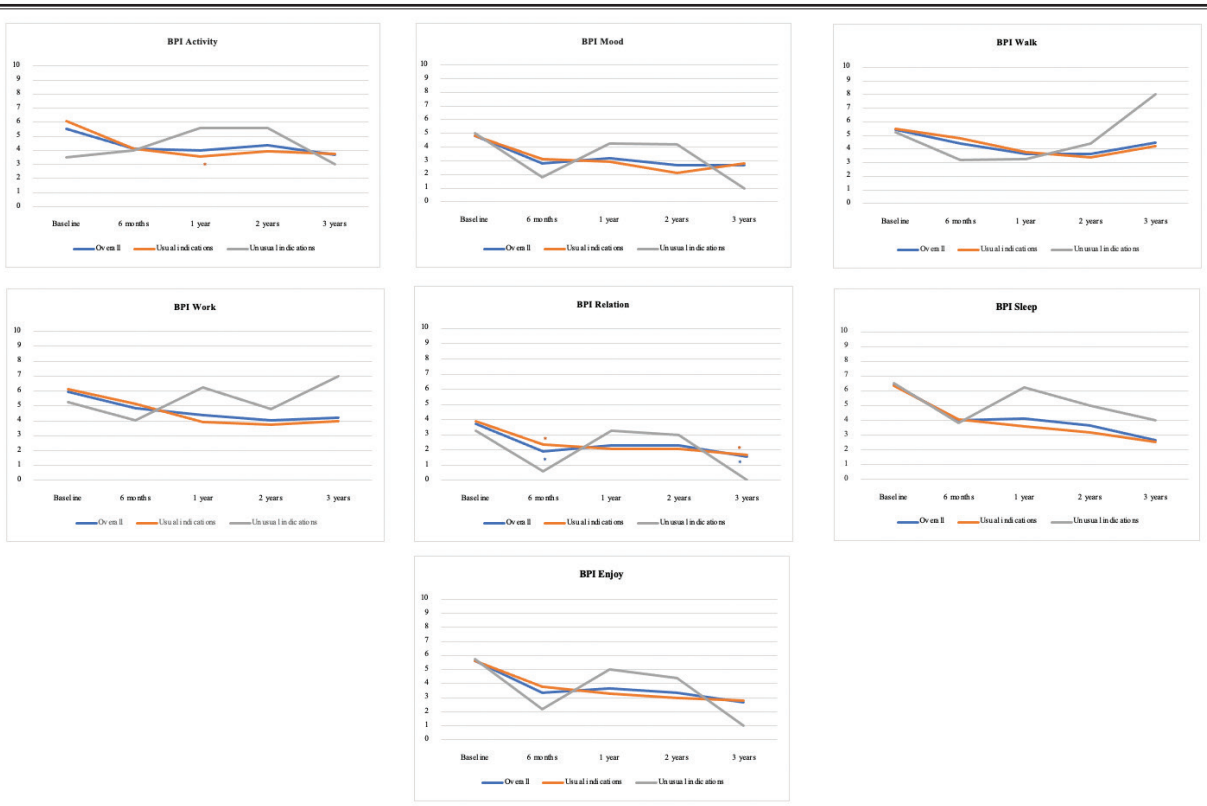

Fig. 6. *Follow-up data on up to 3 years of subscale BPI in all categories overall and on usual and unusual indications. BPI, Brief Pain Inventory. *: $P < 0.05$ is statistically significant. (See Supplemental Tables 6-12 for more detail.)*

implanting than did patients with predominantly axial pain, with an odds ratio of 11.25. This finding is correlated with a certain result found in the systematic literature review: namely, that there is a lack of evidence supporting the idea that traditional low-frequency SCS has a beneficial effect on axial low back pain (29) while a high level of evidence supports the notion that traditional SCS benefits FBSS patients with radicular

