Complications of epidural spinal stimulation: lessons from the past and alternatives for the future

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Running title: **Complications of epidural spinal stimulation**

Giuliano Taccola[1, 2]*, Ph.D., Sean Barber[2], M.D., Phillip J. Horner[2], Ph.D., Humberto A. Cerrel Bazo[3, 4], M.D., and Dimitry Sayenko[2]*, M.D., Ph.D.

[1] Neuroscience Department, International School for Advanced Studies (SISSA), Bonomea 265, Trieste, Italy

[2] Department of Neurosurgery, Center for Neuroregeneration, Houston Methodist Research Institute, Houston, Texas, USA

[3] Ospedale Riabilitativo di Alta Specializzazione (ORAS)-ULSS 2 TV, Motta di Livenza, TV Italy

[4] Department of Neuroscience - Physical Medicine and Rehabilitation, University of Padova, Medical School, Italy

* Corresponding Authors: Giuliano Taccola, PhD
E-mail: taccola@sissa.it

Dimitry Sayenko, MD, PhD
E-mail: dgsayenko@houstonmethodist.org

Abstract

Study Design: Systematic Review

Objectives: Over the past decade, an increasing number of studies have demonstrated that epidural spinal cord stimulation (SCS) can successfully assist with neurorehabilitation following spinal cord injury (SCI). This approach is quickly garnering the attention of clinicians. Therefore, the potential benefits of individuals undergoing epidural SCS therapy to regain sensorimotor and autonomic control, must be considered along with the lessons learned from other studies on the risks associated with implantable systems.

Methods: Systematic analysis of literature, as well as pre-clinical and clinical reports.

Results: The use of SCS for neuropathic pain management has revealed that epidural electrodes can lose their therapeutic effects over time and lead to complications, such as electrode migration, infection, foreign body reactions, and even SCI. Several authors have also described the formation of a mass composed of glia, collagen, and fibrosis around epidural electrodes. Clinically, this mass can cause myelopathy and spinal compression, and it is only treatable by surgically removing both the electrode and scar tissue.

Conclusions: In order to reduce the risk of encapsulation, many innovative efforts focus on technological improvements of electrode biocompatibility; however, they require time and resources to develop and confirm safety and efficiency. Alternatively, some studies have demonstrated similar outcomes of non-invasive, transcutaneous SCS following SCI to those seen with epidural SCS, without the complications associated with implanted electrodes. Thus, transcutaneous SCS can be proposed as a promising candidate for a safer and more accessible SCS modality for some individuals with SCI.

Abbreviations: spinal cord stimulation (SCS), spinal cord injury (SCI)

Keywords: neuromodulation, spinal cord, epidural interface, complications, transcutaneous stimulation

Introduction

Recently, spinal stimulation-based neuromodulation has progressed from an "inhibitory" intervention for pain management [1] to become an important modality for reactivating latent functions of the underlying processing networks [2]. Between 2008-2017, the United States Food and Drug Administration (U.S. FDA) reported over 600,000 individuals were implanted with spinal cord stimulators (www.apnews.com) [3]. Thirteen percent (78,172) of said individuals suffered injuries caused by spinal cord stimulators. These alarming statistics demonstrate why spinal cord stimulators are ranked as the third-highest leading cause of injury among all used medical devices, right after metal hip protheses and insulin pumps. One relevant study was performed recently by Sivanesan et al. [4], where the authors queried the Manufacturer and User Facility Device Experience (MAUDE) database for all entries named 'Dorsal root ganglion stimulator for pain relief' between May 1, 2016 and December 31, 2017, verified by the US FDA. There were 979 cases of implantation identified, almost half of which (47%), were categorized as device-related complications, a quarter (28%) as procedural complications, with the remainder as individual complaints (12%), serious adverse events (2.4%), and 'other' complications (4.6%). The authors warn that although the stimulation device has been publicized as a breakthrough in neuromodulation technologies, one must proceed with caution and reevaluate effectiveness as information becomes available. These outcomes may serve as a representation for a single year and may present a perspective of the rate of complication and adverse events related to implanted spinal cord stimulators. The implantation itself, especially if it involves laminectomy, can lead to a broad variety of complications associated with invasive procedures, including infection or hematoma, and, depending on the type of the electrodes used for spinal cord stimulation (SCS), can be associated with electrode migration. Still, a health economic assessment of application of

