The Impact of Tobacco Cigarette Smoking on Spinal Cord Stimulation Effectiveness in Chronic Spine–Related Pain Patients

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Background and Objectives: Despite the observation that select nicotine receptor agonists have analgesic effects, smokers report higher pain scores and more functional impairments than lifelong nonsmokers, attributable to exaggerated stress responses, receptor desensitization, and altered pharmacokinetics compounded by accelerated structural damage resulting from impaired bone healing, osteoporosis, and advancement of disk disease. We hypothesized that smoking diminishes the analgesic response to spinal cord stimulation (SCS) in patients with chronic spine–related pain conditions.

Methods: A retrospective cohort study was performed at Cleveland Clinic by collecting and assessing data of 213 patients who had been implanted with SCS for spine-pain indications. History of tobacco smoking was subcategorized into 3 categories: past (former smoker), present (current smoker), or those who had never previously smoked (lifelong nonsmokers), and a multivariable linear regression was run to measure the correlation, if any, between smoking status and numerical rating scale pain score. In addition, opioid consumption at baseline and 12-month follow-up, expressed in milligram oral morphine equivalents, was collected and compared.

Results: Adjusted for differences, at 1-year follow-up, current smokers (n = 62) reported numerical rating scale pain score of 7.0, which is 1.93 (P < 0.001) and 1.32 (P = 0.001) points higher than those of lifelong nonsmokers (n = 77) and former smokers (n = 74), respectively. Opioid intake was 2.4 times higher (P = 0.004) in smokers than in lifelong nonsmokers.

Conclusions: Among our SCS-implanted sample, a positive correlation was observed between tobacco use and degree of pain reduction as early as 12 months postimplant; this was evident by the reported higher pain scores and opioid use in current smokers in comparison with former smokers and lifelong nonsmokers.

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Peculiarly, chronic pain is a more common occurrence than expected with a once estimated prevalence of 46.5% among the general population.1 In the United States alone, 116 million Americans are believed to suffer from some form of chronic pain.2 One common association to chronic pain is tobacco smoking. Despite the observation that smoking may provide analgesic effects,3–5 however, smokers have previously reported higher pain scores6,7 and more associated functional impairments than lifelong nonsmokers.8–11

According to the US Centers for Disease Control and Prevention, smoking remains the single most preventable cause of death in the United States.12 Although efforts to reduce the number of smokers in the United States have been successful, accounting for an overall decrease of smokers from 20.9% to 18.1% from the year 2005 to 2012,13 a rising trend in the rate of smoking among chronic pain patients has been observed. Prevalence of smokers in adults with chronic pain has increased from 24.2% to 25.7% to 28.3% corresponding to the years 2000, 2005, and 2010, respectively.14 Of interest is the observation that smokers with chronic pain also have a tendency of consuming more opioids than former smokers and lifelong nonsmokers.14–16

In this study, we focus primarily on the spinal cord–related chronic pain, treated using spinal cord stimulator (SCS), and the effect of smoking on the success of this treatment modality. Limited information is known about how smoking frequency and duration impact chronic spine–related pain disorders and their therapeutic options. Generally speaking, there is evidence to support the association of tobacco use with increased risk of surgical infection17–19 and delayed wound healing.20–23 On a more specific level, focusing on the effect of tobacco on SCS, only 2 studies are available to date.24,25 Although both studies are composed of a limited sample size (<60 patients), both found an association between smoking and an increased chance of lead migration and revision. Because of the lack of evidence on the effect of tobacco smoking on the efficacy of the SCS in terms of pain relief and opioid use, utilizing a large sample size, we aimed to further investigate the correlation, if any, between 3 different smoking categories diagnosed with chronic spinal pain in a retrospective cohort study. Our primary outcome was the degree of change in pain, and our secondary outcome was changes in opioid utilization compared among the 3 groups. We hypothesized that smokers, and possibly former smokers, will demonstrate worse pain control and higher opioid utilization than lifelong nonsmokers.