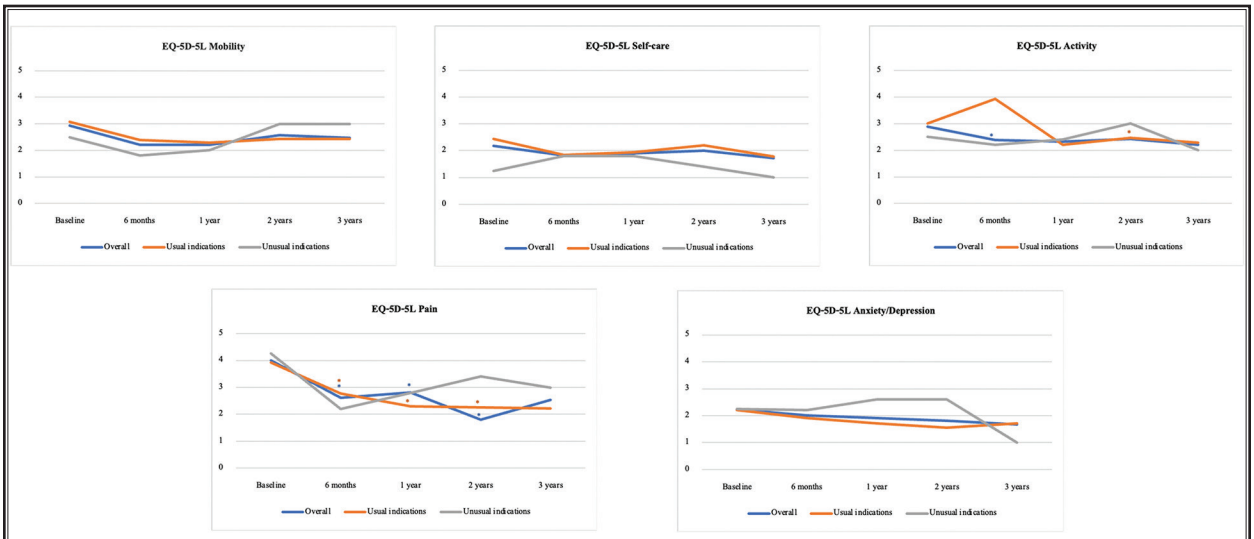

Fig. 7. *Follow-up data on up to 3 years of subscale EQ-5D5L in all categories overall and usual and unusual indications. *: P < 0.05 is statistically significant. (See Supplemental Tables 13-17 for more detail.)*

pain (30). Because about a third of the patients who underwent the SCS trial in our study were classified into the unusual-indications group, our study found that the overall trial-to-implant ratio was 0.65, which was relatively low compared to the standard range of trial-to-implant ratio of 0.63-0.90 (24).

According to the recommendation by the Neuromodulation Appropriateness Consensus Committee, clinicians with trial-to-permanent-implant ratios of < 50% in routine cases should stop implanting devices or consider remedial training. However, the low trial-to-implant ratio (0.4) in patients with unusual indications should not be a reason to exclude these patients from SCS trials. In our study, patients with unusual indications suffer from refractory pain not only after medical treatment or physical therapy; some of the patients have even failed to respond to neuroablative surgical treatments for pain, including cingulotomy, DREZtomy after brachial plexus avulsion, or stump revision due to residual limb pain. Even if SCS provided only a partial response for those patients, the other treatments did not. Moreover, there was no report of explantation caused by loss of the therapeutic effect, even among the patients with unusual indications, so some of those patients might have benefited from SCS. Especially careful and comprehensive consideration of every aspect of SCS, including cost, expectation, risk, and benefit, should be taken by physicians treating patients with unusual indications.

To our knowledge, this was the first prospective study to evaluate the long-term outcome of SCS in the context of developing countries. Additionally, this study was not supported by an industry, so sponsorship bias was unlikely. However, there are several limitations to this study. First, this study was not a randomized trial, and selection bias may be present. Additionally, when group analysis was performed, the study had relatively small sample sizes, which might not represent a significant difference in some outcomes, especially for the group of patients with unusual indications. Lastly, the usual indications should not be limited to FBSS, CRPS and PVD, as they were in our study. Other painful indications for which SCS has strong supporting evidence of efficacy, such as refractory angina (31) or painful diabetic neuropathy (32-33), potentially have a better outcome (34) than unusual indications and should be included in the usual indications.

Conclusion

The study demonstrated that SCS was a safe and effective treatment for chronic refractory pain because the technique decreased pain intensity and tended to improve pain-related interference and health-related quality of life over time. Patients with usual indications, including FBSS, CRPS, and PVD, were associated with a higher success rate in the SCS trial and better short- and long-term outcomes after SCS than patients with unusual indications.

Author Contributions

NS: design, data collection, analysis, NZ: design, recruitment, analysis, MS preparation, PE: recruitment, BS: recruitment, Na S: recruitment, CX Li: MS preparation.

