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REVIEW

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Two Surgeries Do Not Always Make a Right: Spinal Cord Stimulation for Failed Back Surgery Syndrome

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Failed back surgery syndrome (FBBS†) is characterized by chronic pain that persists following spine surgery. In this review, we discuss the use of spinal cord stimulation (SCS) for FBBS treatment and how the clinical use of SCS may be influenced by private manufacturers. While SCS therapy can be promising for the appropriate patient, there remain knowledge gaps in understanding the full potential of SCS technology for delivering optimal therapeutic benefit. We caution that the use of SCS without a complete understanding of the technology may create exploitative situations that private manufacturers can capitalize on while subjecting patients to potentially unnecessary health and financial burdens.

INTRODUCTION

Chronic pain is a condition that places physical and emotional burdens on everyday life, imposing economic and public health challenges on society [1]. Among US adults reporting pain in 2009, 28.1 percent reported having low back pain [2]. While the majority of low back pain is acute, some individuals can develop chronic low back and radicular distribution pain, which is characterized by persistent pain lasting for more than 12 weeks. Treatments to address chronic back related pain include cognitive behavioral and exercise therapy, educational interventions, and pharmacological approaches [3]. If conservative treatments fail, surgical interventions such as spinal fusion or discectomy are considered [4]. However, pain can persist following spine surgeries, resulting in failed back surgery syndrome (FBBS) [5]. Spinal cord stimulation (SCS) is often considered as a treatment option for individuals whose initial spine surgeries failed to reduce pain or even cause new pain symptoms, leading to a redirection towards yet another surgical procedure to implant spinal cord stimulation devices following the development of FBBS [5]. Surgical approaches and their subsequent redirection towards neurostimulation for the treatment of chronic low back pain are becoming more commonplace. In 2008, an estimated 400,000 spinal fu-

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†Abbreviations: FBBS, failed back surgery syndrome; SCS, spinal cord stimulation; DRG, dorsal root ganglion; VAS, visual analog scale; CMS, Centers for Medicare and Medical Service; CME, continuing medical education.

Keywords: Chronic pain, failed back surgery syndrome, spine surgery, spinal cord stimulation, neurosurgery

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sion surgeries were performed in the United States [6] and an estimated 50,000 patients undergo spinal cord stimulator implants each year [7].

The rise in the use of spine surgery and subsequent redirection to spinal cord stimulation for chronic low back pain has been a major topic of controversy in the medical community. In this article, we examine the literature regarding the risks and outcomes associated with spine surgeries and SCS. We discuss the spine implant and devices industry as well as conflict of interest issues that can influence the objectivity and reporting of spine research. Ultimately, although SCS may be a promising therapeutic avenue for FBBS, more research is still needed to fully understand the potential of such surgical approaches so that patients are not subjected to unnecessary health risks and financial burden.

SIZE OF INDUSTRY

The spine implant and devices industry generates significant revenues for the companies involved. This market is expected to be worth approximately $8 billion in 2014 and grow to $16 billion by 2020 [8,9]. Among the key participants are Johnson & Johnson, Medtronic, and Stryker, who accounted for over half of the spinal implant market share [8]. The SCS market alone was estimated to be worth $1.3 billion in 2014 [10]. Major spinal cord stimulator manufacturers include Medtronic, Boston Scientific, Abbott (previously St. Jude Medical), and Nevro.

In addition to being a profitable business for the companies, the spinal implant market also generates significant revenues for the healthcare settings involved. Spinal fusion surgery, a commonly performed procedure for the treatment of chronic low back pain, alone generated more than $16 billion in hospital charges (excluding physician's fees) in 2004 [11]. SCS accounts for about 70 percent of all neuromodulation treatments [12], and approximately 35,000 stimulator systems were sold worldwide in 2008 [13]. The average cost of implanting a spinal cord stimulator is approximately $30,000, with an annual maintenance cost of $10,000 if the patient presents with post-operative complications [13], which are quite frequent [14], whereas the total cost of lumbar posterolateral fusion surgery ranges from $19,989 to $33,804 [15]. The high revenues generated from spine surgery and spinal cord stimulation can create exploitative situations that may be capitalized by private companies and for-profit healthcare entities. Indeed, private practice spine surgeons are more likely to recommend spinal fusion surgery for chronic low back pain than academic spine surgeons [16].

