Trends in Clinical Trials for Spinal Cord Stimulation

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Abstract
Background: Spinal cord stimulation (SCS) is a neuromodulation technology widely used in the treatment of intractable chronic pain syndromes. SCS is now being applied more broadly as a possible therapy for a range of indications, including neurological, cardiac, and gastrointestinal disorders. Ongoing research in this field is critical in order to gain further insights into the mechanisms of SCS, determine its role in new indications, and refine programming techniques for the optimization of therapeutic outcomes. Objective: To assess the state of SCS-related human research by cataloging and summarizing clinical trials that have been recently completed or are currently underway in this field. Methods: A search was conducted for clinical trials pertaining to SCS using the ClinicalTrials.gov database. Trials were analyzed to generate a detailed overview of ongoing SCS-related research. Specifically, trials were categorized by intervention, trial start date, study completion status, clinical phase, projected subject enrollment, condition, country of origin, device manufacturer, funding source, and study topic. Results: In total, 212 relevant clinical trials were identified. 175 trials (82.5%) involved invasive SCS, while the remaining 37 trials (17.5%) used noninvasive forms of spinal stimulation. Most trials examined the efficacy of SCS for chronic pain syndromes or new indications, while others assessed different stimulation parameters. The studies spanned >27 different disorders, with almost 20% of trials pertaining to conditions other than chronic pain syndromes. The majority of SCS trials were US-based (55.7% of studies), but many countries (e.g., Belgium and UK) are becoming increasingly active. The ratio of investigator-sponsored to industry-sponsored trials was 2:1. Emphasizing the need to optimize therapeutic outcomes of SCS, one-quarter of trials predominantly focused on the assessment of alternative stimulation parameters such as burst or high-frequency stimulation. Conclusions: A large number of clinical trials of SCS are underway. Improvements in the treatment of pain and novel indications for SCS constitute the majority of studies. This overview of SCS-related clinical trials provides a window into future new indications, novel stimulation techniques, and a heightened understanding of the mechanisms of action.

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Introduction

Spinal cord stimulation (SCS) is a well-established neuromodulation modality for the treatment of chronic pain [1, 2]. SCS can be either invasive or noninvasive. Invasive SCS involves direct stimulation of the dorsal column using a surgically implanted epidural or intradural device. Noninvasive SCS consists of stimulating the cord via one of several transcutaneous techniques (e.g., transcutaneous SCS, trans-spinal direct current stimulation, spinal transcutaneous electrical nerve stimulation, and spinal magnetic stimulation). Epidural SCS has become a mainstream procedure that provides a safe and effective drug-free treatment that is adjustable and nonpermanent. SCS is most often employed to relieve intractable back/extremity pain and is commonly indicated for spinal cord injury (SCI), failed back surgery syndrome (FBSS), neuropathy, and complex regional pain syndrome (CRPS) [3]. SCS is increasingly being examined for its therapeutic potential across a range of neurological disorders (e.g., Parkinson’s disease) [4], cardiac disorders (e.g., angina pectoris) [5], and gastrointestinal/genitourinary (GI/GU) disorders (e.g., irritable bowel syndrome) [6].

Although SCS has been in use since 1967, its mechanism(s) of action remains poorly understood. The technique is originally based on the gate control theory of pain proposed by Melzack and Wall [7], which suggests that non-painful inputs inhibit painful inputs, thereby preventing pain sensation from reaching the central nervous system. Conventional SCS utilizes paresthesia as non-painful input [8]; however, some patients may not tolerate the persistent perception of paresthesia, thereby negating the clinical benefits. Similarly, approximately 40% of patients do not get adequate pain relief from conventional SCS [9–11], highlighting the need for improved therapy delivery via parameter optimization in order to maximize clinical benefit and minimize adverse effects. This is being addressed by novel stimulation techniques such as kilohertz-frequency [12, 13], burst [14], and multiple waveform [15] stimulation paradigms.

Interest in neuromodulatory approaches such as SCS has increased due to the growing demand for minimally or noninvasive methods to treat intractable pain. Well-designed clinical trials are required to shape the expanding practice of SCS appropriately. As such, this overview of past and current SCS clinical trials highlights the trends in the field and provides insights into novel indications and improved stimulation parameter choices to optimize therapeutic outcomes for patients.