METHODS

Study Population

Following institutional review board approval, a retrospective data collection was performed for all patients with chronic spine–related pain who were managed with SCS at Cleveland Clinic Pain Management Department between the years 1997 and 2013. Among the 986 patients who had undergone a successful SCS trial defined as pain relief of 50% or greater and had subsequently received SCS implant, 330 patients were identified having chronic spine–related condition per protocol inclusion criteria, of which 117 patients were excluded because of incomplete records. Therefore, the final analysis included 213 patients, who were further classified into current smokers (62 patients), former smokers (74 patients), and lifelong nonsmokers (77 patients) as illustrated in Figure 1.
Chronic spine–related pain conditions included post-laminectomy syndrome, cervical/lumbar degenerative disk disease, cervical/lumbar radiculopathy, cervical/lumbar spondylosis, and cervical/lumbar spinal stenosis.

Measurements

Patient's demographic data, smoking status, body mass index (BMI), duration of pain, and history of diabetes, disability, and depression were manually obtained from the electronic medical records (Table 1), in addition to reported numerical rating scale (NRS) and opioid utilization, if any, at baseline and 12 months after SCS implantation. All opioid doses collected were converted into their morphine sulfate (MSO₄, mg) equivalent using their equianalgesic dosing shown in Table 2.26

All patients checking in for an appointment at Cleveland Clinic, once seated in the examination room, are required to answer a set of standardized questions including, but not limited to, NRS pain score and smoking status and frequency. For NRS pain score, patients are asked to report their average pain intensity for the last 24 hours on a scale of 0 to 10, with 0 being no pain, 5 corresponding to moderate pain, and 10 being the worst pain imaginable.27 Smoking status is also collected as part of routine documentation with lifetime nonsmokers documented as such. Former smokers are further asked to provide an estimated quit date (of which the years of abstinence were calculated) and number of smoking years prior to quitting. Finally, smokers are further asked to disclose the number of cigars/cigarettes, on average, that they smoke per day. Both smokers and former smokers are asked if they smoke(d) cigars or cigarettes.

For comparison and analysis purposes, history of tobacco smoking was subcategorized into 3 categories: past (former smokers), present (current smokers), or those who had never previously smoked (lifelong nonsmokers). For current and former smokers, the duration of smoking in years and the number of packs smoked yearly along with whether they smoked cigarettes or cigars were documented. In addition, for former smokers, the number of years of smoking abstinence was also recorded.

Statistical Analysis

The patients with missing smoking status, pain scores, and opioid use at 1-year follow-up were excluded from this study. Baseline characteristics were compared among 3 study groups using standard descriptive statistics. Categorical data are presented as number and percent of total. All baseline variables listed in Table 1 except for smoking history were used for adjustment in all subsequent analyses.

As for the primary hypothesis, the multivariable linear regression model was used to assess the association between smoking status (current smokers vs never smokers) and pain relief after 1 year of SCS therapy. The primary outcome was pain score after 1 year, and the predictor was smoking status. The results were adjusted for baseline pain score, baseline opioid consumption, age, sex, BMI, duration of pain, spine-related pain diagnosis, and diabetes, disability, and depression history. The mean difference in 1-year pain scores between current smokers and lifelong nonsmokers along with 95% confidence interval (CI) was reported.

For the first secondary analysis, we used linear regression to assess if smoking cessation (former smokers vs current smokers and former smokers vs lifelong nonsmokers) was associated with
mean pain at 1-year follow-up with adjustment for potential confounders listed in primary analysis. The mean difference in pain between 2 pairs (former smokers vs current smokers and former smokers vs lifelong nonsmokers) along with CI was reported. Further, we looked at the difference in means of daily opioid consumption at 1-year follow-up on the log scale, comparing current smokers with lifelong nonsmokers. We used the multivariable linear model that allowed for the same potential confounding adjustment as for the primary analysis. Opioid consumptions were log transformed as log (opioid+1) to meet normality assumptions for modeling purpose. The ratio of geometric means daily opioid dose after 1 year of SCS therapy comparing current smokers with lifelong nonsmokers was reported along with CI.

To provide more information on the pathogenic role of smoking on pain management, as an explanatory analysis, we assessed the impact of smoking amount per day among current smokers on pain scores and opioid consumption after 1 year, adjusted for potential confounders listed in primary analysis and the length of smoking. Moreover, we assessed the association between smoking abstinence and the pain score or opioid consumptions among former smokers, adjusted for potential confounders listed in primary analysis.

Two-tailed model-based Wald tests were used for all primary and secondary hypotheses. The type I error for the primary hypothesis was set at the 0.05 level. The type I error for the secondary outcomes was preserved at 0.05 overall by applying Bonferroni correction and using a significance criterion of \( P < 0.05/3 = 0.017 \) for each secondary test. Similarly, the significance criterion for explanatory analysis was \( P < 0.05/4 = 0.013 \) for each test.