The spinal implant industry also financially benefits individual physicians, who often receive significant amounts of money from companies through consultation royalties or other means. For instance, the US Senate Finance Committee staff reported that Medtronic paid a total of approximately $210 million to physician authors of Medtronic-sponsored Infuse studies from 1996 to 2010 for consulting, royalty, and other miscellaneous arrangements [17]. One physician involved received $34 million from Medtronic over the course of 1996 to 2010, during which he received almost $5 million in one year alone [17]. These monetary payments may therefore influence the medical judgement of the physicians involved, which may account for the widespread implementation of SCS after spine surgeries, even though these procedures may not necessarily benefit all patients while subjecting them to health risks and high financial costs. Indeed, Advanced Neuromodulation Systems (an SCS device company) paid $2.95 million to the US Office of Inspector General in a civil monetary penalties settlement following allegations that the company paid physicians $5,000 for every five new patients tested with their product as part of a marketing effort to boost sales [18].

THE GATEWAY: SPINE SURGERY FOR PAIN

Spine surgery is often recommended as the next treatment option when conservative non-surgical care such as medications or physical therapy has failed [4]. The aim of spine surgery is to alleviate pain by helping to correct the structural abnormalities or nervous tissue compression caused by degenerative processes in the spine that are thought to underlie chronic low back pain. A typical candidate for spinal surgery presents with lumbar spinal stenosis, or narrowing of the spinal canal that is addressed by decompression surgery via laminectomy [19]. Surgical care for chronic low back pain has recently become more complex, as decompression surgery is now being increasingly supplemented with spinal fusion to help stabilize the spine by fusing two or more vertebral levels together [20].

There remains much controversy in the field regarding the clinical benefits of spinal fusion surgery for chronic low back pain. Several studies in the 1980s and 1990s supported the widespread use of spinal fusion surgery for relieving chronic pain, suggesting that combined decompression and fusion procedures attenuated pain better than decompression alone [21-23]. However, these studies have been questioned due to their limited sample size. A recent clinical study of approximately 250 patients showed that supplementing decompression surgery with spinal fusion resulted in higher financial costs to patients but not better clinical outcomes compared to decompression surgery alone [24].

In addition to financial burdens, spine surgeries can also pose life-threatening health risks for patients, including death and paralysis [25,26]. A study of 32,152

Medicare recipients who underwent spine surgery indicated a post-surgical mortality rate of 0.4 percent, and 3.1 percent of patients suffered from major medical complications, including cardiopulmonary resuscitation, cardiorespiratory arrest, and respiratory failures [26]. Importantly, higher rates of health complications and mortality were observed in patients who underwent spinal fusion procedures compared to decompressive surgery alone [26]. Beyond serious medical complications and mortality risks, spine surgeries often fail to relieve pain, leading to FBBS in which chronic pain persists or new pain symptoms appear after spine surgeries. The incidence of FBBS following spinal surgery has been reported to be 20 percent [27,28]. Individuals suffering from chronic pain due to FBBS are reported to experience greater levels of pain and lower quality of life compared to patients suffering from other chronic pain conditions [29]. Considering such risks, concerns have been raised regarding whether spinal surgery is necessary at all. Results from randomized controlled clinical trials suggest that spinal fusion is no more effective than conservative non-surgical care with regards to pain relief [30-34]. Moreover, spine degeneration is present in high proportions of asymptomatic individuals, suggesting that spine structural abnormalities may not need to be corrected by surgery [35]. Although it may be possible that there are patients who may benefit from spine surgery**,** validated patient selection criteria has been difficult to achieve [36], and current preoperative prognostic tests have limited usefulness [37].

For individuals with FBBS, SCS has emerged as a popular treatment avenue. The initial spine surgeries resulting in FBBS can therefore be thought of as the gateway to the implantation of spinal cord stimulators, a highly profitable business avenue for companies.

SPINAL CORD STIMULATION: IMPLANTS INVOLVED AND GENERAL OUTCOMES

The SCS system consists of two components: a pulse generator and electrodes that deliver the electrical currents. The pulse generator is implanted subcutaneously in the flank or buttocks of the patients. The electrodes are connected to the pulse generator and are implanted into the epidural space. Before the pulse generator is implanted for long-term treatment, patients typically undergo a trial period with an external power source to determine whether stimulation will be clinically beneficial and to optimize the placement of electrodes. The stimulation devices deliver electrical impulses that are thought to alleviate pain by altering or suppressing the perception of ascending pain signals from the spinal cord to the brain [38,39]. Newer paradigms of SCS have also emerged, including high-frequency stimulation, burst stimulation, and dorsal root ganglion (DRG) stimulation. The potential mechanisms of such newer stimulation paradigms are discussed elsewhere [40,41]. Complications are common following implantation of the stimulation system, including lead migration (12 percent of cases), pain at the site of implantation (9 percent of cases), and wound-related complications (5 percent of cases) that can require further surgical interventions [14].