Materials and Methods

A comprehensive search for past and ongoing clinical trials pertaining to SCS was conducted using the publicly available trial registry, ClinicalTrials.gov (https://clinicaltrials.gov/). This search was conducted on January 26, 2020, and included the search terms, “spinal cord stimulation” or “SCS.” Relevant clinical trial entries identified through other sources were also assessed for eligibility. Studies were separately screened by authors I.E.H. and D.H. to ensure they pertained to SCS, with relevant trials retained for further analysis. Intervention type, trial start date, study completion status, clinical phase, projected subject enrollment, and funding source were recorded as posted in trial entries. Clinical disorder was captured according to the specific condition described in each trial’s entry and subsequently broadly categorized as either “back/extremity pain,” “SCI,” “FBSS,” “neuropathy,” “complex regional pain syndrome,” “neurological disorders,” “cardiac disorders,” “GI/GU disorders,” or “other.” The country of origin was determined according to the country of the responsible party (i.e., the lead center in multicenter studies). The device manufacturer was captured by noting any mention of specific manufacturer’s SCS hardware or relationship with a particular manufacturer in the trial entry. For studies that used multiple device manufacturers, each manufacturer was enumerated; accordingly, these trials were double counted for the analysis of manufacturers. Depending on whether an intervention/treatment was being evaluated, the study design was classified as “interventional” (e.g., study determining the efficacy of a novel indication) or “noninterventional” (e.g., imaging/electrophysiological study examining structural or functional SCS-induced brain changes). Finally, study topic was assessed with reference to whether trials determined the efficacy of novel indications, examined stimulation parameters, measured secondary outcomes (e.g., improved quality of life and opioid reduction), compared devices, or conducted imaging (e.g., CT, MRI, and PET) or electrophysiology (e.g., single-unit recordings, local field potentials, EEG, and MEG) in any capacity beyond standard clinical practice. Where applicable, a “rate of change” metric was calculated to examine how rapidly new clinical trials of different classes, purposes, or origins were being generated.

Results

316 registered clinical trials were generated from our ClinicalTrials.gov database search. A total of 212 entries were identified after we screened for relevance to SCS. This count included trials that were active/recruiting and those with a status of completed, withdrawn, or terminated. Trial registration dates ranged from the year 2000 – when the first trial commenced – to 2020.

Studies by Intervention

The search results were categorized by stimulation intervention to determine a trial’s relevance to this analysis (Table 1). Studies that were ultimately included involved both invasive and noninvasive forms of spinal stimulation.
174 trials (82.1% of all trials) related to epidural spinal cord stimulation (eSCS), while the remaining 38 trials (17.9%) pertained to intradural spinal cord stimulation (0.5%) or noninvasive forms of spinal stimulation such as transcutaneous SCS (13.2%), trans-spinal direct current stimulation (2.8%), spinal transcutaneous electrical nerve stimulation (0.5%), and spinal magnetic stimulation (0.9%). Trials deemed not relevant included interventions that did not focus on stimulating the spinal cord. Instead, they described stimulation of the brain (e.g., deep brain stimula-
**Fig. 2.** Trials by projected enrollment of subjects. 212 trials (100% of all trials) listed since 1997 provided information on projected subject enrollment. Projected enrollment ranged from 1 to 10 subjects (25.0% of trials) to >500 subjects (0.9%), with an enrollment of 11–50 subjects being most common (47.2%). Ten trials (4.7%) reported an enrollment of 0 subjects; however, all these studies were withdrawn.

**Fig. 3.** Trials by clinical disorder. 212 trials (100% of all trials) listed since 1997 provided information on the clinical disorder being studied. 

- Pie chart representing the percentage of clinical trials categorized by disorder class. Sixty-eight trials (32.1%) study back/extremity pain, 44 trials (20.8%) study spinal cord injury, 33 trials (15.6%) study failed back surgery syndrome, 28 trials (13.2%) study neuropathy, 4 trials (1.9%) study complex regional pain syndrome, 16 trials (7.5%) study neurological disorders, 9 trials (4.2%) study cardiac disorders, 4 trials (1.9%) study GI/GU disorders, and 6 trials (2.8%) study other disorders.
- Line plots of the top 4 disorder categories (back/extremity pain, SCI, FBSS, and neuropathy) show cumulative growth in the number of studies from 1997 to 2019.