spinal stimulation as chronic neuropathic pain management performed in the United Kingdom's National Institute of Health and Clinical Excellence, has shown that the therapy is cost-effective [5]. The Incremental Cost Effectiveness Ratio calculated over a 15-year horizon demonstrated high economic benefits mostly referred to the improved health and productivity of the subjects, that have been quantified as 35 times more significant than the cost of the therapy itself, even including the incidence of complications. At the same time, similar analysis on the benefit to cost ratio from the studies recovering motor control using SCS is not available to date, but it would likely show a smaller ratio given that the recovery of independent motor function is rather small, requires intensive therapy, and is limited so far by a person's need for continuous assistance during ambulation.

Spinal stimulation has been shown to have potential for a vast variety of applications in motor and autonomic function recovery, given its high capacity to modulate neural activity in neurorehabilitation of individuals with spinal cord injury (SCI) [2, 6]. The latest available data indicate that stimulation of the spinal cord with the use of task-oriented rehabilitation can be applied to modulate the adaptive activity coming from the spinal cord segments located below the lesion, in order to enhance excitability from spinal networks and regain some voluntary control of various motor tasks including standing [7, 8], stepping [9-11], hand grasping [12], respiration [13], and bladder voiding [14, 15]. From some of these studies, it is difficult to say with certainty whether the intensive training paradigm, spinal stimulation parameter adjustments, or (the most likely case) both variables, play a key role in achieving minimized assistance during standing or stepping in the presence of stimulation [16]. Indeed, previous work has shown that even without SCS, body-weight load during activity-based training (see 'rules of spinal locomotion' [17]), creates the flow of proprioceptive signals which in turn can facilitate spinal locomotor programs

and – after weeks of training – enable individuals with severe but incomplete SCI to carry their own body weight over ground [17-21]. As such, it would be incorrect to state that epidural spinal stimulation applied by itself allows regaining of mobility and independence. Most of the papers in this field should be considered as observations toward better understanding to what extent the spinal networks below the injury, which were previously thought to be non-functional after SCI, can be engaged by spinal stimulation to produce and modulate motor activities. The fact that regaining voluntary motor control can occur within just the first few sessions of epidural spinal stimulation in practically all participants with clinically diagnosed motor complete paralysis (most likely discomplete [8, 22-25]), indicates that spared neural connections spanning the site of SCI, are highly plastic and prepared for functioning in the presence of spinal stimulation and within appropriate somatosensory environment, months or even years following SCI. The fact that when the stimulator was turned OFF, most of the participants were not able to perform these movements, indicates that epidural spinal stimulation, descending signals through the injury, and extrinsic sensory input can synergize within spinal networks to generate voluntary motor activities. The use of this technology will undoubtedly grow consistently in the coming years, and it is likely that there will also be a concomitant increase in the number of individuals experiencing tolerance phenomena and/or requiring invasive spinal surgeries to overcome adverse side effects. Moreover, albeit SCS is considered a fully reversible treatment, removal of epidural electrodes, and especially the paddle electrodes, is not uncommon (5 – 35%). However, it is a quite challenging surgical procedure, as electrodes are often encapsulated by secondary bony overgrowth and epidural fibrous capsule [26, 27]. For instance, explantation of paddle electrodes is associated with potential risks and postoperative complications which occurred in 12% of surgeries, ranging from minor issues, such as infection (9%), to more serious adverse events, as cerebrospinal fluid leak or

epidural bleeding, which causes hematoma and accidental compression of the spinal cord[19]. Research into the underlying causes and risk factors for adverse effects of invasive SCS is therefore paramount to maintain high levels of therapeutic efficiency, decrease complication rates, reduce the need for costly surgeries for electrode revision or scar removal, and improve clinical and functional outcomes. The current perspective paper focuses on the implanted electrode encapsulation and its negative impact on effective and sustainable spinal cord stimulation (SCS).