SAS statistical software version 9.4 (SAS Institute, Cary, North Carolina) for 64-bit Microsoft Windows and R statistical software version 2.3.2 for 64-bit Unix operating system (The R

### TABLE 1. Descriptive Statistics of 3 Study Groups

<table>
<thead>
<tr>
<th>Factor</th>
<th>Current Smoker (n = 62)</th>
<th>Former Smoker (n = 74)</th>
<th>Nonsmoker (n = 77)</th>
<th>Overall P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male), n (%)</td>
<td>30 (48)</td>
<td>34 (46)</td>
<td>30 (39)</td>
<td>0.499</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>50 ± 11</td>
<td>57 ± 12</td>
<td>54 ± 11</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI, mean ± SD, kg/m²</td>
<td>28 ± 6</td>
<td>30 ± 7</td>
<td>31 ± 6</td>
<td>0.039</td>
</tr>
<tr>
<td>Baseline pain score, mean ± SD</td>
<td>7.1 ± 1.7</td>
<td>6.8 ± 1.7</td>
<td>7.7 ± 1.6</td>
<td>0.008</td>
</tr>
<tr>
<td>Baseline opioids consumption in mg oral morphine equivalency, median (Q1, Q3)</td>
<td>30 (20, 68)</td>
<td>30 (20, 60)</td>
<td>30 (20, 60)</td>
<td>0.365</td>
</tr>
<tr>
<td>Duration of pain, median (Q1, Q3), y</td>
<td>5 (3, 10)</td>
<td>6 (2, 9)</td>
<td>3 (2, 6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pain diagnosis, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.215</td>
</tr>
<tr>
<td>Postlaminectomy syndrome</td>
<td>57 (92)</td>
<td>62 (84)</td>
<td>63 (82)</td>
<td></td>
</tr>
<tr>
<td>Degenerative spine disease†</td>
<td>5 (8)</td>
<td>12 (16)</td>
<td>14 (18)</td>
<td></td>
</tr>
<tr>
<td>Diabetes history, n (%)</td>
<td>8 (13)</td>
<td>13 (18)</td>
<td>10 (13)</td>
<td>0.661</td>
</tr>
<tr>
<td>Disability history, n (%)</td>
<td>3 (5)</td>
<td>4 (5)</td>
<td>7 (9)</td>
<td>0.036</td>
</tr>
<tr>
<td>Depression history, n (%)</td>
<td>42 (68)</td>
<td>43 (57)</td>
<td>43 (56)</td>
<td>0.300</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of smoking, median (Q1, Q3), y</td>
<td>25 (18, 32)</td>
<td>20 (10, 30)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Amount of smoking, median (Q1, Q3), pack-year</td>
<td>24 (13, 36)</td>
<td>15 (5, 34)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Smoking type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette, n (%)</td>
<td>58 (94)</td>
<td>72 (97)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Cigar, n (%)</td>
<td>4 (6)</td>
<td>1 (1)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Smoking abstinence, median (Q1, Q3), y</td>
<td>N/A</td>
<td>16 (8, 23)</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

*Differences among 3 groups were examined using \( \chi^2 \) test or Fisher exact test for categorical variables, analysis of variance, or Kruskal-Wallis test for continuous variables.

†Degenerative spine diseases includes degenerative disk disease, cervical/lumbar radiculopathy, spondylisis and spinal stenosis as pain diagnosis at SCS implant treatment.

### TABLE 2. Opioid Conversion Doses

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Oral Dose Equivalent (Medication-MSO₂ Ratio)</th>
<th>Intravenous Dose Equivalent (Parenteral-Oral Ratio)</th>
<th>Transdermal Patch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine sulfate</td>
<td>30 mg</td>
<td>10 mg (1:3)</td>
<td>N/A</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5 mg (1:4)</td>
<td>1.5 mg (1:5)</td>
<td>N/A</td>
</tr>
<tr>
<td>Meperidine</td>
<td>300 mg (10:1)</td>
<td>100 mg (1:3)</td>
<td>N/A</td>
</tr>
<tr>
<td>Methadone</td>
<td>12 mg (1:2.5)</td>
<td>10 mg (1:1.2)</td>
<td>N/A</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20 mg (1:5.1)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30 mg (1:1)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Codeine</td>
<td>200 mg (6.7:1)</td>
<td>120 mg (1:1.67)</td>
<td>N/A</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>N/A</td>
<td>N/A</td>
<td>109 mg (3.6:1)</td>
</tr>
</tbody>
</table>
Foundation for Statistical Computing, Vienna, Austria) were used for all statistical analyses.