GI/GU, gastrointestinal/genitourinary; SCI, spinal cord injury; FBSS, failed back surgery syndrome.
Studies by Start Date and Status of Completion

Approximately two-thirds of all studies commenced within the last 5 years (Fig. 1). All trials that began before 2013 have, at this point, been completed, withdrawn, or...
terminated. The oldest clinical trial that was still listed as actively recruiting started in 2013 and is an interventional study assessing whether epidural stimulation can improve arm motor function in patients with cervical SCI (NCT02313194). Of the 194 trials (91.5% of all trials) with a known completion status, most were either active/recruiting (44.3%) or already completed (33.0%). A considerable portion of trials – 16% in total – was listed as either withdrawn (5.2%) or terminated (10.8%). Regarding the projected trial duration, the mean length of an SCS-related clinical trial was found to be 34.9 ± 1.8 months (SEM). The maximum projected trial length was 158 months for a completed prospective observational study that compared eSCS devices in 10,981 subjects (NCT00959296). The minimum projected trial length was 20 days for a completed interventional study that assessed heart rate variability in 23 patients treated with eSCS (NCT03768791).

**Studies by Phase and Projected Enrollment**

For the 212 clinical trials identified, projected enrollment ranged from 1 to 10 subjects (25.0% of trials) to >500 subjects (0.9%), with an enrollment of 11–50 subjects being most common (47.2%) (Fig. 2). Studies enrolling 51–100 subjects and 101–500 subjects accounted for 13.7 and 8.5% of trials, respectively. Ten trials (4.7%) reported an enrollment of 0 subjects; however, all these studies were withdrawn. Information regarding the study phase was found to be lacking, with 83.9% of trial entries omitting this information.

**Studies by Clinical Disorder**

Registered clinical trials studied a total of 27 different conditions (Table 2). Most registered SCS-related clinical trials pertained to chronic pain syndromes, including back/extremity pain, SCI, FBSS, neuropathy, and CRPS.
(totaling 83.6% of all trials, Fig. 3a). Clinical trials for novel indications such as neurological disorders accounted for 7.5% of studies, followed by cardiac disorders (4.2%) and GI/GU disorders (1.9%). Among the top 4 pain disorder classes, the number of new trials registered per year for back/extremity pain, SCI, FBSS, and neuropathy increased from 0.6, 0.1, 0.2, and 0.2 (1997–2007) to 5.1, 3.2, 2.6, and 2.2 (2008–2019), respectively (Fig. 3b; see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000510775). For the novel indications, the number of new trials registered per year for neurological, cardiac, and GI/GU disorders increased from 0.0, 0.2, and 0.1 (1997–2007) to 1.3, 0.6, and 0.3 (2008–2019), respectively (Fig. 3b; online suppl. Table 1). Some of the more novel indications described, each only totaling 1 study, include major depressive disorder (NCT03433339), hypertension (NCT02828436), and coma/decreased level of consciousness (NCT04010838).

**Studies by Country of Origin**

By country of study origin, the top 5 countries that accounted for the highest percentage of trials include the USA (55.7%), Belgium (7.5%), the UK (7.1%), the Netherlands (4.7%), and France (3.3%) (Fig. 4a; Table 3).

**Table 3. Clinical trials by country of origin**

| Country          | Studies, n | Total studies, % |
|------------------|------------|------------------|
| USA              | 118        | 55.7             |
| Belgium          | 16         | 7.5              |
| UK               | 15         | 7.1              |
| The Netherlands  | 10         | 4.7              |
| France           | 7          | 3.3              |
| Switzerland      | 6          | 2.8              |
| Canada           | 5          | 2.4              |
| China            | 5          | 2.4              |
| Italy            | 3          | 1.4              |
| Norway           | 3          | 1.4              |
| Spain            | 3          | 1.4              |
| Sweden           | 3          | 1.4              |
| Taiwan           | 3          | 1.4              |
| Australia        | 2          | 0.9              |
| Brazil           | 2          | 0.9              |
| Denmark          | 2          | 0.9              |
| Russia           | 2          | 0.9              |
| South Korea      | 2          | 0.9              |
| Argentina        | 1          | 0.5              |
| Austria          | 1          | 0.5              |
| Ireland          | 1          | 0.5              |
| Poland           | 1          | 0.5              |
| Ukraine          | 1          | 0.5              |
| **Total**        | **212**    | **100**          |

While the USA reported its first SCS trials in 2003, other countries did not report any until almost a decade later. Rates of trial registration signifying the number of new trials started per year are represented in Figure 4b and detailed in online suppl. Table 2. The USA also led with the highest number of new trials started per year, showing rapid growth compared to other nations.