Complications of implanted electrodes

Several large studies [28-30, also see Supplementary Appendix (SA) SA31-34] have documented relatively high complication rates (20 – 75%) following SCS, including hardware failure, infection, and even more severe neurological consequences, such as SCI. Side effects may occur both intraoperatively and in the early or late postoperative period [SA32], and require invasive treatments in approximately half of the cases [26].

Among hardware-related problems, lead migration was previously reported as one of the most common risks of SCS, with a variable incidence spanning 13 to 22%, with a higher prevalence for implants in the cervical spine, where the degree of motion of vertebrae is greater [SA35, 36]. Lead migration often requires a new surgical procedure for repositioning or replacing the electrode. However, two recent retrospective studies, analyzing SCS systems implanted from 2008 to 2011, found that lead migration requiring repositioning of the systems occurred in only in 1.4 to 2.1 % of over a hundred of analyzed cases, a much lower incidence rate than previously reported, possibly accounting for hardware and technique improvement, including revised published guidelines by SCS manufacturers on proper fascial anchoring and the use of strain-relief loops [SA37]. Noteworthy, older studies have compared the migration rates of percutaneous leads

and paddle array electrodes [SA38, 39] and reported markedly lower migration rates with paddle electrodes. This is one of the most commonly cited advantages for choosing the paddle-type systems over percutaneous leads. However, because the cited above rate of clinically significant migration is similar to the published rates for paddle electrodes' migration, this argument requires revision. A head-to-head prospective trial comparing revision rates for lead migration between percutaneous leads and paddle electrodes is warranted.

Additional complications originate from an acute biological response to the implant. Infection is one of the major complications with incidences of 5% and requiring antibiotic treatment and even device removal and reinstallation after healing from sepsis [26, SA32-33]. This is a higher value compared to other implantable electronic devices, such as cardiac pacemakers, which have an incidence of infection of about 0.5 to 2.2% [SA40]. For SCS, superficial or subcutaneous infections at the incision site are more common than deep tissue infections with abscesses over the spine. Although meningitis rarely occurred, an intradural abscess resulting in paralysis has been reported [SA41]. Pain in the region around the stimulator has also been registered in 5 to 10% [26, SA32-33]. During surgical or blind percutaneous insertion of electrodes, accidental dural puncture, epidural hematoma, as well as blunt trauma to the cord, have been documented, causing the onset of paraplegia in the 30 days following SCS implantation for 2% of individuals analyzed [42].

Tolerance to SCS

Even in the absence of the above mentioned complications, an estimated 10 to 29% of subjects implanted with epidural electrodes developed tolerance to SCS, defined as the loss of the therapeutic effect over time, even in the presence of fully-functioning stimulating systems [SA34,

43, 44]. Although an increase in pulse amplitude might circumvent the problem for a while [SA45-47], the tolerance phenomenon still often mitigates SCS efficacy if therapy is continued. This phenomenon can develop as early as a few months after implantation and as late as 10 to 15 years following implantation [29, SA48]. Although, psychological affective factors might also contribute to a tolerance to the analgesic effects of SCS [SA46], there is some evidence that suggests the development of tolerance over time results from dropped charges related to the deposit of high impedance biological material progressively encapsulating the electrode after implantation [SA46, 49]. The extent of fibrous tissue growth around the electrode has been positively correlated to impedance increases in studies with cochlear implants [SA50-51]. It is doubtful that tolerance reflects only structural and conductive changes on the surface of the implanted material and can be solved by merely substituting the system. Tolerance originates from more profound changes at the interface between the contact electrode and the underlying tissues. An immune-mediated foreign body response is determined by the implant's materials and causes both the aggregation of mononuclear macrophages and the encapsulation of the device in a collagenous envelope [SA52]. The picture can be further worsened by the local toxicity of metal particles dissolved by the long-term corrosion of electrodes [SA53]. All these events can activate fibroblasts, with a consequent fibrotic growth around the electrode that causes a shallow mechanical depression of the spinal cord regions under the array [SA52]. Moreover, perturbations on the surface of the cord result both in the localized activation of glial cells, and in epidural fibrosis, which can be associated with dural thickening or even superficial scarring, that eventually alter the charge transfer to the surrounding neural structures [SA54].