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Supplemental Table 1. *Patients' pain intensity, pain-related interference, and health-related quality of life, categorized by usual and unusual indications at study enrollment time. Data presented as mean ± SD, or median (interquartile range). P < 0.05 is considered statistically significant.*

		Implantation (30)	Non-implantation (16)	*P* value
Usual indications (31)	NRS, 0-10			
	• Maximum	8 (7-9.75)	8 (7-10)	0.661
	• Minimum	5 (2-7)	4 (2-5)	0.471
	• Average	6 (5-8)	5 (5-8)	0.982
	BPI, 0-70	38.27 ± 16.00	43.60 ± 11.15	0.501
	• Activity	6.07 ± 2.71	7.20 ± 1.92	0.402
	• Mood	4.80 ± 2.51	5.20 ± 3.56	0.784
	• Walk	5.46 ± 2.80	5.80 ± 2.95	0.822
	• Work	6.13 ± 2.70	6.40 ± 2.70	0.850
	• Relation	3.87 ± 2.97	6.60 ± 2.30	0.079
	• Sleep	6.33 ± 3.35	6.60 ± 2.59	0.781
	• Enjoy	5.60 ± 3.48	5.60 ± 3.43	1.000
	EQ-5D-5L, 0-1	0.45 ± 0.18	0.38 ±0.29	0.535
Unusual indications (15)	NRS, 0-10			
	• Max	9.5 (7.25-10)	9 (6.5-10)	0.852
	• Minimum	3.5 (3-5.75)	4 (2-7)	0.755
	• Average	7 (4.75-8.25)	6 (5-8)	0.731
	BPI, 0-70	34.50 ± 24.57	39.83 ± 15.35	0.680
	• Activity	3.50 ± 4.12	5.67 ± 2.50	0.326
	• Mood	5.00 ± 4.76	4.50 ± 3.39	0.850
	• Walk	5.25 ± 4.57	7.17 ± 2.23	0.396
	• Work	5.25 ± 3.86	7.00 ± 2.53	0.407
	• Relation	3.25 ± 3.95	3.50 ± 4.04	0.925
	• Sleep	6.50 ± 3.87	6.17 ± 2.64	0.874
	• Enjoy	5.75 ± 2.63	5.83 ± 2.32	0.959
	EQ-5D-5L, 0-1	0.52 ± 0.18	0.44 ± 0.37	0.693

NRS = numeric rating scale, BPI = Brief Pain Inventory, N/A = not applicable.

Supplemental Table 2. *Follow-up data on up to 3 years of pain intensity measured by Numeric Rating Scale (NRS) overall and on usual and unusual indications. Data are presented as a median (interquartile range). P-value is compared with the baseline. P < 0.05 is considered statistically significant. N/A = not applicable.*

	Baseline	6 months		One year		2 years		3 years	
		NRS	*P* value	NRS	*P* value	NRS	*P* value	NRS	*P* value
Overall	6 (5-8)	3 (2-5)	< 0.001	5 (2.25-5.75)	0.001	4 (2-6)	0.003	4 (1.5-5)	0.004
Usual indications	6 (5-8)	3 (2-5)	0.001	4 (2-5)	0.001	3.5 (2-5.25)	0.001	3 (2-5)	0.004
Unusual indications	7 (5.25-8)	3.5 (2.25-4)	0.078	5.5 (5-6.5)	0.655	7 (4-8)	0.786	5 (5-5)	N/A

Supplemental Table 3. *Follow-up data on up to 3 years of pain-related interference measured by Brief Pain Inventory (BPI) overall and on usual and unusual indications. Data presented as mean ± SD. P-value is compared with the baseline. P < 0.05 is considered statistically significant.*

	Baseline	6 months		One year		2 years		3 years	
		BPI	*P* value	BPI	*P* value	BPI	*P* value	BPI	*P* value
Overall	37.50 ± 17.38	25.37 ± 14.88	0.033	25.30 ± 16.96	0.042	23.75 ± 20.03	0.336	21.40 ± 29	0.025
Usual indications	38.27 ± 16.00	27.43 ± 15.26	0.054	23.13 ± 15.07	0.009	21.20 ± 19.52	0.186	21.27 ± 19.96	0.059
Unusual indications	34.50 ± 24.56	19.60 ± 13.54	0.425	34.00 ± 23.68	0.977	31.40 ± 21.78	0.686	24.00	N/A

N/A = not applicable.