Clinical investigations to assess the efficacy of SCS have produced mixed results. Numerous observational studies claim that SCS alleviates pain in 50 to 88 percent of patients [42-46], while a study of workers' compensation recipients suggested that there was no difference in pain relief between those who received SCS therapy and those who did not [47]. Other works have also suggested that SCS and physical therapy both provide similar benefits, yet, most subjects would still undergo the same implant for the same result [48]. To date, there have been eight published randomized controlled clinical trials of SCS for FBBS (summarized by Table 1) [49-59]. Some of these randomized controlled trials showed that neurostimulation was more effective at pain relief compared to surgical re-operation [49,50] or conventional medical therapy [51,52]. Others have also suggested that high-frequency stimulation and burst stimulation may potentially provide more pain relief than traditional SCS [55-58]. However, these results have also been contrasted by a placebo-controlled trial showing that high-frequency stimulation produced similar results to placebo stimulation [54]. With regards to cost-effectiveness, some reports have concluded SCS to be safe and cost-effective for FBBS [40,60,61], while others have disagreed and suggested that more randomized controlled clinical trials and more rigorous prospective cost-utility analyses are still needed in order to fully understand the utility of neurostimulation [62-64]. While these mixed results do not necessarily indicate that SCS should not be utilized, further research is still needed to optimize the stimulation paradigms and to clarify when this technology should be used for patients.

Despite the number of trials that support the use of SCS for FBBS, there are a number of caveats in these studies that are important to consider. First, it may be possible that the real-world experience of stimulation therapy is different from the experience of clinical trials, as is true with medical therapies studied in large populations after regulatory approval. It is important to note that efficacy studies often rely on patient-based outcome measures to quantify pain relief, such as the pain visual analog scale (VAS) and patient satisfaction. Such measures are subjective, and patients may report high satisfaction via placebo effects, clinician influences, or secondary gain reasons. The long-term effects and/or benefits of SCS for back pain are also unclear. Most trials had relatively short follow-ups of six to 12 months or even less, and only three

Table 1. Randomized Controlled Trials of Spinal Cord Stimulation for Failed Back Surgery Syndrome.

Publication	Sample size	Blinded?	Follow-up	Funding	Conflicts of interest	Conclusions
North *et al*., 1995, 2005	45 patients	No	24 months	Medtronic	First author sold assets of a company to Medtronic, and university received a share of proceeds	Stimulation more effective at pain relief compared to reoperation
Kumar *et al*., 2007, 2008	100 patients	No	24 months	Medtronic	Data collected & analyzed by sponsor	Stimulation more effective at pain relief compared to medications alone
Schultz *et al*., 2012	79 patients	No	12 weeks total (weekly contact)	Medtronic	Sponsor had full control of data and performed analysis	Automatic position-adaptive stimulation more effective at pain relief than manual programming adjustment alone
Perruchoud *et al*., 2013	33 patients	Double-Blinded	2 weeks	Medtronic	Sponsor provided technical support, but did not participate in study design or data collection and analysis	High-frequency stimulation produced similar results to sham condition
Schu *et al*., 2014	20 patients	Double-Blinded	1 week	Not reported	Several authors are consultants to Spinal Modulation, Inc. An employee of Spinal Modulation, Inc., participated in data analysis and manuscript preparation	Burst stimulation more effective at pain relief compared to 500-Hz tonic stimulation and placebo stimulation
Kapural *et al*., 2015, 2016	198 patients	No	24 months	Nevro Corp	Several authors received grants and personal fees from Boston Scientific, St. Jude Medical, and Nevro Corp.	10-kHz high-frequency stimulation more effective at pain relief compared to traditional stimulation
Deer *et al*., 2018	88 patients	No	12 months	Abbott	Several authors serve as paid consultants to Abbott; One co-author is an Abbott employee who also participated in design of clinical trial, data collection, and manuscript preparation	Burst stimulation provides better pain relief than traditional stimulation
Thomson *et al*., 2018	20 patients	Double-Blinded	3 months	Boston Scientific	First and second authors are consultants to Boston Scientific; An employee of Boston Scientific participated in manuscript writing	1 to 10 kHz stimulation provided pain relief

trials have had follow-ups of up to 24 months (Table 1). Indeed, one study has suggested that while pain relief can be observed after six months, these benefits from SCS dissipated after 12 months [48]. Thus, it remains unclear whether SCS provides meaningful long-term benefits to all patients. Overall, more research is needed to definitively understand the utility of SCS treatment and clarify which population of patients will benefit most from the procedure. Indeed, more clinical trials of SCS for FBBS are underway, and the results are pending publication [65]. New stimulation paradigms, such as burst and high-frequency stimulation, may also be promising alternatives, however, these techniques are even less understood than traditional dorsal column stimulation and have had shorter market times with poorer available data supporting their use [66].