Epidural electrode encapsulation has been documented in numerous reports (Table 1), and can lead not only to tolerance, but occasionally also to severe spinal cord compression and neurological deficits.

Histological Findings in Fibrous Encapsulationsu

Despite the rarity of negative published results in the field of SCS, there have been at least 20 reported cases of severe spinal compression related to fibrous lead encapsulation developing 3 to 17 years after electrode implantation (Table 1, mean onset = 7 ± 5 years) [SA43, 55, 56]. Oftentimes, these cases began as tolerance, eventually resulting in the development of neurological deficits, such as myelopathy [SA43, 57], worsened spasticity [SA45], and increased paralysis [SA43, 45, 56, 58]. In all 20 reported cases, delicate surgical procedures on the spinal cord to remove the whole electrode and the scar tissue that surrounded it inside the epidural space were necessary, sometimes in response to tolerance [SA43, 45, 47, 55-57, 59-64]. Also, in some reported cases, analysis of the extracted scar tissue revealed the presence of excessive fibrosis around the electrode itself – both for paddle electrodes implanted via laminectomy and those implanted percutaneously into the epidural space [29, SA43, 48]. Still, the vast majority of published clinical reports about failures and complications of SCS unfortunately do not comment on end-term tissue and array conditions. Rather, a more detailed exploration of electrode-associated fibrous tissue comes primarily from the few animal studies that have explored this issue. Notably, histological examination of cortical epidural implants has revealed an overgrowth of connective tissue [SA54, 65] and an aggregation of cortical microglia in a resting state morphology in the first week after implantation [SA52] that is followed in the subsequent week by the accumulation of a layer of astrocytes [SA66]. Further studies have documented the presence of granulomatous tissue and a

nonspecific chronic inflammatory reaction [SA57] characterized by multinucleate macrophages (giant cells) aggregating in response to the foreign body and engulfing the implant [SA61]. Underlying dural thickening and fibrous implant encapsulation has also been seen in experimental animal models within the first month after implantation of cortical epidural arrays [SA54, 65]. This fibrous envelope consists of both fibroblasts and Collagen I, with the "collagenous" tissue located in the distal part of the implanted array mimicking healthy dura mater while the more proximal region contains "cellular" tissue with increased inflammatory cell activity [SA52]. The thickness and density of cortical neural tissue, however, does not seem to change appreciably, even with long-term array implantation [SA52]. There has been a number of documented cases of fibrous masses developing in humans in association with SCS, often requiring electrode explantation or revision due to some combination of tolerance and/or neurological deficits (Table 1). Moreover, many of said cases have reported histological findings similar to those seen in animals, including dense fibroconnective tissue, variable non-specific inflammatory infiltrates, multinucleated giant cells, noncaseating granulomas indicative of a foreign body reaction [SA45, 55-58, 61, 67]. Furthermore, in a recent clinical report [SA68], histologic examination of the fibrous tissue around the electrode used for SCS revealed granulomatous inflammation and phagocytic reaction of neutrophils and macrophages due to a metallic irritation of the dura mater. Putatively, metallosis due to the deposition of metal debris on the dura mater was secondary to the corrosion of the protective silicon and urethane coating around the lead of the SCS paddle electrode. Uncovering of the silicon and urethane coating was likely caused by the micromotion and friction between the electrode and the dura mater.

Although, an invasive histological examination of paddles is not always recommended in clinics, in case of electrode failure one should always carefully consider lead encapsulation and epidural fibrotic mass formation, especially if associated to mild neurological symptoms.