Supplemental Table 4. *Follow-up data on up to 3 years of health-related quality of life measured by EQ-5D-5L overall and on usual and unusual indications. Data presented as mean ± SD. P-value is compared with the baseline. P < 0.05 is considered statistically significant.*

	Baseline	6 months		One year		2 years		3 years	
		EQ-5D-5L	*P* value	EQ-5D-5L	*P* value	EQ-5D-5L	*P* value	EQ-5D-5L	*P* value
Overall	0.46 ± 0.18	0.69 ± 0.17	0.01	0.66 ± 0.23	0.019	0.63 ± 0.27	0.327	0.70 ± 0.26	0.091
Usual indications	0.45 ± 0.18	0.66 ± .0.18	0.015	0.67 ± 0.22	0.013	0.68 ± 0.24	0.042	0.70 ± 0.27	0.191
Unusual indications	0.52 ± 0.18	0.77 ± 0.10	0.071	0.63 ±0.30	0.722	0.48 ± 0.33	0.283	0.79	N/A

N/A = not applicable.

Supplemental Table 5. *Follow-up data on up to 3 years of percentages of patients who reported a decrease of 50% or more in pain intensity measured on the Numeric Rating Scale (NRS) compared to the baseline overall and usual and unusual indications. Data are presented as percentages. P-value compared with baseline.*

	6 months		One year		2 years		3 years	
		NNT		NNT		NNT		NNT
Overall (30 patients)	59.09% (13/22)	1.69	35.00% (7/20)	2.86	47.62% (10/21)	2.10	43.75% (7/16)	2.29
95% CI	38.73% to 76.74%		18.12% to 56.71%		28.34% to 67.63%		23.10% to 66.82%	
Usual indications (24 patients)	56.25% (9/16)	1.78	43.75% (7/16)	2.2.9	56.25% (9/16)	1.78	46.67% (7/15)	2.14
95% CI	33.18% to 76.90%		23.10% to 66.82%		33.18% to 76.90%		24.81% to 69.88%	
Unusual indications (6 patients)	66.67% (4/6)	1.50	0% (0/4)	N/A	20.00% (1/5)	5.00	0% (0/1)	N/A
95% CI	30.00% to 90.32%		0.00% to 48.99%		3.62% to 62.45%		0.00% to 79.35%	

NNT = number needed to treat, N/A = not applicable.

Supplemental Table 6. *Follow-up data on up to 3 years of activity on the Brief Pain Inventory (BPI) subscale overall and on usual and unusual indications. Data are presented as mean ± SD. P-value is compared with the baseline. P < 0.05 is considered statistically significant.*

	Baseline	6 months		One year		2 years		3 years	
			P value		*P* value		*P* value		*P* value
Overall	5.53 ± 3.12	4.11 ± 2.79	0.162	4.00 ± 2.94	0.139	4.35 ± 3.22	0.505	3.69 ± 3.24	0.057
Usual indications	6.07 ± 2.71	4.14 ± 2.88	0.098	3.56 ± 2.48	0.021	3.93 ± 2.79	0.071	3.73 ± 3.35	0.106
Unusual indications	3.50 ± 4.12	4.00 ± 2.83	1.000	5.57 ± 4.35	0.465	5.60 ± 4.39	0.144	3.00	N/A

N/A = not applicable.

Supplemental Table 7. *Follow-up data on up to 3 years on the Brief Pain Inventory (BPI) mood subscale overall and on usual and unusual indications. Data are presented as mean ± SD. P-value is compared with the baseline. P < 0.05 is considered statistically significant. N/A = not applicable.*

	Baseline	6 months		One year		2 years		3 years	
			P value		*P* value		*P* value		*P* value
Overall	4.84 ± 2.95	2.79 ± 2.37	0.115	3.20 ± 2.50	0.097	2.65 ± 2.81	0.229	2.67 ± 3.29	0.312
Usual indications	4.80 ± 2.51	3.14 ± 2.41	0.220	2.94 ± 2.49	0.056	2.13 ± 2.64	0.150	2.79 ± 3.38	0.574
Unusual indications	5.00 ± 4.76	1.80 ± 2.17	0.273	4.25 ± 2.63	0.655	4.20 ± 3.03	1.000	1.00	N/A

Supplemental Table 8. *Follow-up data on up to 3 years of the Brief Pain Inventory (BPI) walk-in subscale overall and on usual and unusual indications. Data presented as mean ± SD. P-value is compared with the baseline. P < 0.05 is considered statistically significant. N/A = not applicable.*