Power Consideration

Power calculation was based on the primary outcome. Assuming pain score SD of 2.5, a sample size of 60 smokers and 60 lifelong nonsmokers provides 90% power to detect difference of 1.5 and larger in pain scores at the significance level of 0.05.

RESULTS

A summary of the various factors and their statistical significance, all of which were used in the primary and secondary analyses for adjustment purposes, is shown in Table 1. Age, BMI, duration of pain, baseline pain score, and proportion of disabled were significantly different among 3 groups \( (P < 0.05) \). The majority of our sample was being treated for postlaminectomy syndrome. Current smokers had been smoking for a median of 25 years, and the median quit time for former smokers was 16 years prior to SCS implant.

The NRS pain scores and opioid consumption at the 12-month post-SCS implant benchmark are shown in Figure 2. Among current smokers, former smokers, and lifelong nonsmokers, the means (SDs) of pain scores were 7.0 (2.0), 5.2 (2.8), and 5.1 (1.9), respectively, whereas the medians (Q1, Q3) of opioid consumption were 40 (20, 70), 23 (0, 45), and 23 (0, 45) in mg morphine equivalent. At 12-month post-SCS implant, current smokers illustrated higher NRS pain scores in addition to higher levels of opioid consumption in comparison to both former smokers and lifelong nonsmokers. Interestingly, former smokers and nonsmokers demonstrated similar pain and opioid consumption levels to each other.

Results of the primary and secondary statistical analyses are shown in Table 3. Statistically significant results arose from both our primary and secondary analyses. Primary analysis compared between current and nonsmokers NRS pain scores and the adjusted mean difference was 1.93 \( (95\%\ CI, 1.16–2.71; P < 0.001) \) at 12 months. Secondary analysis, which compared current smokers with former smokers’ NRS pain scores, showed a mean difference between the 2 groups of 1.32, also statistically significant \( (95\%\ CI, 0.38–2.26; P = 0.001) \). On the other hand, although not statistically significant, NRS comparison between former smokers and lifelong nonsmokers yielded a mean pain score difference of 0.62 units \( (95\%\ CI, –0.27 to 1.51; P = 0.096) \). As for the daily opioid consumption, as previously mentioned, smokers showed statistically significant higher oral morphine-equivalent usage than lifelong nonsmokers with a ratio of geometric means in milligrams of 2.37 \( (95\%\ CI, 1.15–4.87; P = 0.004) \), which indicates that the estimated opioid consumption after 1 year among smokers was 2.37 times higher than that of nonsmokers. All comparisons previously stated were adjusted for sex, age, BMI, duration of pain, spine-related pain diagnosis, diabetes, disability, and depression history. An illustrative summary of each comparison can be seen in Figure 2, with CIs marked at their corresponding significance level.

Last but not least, an additional analysis was performed to investigate the correlation of NRS and opioid utilization in 2 scenarios: amount of cigarettes smoked per day for current smokers and the years of abstinence for former smokers. Although none...
of the findings hereby were found to be statistically significant, nonetheless, lower NRS pain scores were observed with increased number of packs smoked following SCS treatment. A decrease in pain by 1.23 NRS units (95% CI, −2.59 to 0.13; \( P = 0.023 \)) was found per each extra 1 pack-day. Moreover, for the impact of smoking abstinence, we found that 1 more year of quitting smoking was associated with 0.6-unit decrease (95% CI, −1.65 to 0.43; \( P = 0.090 \)) in NRS pain scores after SCS implant, adjusted for all potential confounders.