**Studies by Manufacturer and Funding Source**

Out of the 212 studies identified, 127 (59.9% of all trials) listed a manufacturer. The different device manufac-
Manufacturers for each spinal stimulation intervention are listed in Table 4. Among epidural SCS studies, Medtronic and Boston Scientific contributed to the highest percentage of registered trials at 37.3 and 32.7%, respectively (Fig. 5a). Other top eSCS device manufacturers included Abbott Laboratories (formerly St. Jude Medical), Nevro, and Nuventra, which accounted for 16.4, 9.1, and 4.5% of trials, respectively. Figure 5b shows the cumulative growth in the number of studies using the top 5 eSCS device manufacturers from 1997 to 2019. eSCS, epidural spinal cord stimulation.

Fig. 5. Trials by eSCS device manufacturer. 127 trials (59.9% of all trials) listed since 1997 provided information on the device manufacturer, which was obtained by documenting any relationship to a specific manufacturer in the trial entry, that is, manufacturer-sponsored trial or use of specified manufacturer equipment. a Pie chart represents the percentage of eSCS clinical trials categorized by the manufacturer. Only the top 5 device manufacturers are represented, of which Medtronic and Boston Scientific contributed to the highest percentage of registered trials at 37.3 and 32.7%, respectively. b Line plots of the top 5 contributing eSCS device manufacturers show cumulative growth in the number of studies from 1997 to 2019. eSCS, epidural spinal cord stimulation.

Completion status, industry-sponsored trials are more likely to be completed (50.0% industry vs. 22.5% nonindustry) or withdrawn/terminated (23.0% industry vs. 11.7% nonindustry). Trials that are funded by industry are also larger in size; studies enrolling >100 subjects are funded by industry 85.0% of the time, whereas studies enrolling 11–50 subjects are only funded by industry 27.0% of the time.

Studies by Design and Primary Topic

The 212 studies were first classified as either interventional (91.5%) or noninterventional (8.5%) to survey the main content and design of the identified clinical trials. Of the 194 interventional studies that provided information about randomization design, 83.8% of trials were randomized, and the remaining 16.2% were nonrandomized. Just over half of all trials (53.6%) examined the efficacy of spinal stimulation for chronic pain syndromes.
Clinical Trials for Spinal Cord Stimulation

or new indications. A quarter of trials (25.6%) were parameterization studies that involved testing different stimulation settings (i.e., conventional vs. burst or high-frequency stimulation) to optimize therapeutic outcomes. The remaining trials examined research topics that included measuring secondary outcomes (9.0%), comparing devices or implantation techniques (6.1%), and neuroimaging (4.3%). The research topic of parameterization is relatively new. Only 1 study that began between 1997 and 2007 explored the effect of varying parameters (NCT00399516), while 53 studies initiated between 2008 and 2019 explored parameterization. Over half (55.6%) of parameter-related studies commenced in the last 3 years.

Discussion

We identified and categorized 212 clinical trials that spanned 2 decades of SCS-related research. Overall, the number of registered SCS trials has greatly increased – especially within the last 5 years – suggesting that this field is still rapidly growing, and formal documentation of research progress is becoming routine.

Current Trends and Future Directions

Several interesting trends were identified from our analyses of SCS-related clinical trials. Regarding country of origin, the USA has conducted the most SCS trials of any country to date by a considerable margin. Belgium has the second highest number of registered clinical trials, followed by the UK, the Netherlands, and France.

Interestingly, China was not among the top contributors to SCS clinical trials. In the related field of DBS, China showed rapid growth despite its late entry in the field [16]; however, this same trend does not currently apply for SCS. This may change since the 5 Chinese trials that were listed all commenced in 2019, potentially signaling growth over the coming years. China may also contribute to establishing novel indications for SCS, given that one of their active trials is a feasibility study of epidural stimulation in patients with disorders of consciousness (NCT04010838).