	Baseline	6 months		One year		2 years		3 years	
			P value		*P* value		*P* value		*P* value
Overall	5.42 ± 3.10	4.37 ± 2.77	0.287	3.65 ± 2.74	0.054	3.63 ± 3.48	0.191	4.47 ± 3.48	0.495
Usual indications	5.47 ± 2.80	4.79 ± 2.81	0.360	3.75 ± 2.52	0.049	3.36 ± 3.30	0.140	4.21 ± 3.47	0.750
Unusual indications	5.25 ± 4.57	3.20 ± 2.59	0.465	3.25 ± 3.95	0.593	4.40 ± 4.28	1.000	8.00	N/A

Supplemental Table 9. *Follow-up data on up to 3 years of the Brief Pain Inventory (BPI) work subscale overall and usual and unusual indications. Data are presented as mean ± SD. P-value compared with baseline. P < 0.05 is considered statistically significant. N/A = not applicable.*

	Baseline	6 months		One year		2 years		3 years	
			P value		*P* value		*P* value		*P* value
Overall	5.95 ± 2.88	4.84 ± 2.52	0.123	4.40 ± 2.76	0.095	4.00 ± 2.71	0.531	4.19 ± 3.35	0.231
Usual indications	6.13 ± 2.70	5.14 ± 2.69	0.154	3.94 ± 2.35	0.005	3.73 ± 2.71	0.307	4.00 ± 3.38	0.356
Unusual indications	5.25 ± 3.86	4.00 ± 2.00	0.465	6.25 ± 3.86	0.715	4.80 ± 2.86	0.705	7.00	N/A

Supplemental Table 10. *Follow-up data on up to 3 years of the Brief Pain Inventory (BPI) relationship subscale overall and usual and unusual indications. Data are presented as mean ± SD. P-value is compared with the baseline. P < 0.05 is considered statistically significant. N/A = not applicable.*

	Baseline	6 months		One year		2 years		3 years	
			P value		*P* value		*P* value		*P* value
Overall	3.74 ± 3.09	1.89 ± 2.23	0.020	2.30 ± 2.89	0.125	2.30 ± 2.99	0.552	1.56 ± 2.45	0.011
Usual indications	3.87 ± 2.97	2.36 ± 2.34	0.024	2.06 ± 2.41	0.065	2.07 ± 2.84	0.462	1.67 ± 2.50	0.018
Unusual indications	3.25 ± 3.95	0.60 ± 1.34	0.285	3.25 ± 4.72	1.000	3.00 ± 3.67	1.000	0	N/A

Supplemental Table 11. *Follow-up data on up to 3 years of the Brief Pain Inventory (BPI) sleep subscale overall and usual and unusual indications. Data are presented as mean ± SD. P-value compared with the baseline. P < 0.05 is considered statistically significant. N/A = not applicable.*

	Baseline	6 months		One year		2 years		3 years	
			P value		*P* value		*P* value		*P* value
Overall	6.37 ± 3.35	4.00 ± 2.45	0.012	4.10 ± 3.06	0.086	3.65 ± 3.44	0.312	2.63 ± 3.03	0.012
Usual indications	6.33 ± 3.35	4.07 ± 2.40	0.036	3.56 ± 2.50	0.073	3.20 ± 3.34	0.248	2.53 ± 3.11	0.018
Unusual indications	6.50 ± 3.87	3.80 ± 2.86	0.144	6.25 ± 4.50	1.000	5.00 ± 3.74	0.785	4.00	N/A

Supplemental Table 12. *Follow-up data on up to 3 years of the Brief Pain Inventory (BPI) enjoyment subscale overall and usual and unusual indications. Data are presented as mean ± SD. P-value compared with the baseline. P < 0.05 is considered statistically significant. N/A = not applicable.*

	Baseline	6 months		One year		2 years		3 years	
			P value		*P* value		*P* value		*P* value
Overall	5.63 ± 3.25	3.37 ± 2.75	0.018	3.65 ± 2.89	0.054	3.35 ± 3.13	0.188	2.69 ± 3.32	0.075
Usual indications	5.60 ± 3.48	3.79 ± 2.83	0.091	3.31 ± 2.96	0.057	3.00 ± 3.14	0.203	2.80 ± 3.41	0.123
Unusual indications	5.75 ± 2.63	2.20 ± 2.39	0.068	5.00 ± 2.45	0.593	4.40 ± 3.21	0.715	1.00	N/A

Supplemental Table 13. *Follow-up data on up to 3 years on the mobility subscale of the EQ-5D-5L overall and on usual and unusual indications. Data are presented as mean ± SD. P-value is compared with the baseline. P < 0.05 is considered statistically significant. N/A = not applicable.*