### DISCUSSION

Just over 50 years ago, in 1967, the first SCS device was implanted by Dr Norman Shealy, a Harvard-trained neurosurgeon at Case Western Reserve University.\(^28\) In 1989, it was later approved by the US Food and Drug Administration. Since then, SCS has become increasingly popular with an estimated annual patient SCS implant count, in the United States alone of 34,000.\(^29\) The efficacy of SCS for chronic spine-related pain has been supported in several studies as successfully providing sufficient pain relief in the majority of cases.\(^30\)–\(^34\) Despite this success, there remains a portion of patients who fail to respond or show decreased efficacy over time to spinal cord therapy without a well-founded explanation.\(^35\)–\(^36\) Theories involving failure of SCS or show decreased efficacy over time to spinal cord therapy with or without a well-founded explanation.\(^35\)–\(^36\) Theories involving failure of SCS and duration,\(^35\) psychological factors,\(^37\)–\(^40\) and the number of preimplant surgeries,\(^35\) which are all common contributors. Our primary goal in this study was to determine if regular tobacco use has an effect on the response to SCS neuromodulation therapy specifically in spine-related chronic pain etiologies. The acute analgesic effects of nicotine and tobacco in cigarettes have consistently been demonstrated in experimental animals,\(^31\)–\(^42\) albeit in human subjects the results have been controversial with the existence of paradoxical evidence.\(^3\)–\(^5\) Whereas some studies presented smoking as an adequate pain reliever in humans,\(^5\)–\(^43\) others found that they accentuate the sensation of pain\(^44\)–\(^46\) as well as cause functional impairment.\(^8\)–\(^11\) Findings of our study indicate that chronic spine-related pain patients who were managed with spinal cord stimulation do indeed report higher pain scores if they continue to smoke compared with both former smokers and lifelong nonsmokers, which goes in concordance with the majority of literature published about tobacco smoking and chronic pain.

The effect of smoking in chronic spinal pain was explored in a cross-sectional postal survey of 29,424 people by Leboeuf-Yde et al.,\(^45\) who found a positive association between smoking and low-back pain, which was strongest for low-back pain of long duration. Similar results originated from the systematic review by Goldberg et al.,\(^46\) who concluded that evidence exists supporting the theory that smoking is associated with increasing incidence and prevalence of nonspecific back pain, however, urged the necessity of additional long-term studies to be able to state unequivocally that smoking precedes back pain. Another study involving 862 subjects found statistically significant evidence that smoking men had more frequent pain problems compared with women. In addition, in comparison with nonsmokers, smokers were found to have back pains more frequently.\(^47\) Richardson et al.\(^48\) conducted a randomized, double-blind, placebo-controlled crossover study to show the effect of nicotine on pain score level in patients with spinal cord injury. The results showed that nonsmokers reported less pain scores on NRS in comparison to patients who were acutely exposed to nicotine gum. Similarly, in a meta-analysis done by Shiri et al.,\(^49\) patients who have smoked or are actively smoking demonstrated worse or higher visual analog scale scores throughout the treatment course of spinal disorders. The exact cause of the correlation between smoking and spinal pain is obscure; nonetheless, there are several possible explanations for the causality. One of the postulations is that chronic exposure to nicotine leads to altered pain perception.\(^50\) Another theory is that cigarette smokers may develop autonomic nervous system imbalance that could result in sympathetic predominance and aggravated pain sensations.\(^51\)

Furthermore, the precise underlying mechanism of advanced disk and intervertebral disk degeneration and its relation to smoking are also not fully understood. One possible explanation can be linked to nicotine's vasoconstrictive effect, which may lead to diminution of blood flow to the disk and its endplates, and because the intervertebral disks are avascular and receive their nutrition via diffusion through pores in the
endplate, this ultimately may impair the disk and intervertebral disk metabolism.\textsuperscript{52} Moreover, smoking-induced chronic cough may result in internal disk disruption via intermittent increase in intradiscal pressure.\textsuperscript{52,53} Nicotine also affects intervertebral disk health down-regulation of the proliferation rate and glycosaminoglycan biosynthesis.\textsuperscript{54}

From another perspective, smoking stimulates neutrophils in the pulmonary capillaries to release elastase and protease enzymes into the systemic circulation.\textsuperscript{55} This is in addition to cigarette smoking inhibiting α1 antiprotease, which is the most potent protease inhibitor. The latter further aggravates serum proteolytic activity.\textsuperscript{56,57} This effect is intensified in smokers because of the higher levels of white blood cells residing in the smokers' lungs.\textsuperscript{55,58,59} This theory is supported by study findings showing that the activities of proteolytic enzymes are higher in degenerated disks when compared with normal disks, evidently increasing the grade of degeneration.\textsuperscript{60,61}

Chronic smoking behavior was associated with maladaptive chronic behavioral issues including preference of inactivity, reliance on medical management, and a high level of emotional distress.\textsuperscript{62} Jamison et al\textsuperscript{62} surveyed chronic pain patients and found that 54% of patients with back pain were smoking cigarettes. Fifty-seven percent of the patients reported resorting to smoking when their chronic pain is intensified. As chronic smokers lose their social reinforcers (eg, work, social recreational activities), they compensate by increasing other reinforcing behaviors such as eating and smoking.