The use of SCS to improve function in SCI is an emerging area. Work that was done in the USA [17] and Switzerland [18] is breaking new ground in improving motor function after SCI with paired targeted epidural spinal stimulation and the use of robot-assisted rehabilitation. Courtine et al. [18] have helped paralyzed patients walk again with the advent of a spinal cord implant that mimics how the brain activates the spinal cord in real time. Ongoing clinical trials are assessing the feasibility of their Stimulation Movement Overground (STIMO) method to improve mobility recovery in patients with subacute SCI (NCT02936453, NCT04196114, and NCT04052776).

Perhaps unsurprisingly, the majority of SCS trials focused on pain management. SCS was first approved by the US Food and Drug Administration (FDA) in 1989 to relieve chronic pain from nerve damage in the trunk, arms, or legs. SCS is particularly useful for relieving pain that is neuropathic in origin, which arises from nerve damage (e.g., due to accident, injury, or disease), and does not serve a protective purpose. In contrast, SCS is not optimal for treating nociceptive pain (i.e., pain caused by tissue damage).

SCS has been well established for pain conditions of neuropathic nature, such as intractable back pain, FBSS, neuralgia, and CRPS (SCS trials for these conditions totaled 83.6% of all trials). Since the clinical efficacy of SCS for these pain conditions is generally accepted, pertinent trials tend to investigate novel SCS parameters to optimize therapy [13, 14], secondary outcomes such as changes in quality of life and opioid use (NCT03249922, NCT02727985), and SCS-induced brain alterations to provide insight into the mechanisms of actions underlying SCS (NCT02650362). For painful diabetic neuropathy – a common complication of diabetes mellitus that affects 132 million people worldwide [19] – a prospective, multicenter, randomized controlled trial is currently underway to assess the efficacy of high-frequency SCS at 10 kHz as an adjuvant therapy to conventional medical management [20] (NCT03228420).

By contrast, novel or less common indications constituted less than one-fifth of clinical trials. However, over 70% of these trials commenced within the past 5 years, suggesting that there is a growing trend for assessing SCS efficacy for new indications. Although SCS indications have been classified as belonging to neurological (7.5%), cardiac (4.2%), and GI/GU (1.9%) disorders, for most of these indications, SCS is used as a treatment modality for pain associated with these conditions. For instance, SCS effectively relieves severe chest pain in patients suffering from refractory angina [5]. Similarly, SCS reduced the pain in irritable bowel syndrome but did not significantly reduce the number of attacks or diarrheal occurrences [6]. Although not extensively studied, findings suggest that SCS may provide improved pain control in patients with intractable central poststroke pain [21]. However, there are indications in which SCS is being used to treat pri-
ry (non-pain) symptoms of a specified disorder. This includes the use of spinal stimulation for major depressive disorder (NCT03433339), hypertension (NCT02828436), coma/decreased level of consciousness (NCT04010838), and gait disturbances in Parkinson’s disease [4].

Although SCS owes its inception to the gate control theory, its mechanism of action involves more than the direct inhibition of pain transmission in the dorsal horn of the spinal cord. If this were the principal mode of action, then SCS should be effective in controlling acute nociceptive pain. But with some notable exceptions [22], this is not generally the case. Early studies examining EEG potentials evoked by dorsal column stimulation suggested pain processing occurred in the cerebrum, thalamus, or brainstem rather than the spinal cord [23]. This supraspinal effect may be important for the mechanism of action of SCS.

Studies have reported that psychological distress and psychogenic pain are related to poor outcomes in patients undergoing surgery for chronic low back pain [24]. The role of stimulation in the context of these comorbidities is unclear. There are no fibromyalgia-specific registered SCS trials and only 1 feasibility trial for chronic migraine (NCT01653340). A retrospective survey reported that high-cervical SCS was effective in improving pain associated with intractable migraine in 17 patients [25]. The literature suggests that it is more common to treat chronic headache with occipital nerve stimulation [26], but the role of stimulation in headache disorders requires further investigation.

Our results also highlight the growing popularity of trials that test a wide spectrum of stimulation settings. These parameterization studies are important in optimizing therapeutic outcomes for patients. One such parameter is stimulation frequency. In 2013, high-frequency SCS at 10 kHz was introduced as a novel stimulation paradigm for the management of chronic back pain [27]. Although kilohertz-frequency stimulation is becoming more common, given its therapeutic efficacy and reduction of adverse effects (i.e., paresthesia), its mechanisms of action are not well understood. One such study has even applied ultra-high frequency at 500 kHz, far beyond that of the biological firing rate of human neurons (NCT03543085). Other clinical trials are assessing structural and functional brain changes during kilohertz-frequency SCS to provide insights into the underlying mechanisms (NCT02751216 and NCT03852381).