Approaches for avoiding fibrous encapsulation

The relevance of epidural electrodes' encapsulation in current practice is supported by the many ongoing research efforts underway to reduce encapsulation. One common theory is that the exuberant fibroblastic response may be dependent on the materials used for electrode fabrication [SA45]. Thus, several studies have improved the integration of implanted devices in the central nervous system by modifying the electrode materials in an attempt to minimize the foreign body response. These recent approaches include shape alteration of the array substrate [SA54, 65, 69], increased array flexibility [SA70-72], the release of anti-inflammatory drugs through the array itself, either from the substrate or from the electrodes [SA73, 74], and the application of anti-fouling or biomimetic surface treatments [SA75, 76], such as different materials and techniques of coating and lamination [SA66, 77]. Albeit promising, these approaches require a considerable amount of time and resources both for preclinical development and also for safety and efficiency testing prior to use [SA77], ultimately delaying their availability in the clinic. Interestingly, Reynolds and Shetter [SA45] theorized that the fibrotic and inflammatory response associated with implanted electrodes might be related to the electrical stimulation through the electrode; but, evidence in support of this is lacking. While intraoperative stimulation is often performed to guide electrode placement, both in research and in clinics, continuous stimulation is seldom delivered right after implantation. Rather, stimulation begins in a delayed fashion, after an initial week of post-surgical rest [8, SA78-79]. Interestingly, research suggests that development of fibrosis and

glia around the electrode begins during the initial week of post-surgical rest following implantation [SA66]. These results imply that electrode-associated fibrosis occurs independent of stimulation. However, it is still unclear whether low intensity stimulation in the first week following implantation may limit the development of electrode-associated fibrosis. Stimulation amplitudes commonly used to neuromodulate physiological state of the spinal cord [SA79, 80], which are based on previous preclinical studies [SA78], are much greater in magnitude than the amplitudes reported in the literature as being endogenous to the nervous system. For example, in vertebrate embryos, glia are sensitive to electrical fields of physiological strength (50-500mV/mm) [SA81]. These electrical fields play a pivotal role not only in retracting and aligning astrocytes processes, thereby leading their orientation perpendicular to the voltage gradient [SA81], but also in promoting and directing neurite growth in the developing central nervous system [SA82-83] where endogenous electric fields are generated by a polarized voltage gradient [SA84]. Based on this evidence, we believe that future research could exploit this range of low intensities to create a physiological electrical stimulation to be delivered during the initial days following implantation that would help to not only orient glia and neurite regrowth, but also repel fibrosis from the electrode without damaging the recovering spinal cord. At the same time, it is difficult to see how this could be done without substantial increases in knowledge based on animal experiments. Further, a valuable perspective in the field should be the design of neural interfaces in which the delivery of distinct patterns of subthreshold electrical stimulation, that is stimulation at the intensity just below motor threshold [SA85], guides the proliferation of glial cells along a re-absorbable array frame eventually leaving only working metal electrodes and connections stably integrated in the epidural connective tissue. These implantable Glio-Electrode Arrays should be considered as a more biocompatible technology for future preclinical research trials.

In addition to material interface engineering solutions and stimulation protocols to prevent gliosis and encapsulation, mechanical design may be an important option for advancing the success of implanted electrodes. Theorized designs based on matching the elastic modulus of tissue surrounding the implant or micro-scaling of electrodes is a growing trend for the prevention of scar formation and increasing the working cycle of electrodes [SA86-87]. Development of flexible, microscale electrode arrays that can be inserted as part of a two-component, rigid and flexible, delivery system show promise for application in small and large animals [SA88-91]. Optogenetic based flexible optical fibers, especially utilizing tissue penetrating, long-wavelength light, are also being explored to circumvent the problem of decaying electrical current delivery [SA92-94]. Few of these approaches have been either scaled or tested in large animal models. Miniaturization is likely to also create design challenges in terms of the long-term durability needed to work over extended periods. Further, implantable, flexible arrays require surgical placement and thereby will inherently lack flexibility for re-positioning or covering multiple sites along a neural pathway. Nevertheless, the future may hold design solutions that bring together material innovations to solve scaling, durability and flexibility in the future.