In our study, mean opioid intake was 2.4 mg higher (CI, 1.2–4.9 mg; \( P < 0.001 \)) in smokers compared with lifelong nonsmokers despite pain scores approaching implant NRS reports (7.1 ± 1.7). Ironically, smokers end up consuming more analgesics despite pain scores approaching preimplant NRS reports (7.1 ± 1.7). A synergistic effect would be expected between nicotine and pentazocine, and hence their urine levels of the metabolites were reduced by 40%. The effect of smoking on codeine was studied by Yue et al\textsuperscript{68} and concluded that smoking induced the glucuronidation of codeine.\textsuperscript{68,69} We can extrapolate from the previous studies that patients with chronic back pain who smoke will have increased opioid consumption due to either increased metabolism of the medications or as a mean of compensation for diminished social reinforcers.

Explanatory analysis was done to realize if the effect of smoking on SCS therapy was dose dependent. Although we did not find any significant associations in explanatory analyses (Table 4), we observed that higher smoking amount was moderately related with lower NRS pain scores after SCS treatment with decrease in pain by 1.2 NRS units per each extra 1 pack-day. Moreover, we found that 1 more year of quitting smoking was associated with 0.6-unit decrease in NRS pain scores after SCS implant.

While our study demonstrates the negative impact of smoking on SCS therapy, it also raises many questions urging the need for further studies.

**Limitations**

As with all retrospective studies, we cannot be certain that the independent association we found was causal in nature. Although we accounted for 10 potentially confounding baseline factors, residual bias due to uncontrolled confounding variables may remain. In addition, because approximately 35% of the sample who had met the inclusion criterion was excluded from the analysis because of missing data, results could potentially be biased. Moreover, we noticed the heterogeneity of former smokers on quit-smoking time, which ranges from 2 months to 54 years with a median at 16 years. The effects of quit-smoking time on pain reduction after SCS could be further assessed in future studies.

**CONCLUSIONS**

Our results demonstrated that the pain scores after 1 year of SCS therapy among smokers were higher than those among lifelong nonsmokers. The daily opioid consumption was higher for smokers than that for lifelong nonsmokers as well. In addition, the former smokers who quit smoking before SCS implant had lower pain scores compared with active smokers after 1 year of therapy. Our results suggest a negative association between smoking and SCS efficacy in chronic spine-related pain patients.

### TABLE 4. Results of Explanatory Analyses

<table>
<thead>
<tr>
<th>Pain Scores: NRS Scale</th>
<th>Opioid Consumption: mg Oral Morphine-Equivalent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Difference in Means (95% CI)</td>
</tr>
<tr>
<td>Amount of daily smoking for current smokers per 1 pack-day‡†‡</td>
<td>(-1.23 (−2.59 to 0.13))</td>
</tr>
<tr>
<td>Smoking abstinence for former smokers per 1 y†‡‡</td>
<td>(-0.61 (−1.65 to 0.43))</td>
</tr>
</tbody>
</table>

* The association between amount of daily smoking and 2 outcomes was adjusted for baseline pain scores, baseline opioid consumption, age, sex, BMI, duration of pain, spine-related pain diagnosis, diabetes, disability, depression history, and length of smoking.

† The association between smoking abstinence and 2 outcomes was adjusted for baseline pain scores, baseline opioid consumption, age, sex, BMI, duration of pain, spine-related pain diagnosis, diabetes, disability, and depression history.

‡ Significant criterion is \( P < 0.013 \) by applying Bonferroni correction (ie, 0.05/4) to preserve it at the 0.05 level overall. Correspondingly, 98.7% CIs, as 95% CIs adjusted for multiple comparisons, are reported.
REFERENCES


57. Lauret P, Bieth JG. Cigarette smoke decreases the rate constant for the association of elastase with α1-proteinase inhibitor by a non-oxidative mechanism. Biochem Biophys Res Commun. 1985;126:275–281.