An additional major concern with the SCS efficacy studies is that they tend to be industry funded with numerous financial conflicts of interest. For instance, seven out of the total eight randomized controlled trials for SCS in chronic low back pain reported sponsorship by manufacturers (Table 1). Furthermore, all eight of the trials reported conflicts of interest, ranging from financial relationships between authors of the study and commercial manufacturers to the manufacturer having full control of the data and performing analysis (Table 1). Such financial relationships between the studies and the device manufacturers raise concerns about potential conflicts of interests and research biases. In the section below, we discuss the influence of private industry on healthcare research, and how such influence may impact our interpretation of efficacy studies funded by profit-driven companies that have financial stakes in the clinical trials.

INDUSTRY INFLUENCE ON NEUROMODULATION FOR CHRONIC PAIN

Recent trends indicate that clinical trials independently funded by the NIH are declining while those funded by industry are rising. Between 2006 and 2014, the number of industry-funded trials have increased by 43 percent, while the number of NIH-funded trials have decreased by 24 percent [67]. The growth of industry-financed clinical trials raises concerns regarding conflicts of interest, as the objectivity in research can be compromised by commercial interests. Indeed, a survey of 3,247 scientists showed that 15.5 percent admitted to changing the design, methodology or results of a study in response to pressure from a funding source [68]. Although the authors of the survey never asked respondents to distinguish between industry funding or independent funding, the number of industry-funded trials greatly outnumbered the number of NIH-funded trials (35.6 percent vs 5.7 percent of all trials registered in 2014) [67]. It is therefore likely that much of the pressure to alter the design or emphasis of the research studies was due to industry funding sources, especially with regards to studies that may impact financial interests of companies.

Financial conflicts of interest are widespread in the spine surgery field, raising concerns regarding the influence of industry on the objectivity of clinical spine research [69]. An analysis of the Centers for Medicare and Medical Services (CMS) Database revealed that 92 percent of spine surgeons in the US have at least one financial relationship with industry, and surgeons receiving at least $1 million from industry accounted for approximately seven percent of the database [70]. Furthermore, academic practice setting was associated with industry payments [70]. A review of papers on interspinous devices and cervical disc prostheses from 2008 to 2010 showed that authors with a disclosed financial relationships were less likely to publish studies with neutral or negative conclusions [71]. Another study showed an association between source of funding and outcome of spinal research, in which industry funded research tended to provide Level IV evidence (the levels range from I-V, in which I is the highest evidence-randomized control trial and V is the lowest-expert opinion) and report favorable outcomes [72,73]. These studies demonstrate that industry funding creates serious conflicts of interest that may bias authors. These systematic biases threaten research objectivity by potentially causing authors to exaggerate favorable outcomes, underreport unfavorable outcomes, and employ flawed study designs [74]. Indeed, external reviews of data from Medtronic-sponsored Infuse studies revealed that the potential benefits of the bone graft treatment were exaggerated while adverse outcomes were underreported [75,76].

In addition to funding spine and SCS related research, the industry also provides significant financial support for continuing medical education (CME). In 2015, the industry provided $693 million of funding support for CME, according to the Accreditation Council for Continuing Medical Education [77]. Although a survey showed that the general population does not believe that the quality of their care would be diminished due to industrial funding of CME [78], a study of German CME courses demonstrated conflict of interest issues that resulted in biased educational curriculum that financially favored the funding source [79].

As a whole, private companies do have important contributions to the healthcare system. Collaborations between physicians and private industry are necessary for delivering health products into the market for patients, and an absolute fear of the private pharmaceutical and health devices industry can hamper medical innovation that benefits healthcare [80]. However, it is also important to consider that direct and indirect industry influ-

ences may threaten the neutrality of spine and chronic pain research, thereby leading to biased research studies that financially benefit the industry at the expenses of patients. The reported efficacy of SCS for chronic pain should therefore be carefully interpreted in light of biases due to conflicts of interest introduced by industry sponsorship. While we acknowledge the vital roles that private companies have played in medical innovation, we also caution the possibility that industry influence on SCS research may have led to biased efficacy studies that are used as justifications for the overuse of technology after spine surgeries for chronic pain.

CONCLUSIONS

Chronic low back pain is a serious medical condition. Spine surgeries and SCS continue to grow as widespread treatment options for individuals who still present with pain symptoms following conservative medical care. However, spine surgery often leads to FBBS, which is then used as the justification for the implantation of spinal cord stimulator devices. Spine surgery has become a gateway to neurostimulation for chronic pain issues, which may benefit commercial interests over the interests of patients who are subjected to health and financial burdens. Given the possibility of biased efficacy studies due to physician-industry conflict of interests, it still remains unclear whether spine surgeries and/or SCS are beneficial to all patients. We therefore interpret current trends to be a possible overuse of spine surgeries and technology, and future research needs to further clarify which patient populations will benefit most from surgeries and neurostimulation as well as explore alternative non-surgical care that may provide similar or more benefits with less financial and health burdens.

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