Potentially interesting new approaches come from the technology used in cochlear stimulating implants for treating hearing loss. Here, potent anti-inflammatory glucocorticoids, such as triamcinolone or dexamethasone, able to reduce fibrous tissue growth around the electrode, are locally applied as a single dose [SA95] or through micro-osmotic pump delivery [SA96]. In a more recent study, the silicone frame of the electrode array has been used as a carrier to release the previously incorporated drug. The continuous release of dexamethasone over an observational period of 91 days, largely attenuated the electrode impedance, yet exploiting the performance of the device [SA50]. In non-human primates, a non-toxic crystalline formulation for the controlled

delivery of the antifibrotic agent GW2580, prevented cellular infiltration and collagen deposition on implanted biocompatible materials for more than a year. Moreover, this crystalline formulated drug can be mixed into polydimethylsiloxane or loaded for surface coatings of other materials, including plastic composites and metal alloys, becoming one of the best candidates for improving the long-term performance of multicomponent stimulating devices [SA97].

Transcutaneous SCS

Recently, several research groups have demonstrated the feasibility of non-invasive, transcutaneous SCS to neuromodulate excitability at multiple spinal levels, ranging from the cervical to the coccygeal segments, and facilitating both motor [SA98-105] and autonomic [SA106-107] functions. These findings provide some evidence that human spinal networks feature the critical level of motor task-specific automaticity, which can be exploited using both invasive and non-invasive spinal neurostimulation. Further, they can effectively function even in the lack of supraspinal excitatory drive. Electrophysiological [SA108-110] and computational [SA111-113] studies demonstrated that the structures, stimulated electrically by epidural or transcutaneous SCS, are primarily afferent fibers of the posterior roots. Additionally, many other neural structures can be directly impacted by the electrical field, including axons, synapses, neuronal cell bodies, and glial cells [2]. As such, both invasive and non-invasive spinal neuromodulation may engage spinal interneural networks via synaptic projections, as well as antidromic activation of ascending fibers in the dorsal columns [SA105, 114-116]. Currently, the dominating hypothesis is that the mechanisms through which invasive and non-invasive SCS can improve motor function after paralysis include activation of residual, longitudinal fibers across and below the level of injury, which were functionally silenced during SCI, and emerging responsiveness of spinal networks to

voluntary commands and sensory inputs [2, 6]. Most recently, Hofstoetter et al. (2018) [SA117] directly compared spinally evoked motor potentials using transcutaneous and epidural electrodes and confirmed the activation of common neural input structures by both techniques. However, a direct comparison of the *functional* neuromodulatory effects using each approach has yet to be performed. As such, it is important to establish the relative effectiveness of transcutaneous SCS versus the invasive epidural SCS in restoration of sensorimotor function.

At the same time, individual sensorimotor responses to spinal neuromodulation, whether it be transcutaneous or epidural, vary significantly across participants, making it difficult to determine which research subject will benefit and which stimulation paradigm will be the most effective. To the best of our knowledge, every study utilizing epidural SCS for motor recovery after motor complete SCI has been successful so far in regaining muscle-specific control below the lesion, and executing voluntary tasks with selectivity of appropriate motor pools, in the presence of epidural stimulation [9-11, 24]. Although transcutaneous SCS can augment and enable stepping movements [SA98-102, 118] and postural control during sitting [SA104] and standing [SA105], the fine and selective voluntary activation of specific agonists (with minimum co-contraction of antagonists) below spinal lesion after clinically diagnosed motor "complete" (but, in fact, discomplete [9, 22]) SCI remains a prerogative of epidural SCS alone. Such difference in engagement of specific muscles can be not at least because of the difference in stimulating electrodes' size and focal stimulation of the particular motor pool in the case of epidural SCS, while the current overload over the adjacent motor pools in the case of transcutaneous SCS.