	Baseline	6 months		One year		2 years		3 years	
			P value		*P* value		*P* value		*P* value
Overall	2.94 ± 1.11	2.22 ± 1.1	0.076	2.22 ± 1.19	0.098	2.57 ± 1.33	1.000	2.47 ± 1.30	0.408
Usual indications	3.07 ± 1.07	2.39 ± 1.19	0.202	2.29 ± 1.16	0.168	2.44 ± 1.32	0.257	2.43 ± 1.34	0.577
Unusual indications	2.50 ± 1.29	1.80 ± 0.84	0.180	2.00 ± 1.41	0.414	3.00 ± 1.41	0.180	3.00	N/A

Supplemental Table 14. *Follow-up data on up to 3 years of the self-care subscale of the EQ-5D-5L overall and on usual and unusual indications. Data are presented as mean ± SD. P-value compared with the baseline. P < 0.05 is considered statistically significant. N/A = not applicable.*

	Baseline	6 months		One year		2 years		3 years	
			P value		*P* value		*P* value		*P* value
Overall	2.17 ± 1.15	1.83 ± 0.79	0.395	1.91 ± 0.97	0.388	2.00 ± 1.05	0.480	1.73 ± 0.96	0.257
Usual indications	2.43 ± 1.16	1.85 ± 0.80	0.066	1.94 ± 1.03	0.102	2.19 ± 1.05	0.564	1.79 ± 0.97	0.257
Unusual indications	1.25 ± 0.50	1.80 ± 0.84	0.180	1.80 ± 0.84	0.083	1.40 ± 0.89	0.655	1.00	N/A

Supplemental Table 15. *Follow-up data on up to 3 years of the activity subscale of the EQ-5D-5L in overall, usual indications, and unusual indications. Data are presented as mean ± SD. P-value is compared with the baseline. P < 0.05 is considered statistically significant. N/A = not applicable.*

	Baseline	6 months		One year		2 years		3 years	
			P value		*P* value		*P* value		*P* value
Overall	2.89 ± 1.113	2.39 ± 0.78	0.046	2.32 ± 1.13	0.118	2.43 ± 0.98	0.739	2.20 ± 1.01	0.317
Usual indications	3.00 ± 1.11	3.93 ± 0.83	0.107	2.21 ± 1.19	0.062	2.46 ± 0.78	0.046	2.29 ± 1.16	0.564
Unusual indications	2.50 ± 1.29	2.20 ± 0.84	0.157	2.40 ± 1.14	0.564	3.00 ± 1.00	0.180	2.00	N/A

Supplemental Table 16. *Follow-up data on up to 3 years of the pain subscale of the EQ-5D-5L overall and on usual and unusual indications. Data are presented as mean ± SD. P-value is compared with the baseline. P < 0.05 is considered statistically significant. N/A = not applicable.*

	Baseline	6 months		One year		2 years		3 years	
			P value		*P* value		*P* value		*P* value
Overall	4.00 ± 0.77	2.61 ± 0.92	0.005	2.82 ± 0.91	0.004	1.81 ± 1.03	0.014	2.53 ± 1.30	0.063
Usual indications	3.93 ± 0.83	2.77 ± 0.83	0.026	2.29 ± 1.16	0.009	2.25 ± 0.93	0.038	2.21 ± 1.05	0.102
Unusual indications	4.25 ± 0.50	2.20 ± 1.10	0.066	2.80 ± 1.30	0.157	3.40 ± 0.89	0.157	3.00	N/A

Supplemental Table 17. *Follow-up data on up to 3 years of the anxiety/depression subscale of the EQ-5D-5L overall and usual and unusual indications. Data are presented as mean ± SD. P-value is compared with the baseline. $P < 0.05$ is considered statistically significant. N/A = not applicable.*

	Baseline	**6 months**		**One year**		**2 years**		**3 years**	
			***P* value**		***P* value**		***P* value**		***P* value**
Overall	2.22 ± 1.17	2.00 ± 0.97	0.377	1.91 ± 0.97	0.571	1.81 ± 1.03	0.951	1.67 ± 0.98	0.414
Usual indications	2.21 ± 1.19	1.92 ± 0.95	0.160	1.71 ± 0.85	0.141	1.56 ± 0.81	0.429	1.71 ± 0.99	0.655
Unusual indications	2.25 ± 1.26	2.20 ± 1.10	0.705	2.60 ± 1.14	0.276	2.60 ± 1.34	0.180	1.00	N/A