Randomized controlled trials have suggested that SCS at 10 kHz is more effective than conventional stimulation [28]. However, these trials did not include a sham stimulation arm, making it difficult to ascertain how much benefit was directly related to the stimulation per se. New stimulation paradigms, including burst and multiple waveforms, challenge kilohertz paradigms by also treating pain without paresthesia [29, 30]. When comparing burst versus 10-kHz SCS in patients with FBSS, Muhammad et al. [31] reported more pain relief with burst stimulation after 1 year. Another study demonstrated that personalizing treatment with multiple waveforms effectively treated chronic pain in patients who previously did not respond to SCS at 10 kHz [15]. Given that over half (55.6%) of parameter-related studies commenced in the last 3 years, we can expect continued research developments in optimizing SCS delivery.

SCS research is inherently influenced by industry partnerships and funding sources, both of which are necessary for driving innovation and technological advancements. In 2019, the global market value of SCS devices was estimated at USD 2.4 billion and was projected to increase by 4.8% over the next 5 years [32]. Several different companies manufacture SCS systems; some of these have existed for decades (e.g., Medtronic since 1949, Boston Scientific Corp. since 1979), while others are relatively new to the scene (e.g., Nevro Corp. since 2006). Although several new SCS manufacturers have emerged over the past decades, Medtronic and Boston Scientific remain the most prominent SCS device manufacturers used in clinical research. In part, these manufacturers shape the type of clinical research being conducted by determining the availability and accessibility of novel devices. For example, high-frequency spinal cord stimulators – currently produced only by Nevro – permit programming optimization research that is otherwise not possible. Although the information on funding sources was limited, results showed that one-third of the studies were sponsored by industry. This is more than what was reported for clinical trials for DBS, in which the ratio of investigator-sponsored to industry-sponsored trials was 3:1 [16]. We want to highlight the importance of reporting funding sources and the role of the funder at the time of publication to ensure transparency in the field.

Beyond technological advances in parameterization that include kilohertz-frequency, burst, and multiple waveform stimulation paradigms to deliver paresthesia-free therapy, other cutting-edge SCS research involves the use of wireless stimulation devices and closed-loop systems. In 2015, Stimwave Technologies released its Freedom SCS system, which is capable of wirelessly delivering spinal stimulation. Patients are implanted with stimulators with embedded receivers and wear a small,
external energy source with a rechargeable transmitter. This minimally invasive device is 95% smaller than other stimulators on the market. It also eliminates the need for wires, tunneling, and large pockets that are a source of discomfort, pain, or infection. Several clinical trials sponsored by Stimwave have assessed the effectiveness of their new wireless neuromodulation technology (NCT02787252, NCT02514590, and NCT02403518). They recently reported that wireless SCS is effective in treating chronic pain in patients with FBSS over a study period of 7 months [33]. Other companies such as Saluda Medical have developed closed-loop SCS systems to try and optimize stimulation delivery using feedback signals to maintain activation within patients’ therapeutic window. A randomized controlled trial is ongoing to test their Evoke® SCS system that measures and records evoked compound action potentials to guide stimulus intensity (NCT02924129).

Conclusions

This analysis provides an update on the current state of affairs for SCS-related clinical trials. Past and present trials have been characterized to highlight trends in worldwide topography, subject matter, and pragmatic factors that shape the field of SCS research. This overview offers insight into novel indications, stimulation paradigms, and advanced SCS technologies that we can expect in the future.

Statement of Ethics

Ethics approval was not required for this study.

Conflict of Interest Statement

A.M.L. has served as a consultant for Abbott, Boston Scientific, Functional Neuromodulation, Medtronic, Nevro, PINS, and SceneRay. All other authors declare no conflicts of interest.

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Author Contributions

Study design: I.E.H., G.J.B.E., and A.M.L. Writing and figure preparation: I.E.H. and D.H. prepared the initial draft of the manuscript and figures; all authors reviewed and edited the manuscript and approved the submitted version. Analysis: I.E.H. and D.H. performed analyses of data. Study supervision: A.M.L.

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