The adverse events during or following transcutaneous SCS are currently unknown, except one known report wherein an individual with SCI began experiencing spasms and pain in his lower body following the repeated sessions of transcutaneous SCS [SA119]. However, it is unclear if

said complications were directly related to the study, especially given the reported findings that transcutaneous SCS can, in fact, decrease spasticity after SCI [SA120, 121]. Potential complications associated with transcutaneous SCS include the variety of events associated with any non-invasive electrical stimulation, including discomfort or pain due to activation of nociceptors in the skin beneath the stimulating electrodes, skin irritation, or breakage due to current concentration under the electrodes, and muscle contractions caused by the stimulation. Said events, in turn, may provoke autonomic dysreflexia in participants with SCI. Thus, although this approach is non-invasive, it may be premature to translate into home-based training programs without supervision of clinicians. Both researchers and clinicians must exercise standard precautions, including blood pressure monitoring and adjustment of the stimulation parameters to minimize the discomfort using SCS. Nevertheless, it is our opinion that the advantages of transcutaneous SCS approach should be recognized in its non-invasiveness, cost-effectiveness, flexibility in delivery, including multi-cite and multi-frequency stimulation, and further, its compatibility with other therapeutic and research techniques. We suggest that transcutaneous SCS can be considered as a tool for mechanistic research to delineate the underlying mechanisms and effects of either SCS. For instance, transcutaneous SCS can be utilized to guide research subject selection as well as training and provide a critical readout prior to invasive SCS, and perhaps even to drive the evolution of combinatorial invasive and non-invasive therapies to maximize restorative plasticity.

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Conflicts of interest statement

No conflicts of interest, financial or personal relationship with other people or organizations that could inappropriately influence their work, are declared by the authors.

Authors' contributions

GT conceptualized the review. GT, SB, PH, HBC, and DS screened potential studies. GT, SB, and DS performed the search. GT prepared the figure and table. GT and DS interpreted results and drafted the manuscript. All authors revised the manuscript, and approved the final version. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

[1] Verrills P, Sinclair C, Barnard A. A review of spinal cord stimulation systems for chronic pain. Journal of pain research. 2016;9:481.

[2] Taccola G, Sayenko D, Gad P, Gerasimenko Y, Edgerton VR. And yet it moves: Recovery of volitional control after spinal cord injury. Prog Neurobiol. 2018;160:64-81.

[3] Weiss M, Mohr H. Spinal-cord stimulators help some patients, injure others https://apnews.com/86ba45b0a4ad443fad1214622d13e6cb2018 [Available from: https://apnews.com/86ba45b0a4ad443fad1214622d13e6cb.

[4] Sivanesan E, Bicket MC, Cohen SP. Retrospective analysis of complications associated with dorsal root ganglion stimulation for pain relief in the FDA MAUDE database. Regional Anesthesia & Pain Medicine. 2019;44(1):100-6.

[5] Taylor RS, Ryan J, O'Donnell R, Eldabe S, Kumar K, North RB. The cost-effectiveness of spinal cord stimulation in the treatment of failed back surgery syndrome. Clin J Pain. 2010;26(6):463-9.

[6] Minassian K, McKay WB, Binder H, Hofstoetter US. Targeting Lumbar Spinal Neural Circuitry by Epidural Stimulation to Restore Motor Function After Spinal Cord Injury. Neurotherapeutics. 2016;13(2):284-94.

[7] Rejc E, Angeli C, Harkema S. Effects of Lumbosacral Spinal Cord Epidural Stimulation for Standing after Chronic Complete Paralysis in Humans. PLoS One. 2015;10(7):e0133998.

[8] Grahn PJ, Lavrov IA, Sayenko DG, Van Straaten MG, Gill ML, Strommen JA, et al. Enabling Task-Specific Volitional Motor Functions via Spinal Cord Neuromodulation in a Human With Paraplegia. Mayo Clin Proc. 2017;92(4):544-54.

[9] Gill ML, Grahn PJ, Calvert JS, Linde MB, Lavrov IA, Strommen JA, et al. Neuromodulation of lumbosacral spinal networks enables independent stepping after complete paraplegia. Nature medicine. 2018;24(11):1677-82.

[10] Angeli CA, Boakye M, Morton RA, Vogt J, Benton K, Chen Y, et al. Recovery of Over-Ground Walking after Chronic Motor Complete Spinal Cord Injury. The New England journal of medicine. 2018;379(13):1244-50.

[11] Wagner FB, Mignardot JB, Le Goff-Mignardot CG, Demesmaeker R, Komi S, Capogrosso M, et al. Targeted neurotechnology restores walking in humans with spinal cord injury. Nature. 2018;563(7729):65-71.

[12] Lu DC, Edgerton VR, Modaber M, AuYong N, Morikawa E, Zdunowski S, et al. Engaging Cervical Spinal Cord Networks to Reenable Volitional Control of Hand Function in Tetraplegic Patients. Neurorehabil Neural Repair. 2016;30(10):951-62.

[13] DiMarco AF, Geertman RT, Tabbaa K, Nemunaitis GA, Kowalski KE. Restoration of cough via spinal cord stimulation improves pulmonary function in tetraplegics. The journal of spinal cord medicine. 2019:1-7.

[14] Walter M, Lee AH, Kavanagh A, Phillips AA, Krassioukov AV. Epidural spinal cord stimulation acutely modulates lower urinary tract and bowel function following spinal cord injury: a case report. Frontiers in physiology. 2018;9:1816.

[15] Herrity AN, Williams CS, Angeli CA, Harkema SJ, Hubscher CH. Lumbosacral spinal cord epidural stimulation improves voiding function after human spinal cord injury. Sci Rep. 2018;8(1):8688.

[16] Wernig A. No dawn yet of a new age in spinal cord rehabilitation. Brain. 2014;138(7):e362-e.

[17] Wernig A, Müller S, Nanassy A, Cagol E. Laufband therapy based on 'rules of spinal locomotion'is effective in spinal cord injured persons. European Journal of Neuroscience. 1995;7(4):823-9.

[18] Wernig A, Muller S. Laufband locomotion with body weight support improved walking in persons with severe spinal cord injuries. Paraplegia. 1992;30(4):229-38.

[19] Wernig A, Nanassy A, Muller S. Maintenance of locomotor abilities following Laufband (treadmill) therapy in para- and tetraplegic persons: follow-up studies. Spinal cord. 1998;36(11):744-9.

[20] Wernig A, Nanassy A, Müller S. Laufband (treadmill) therapy in incomplete paraplegia and tetraplegia. Journal of neurotrauma. 1999;16(8):719-26.

[21] Dietz V, Wirz M, Colombo G, Curt A. Locomotor capacity and recovery of spinal cord function in paraplegic patients: a clinical and electrophysiological evaluation. Electroencephalogr Clin Neurophysiol. 1998;109(2):140-53.

[22] Sherwood AM, Dimitrijevic MR, McKay WB. Evidence of subclinical brain influence in clinically complete spinal cord injury: discomplete SCI. Journal of the neurological sciences. 1992;110(1-2):90-8.

[23] McKay WB, Lim HK, Priebe MM, Stokic DS, Sherwood AM. Clinical neurophysiological assessment of residual motor control in post-spinal cord injury paralysis. Neurorehabil Neural Repair. 2004;18(3):144-53.

[24] Angeli CA, Edgerton VR, Gerasimenko YP, Harkema SJ. Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. Brain. 2014;137(Pt 5):1394-409.

[25] Darrow D, Balser D, Netoff TI, Krassioukov A, Phillips A, Parr A, et al. Epidural Spinal Cord Stimulation Facilitates Immediate Restoration of Dormant Motor and Autonomic Supraspinal Pathways after Chronic Neurologically Complete Spinal Cord Injury. J Neurotrauma. 2019;36(15):2325-36.

[26] Kleiber J-C, Marlier B, Bannwarth M, Theret E, Peruzzi P, Litre F. Is spinal cord stimulation safe? A review of 13 years of implantations and complications. Revue neurologique. 2016;172(11):689-95.

[27] Maldonado-Naranjo AL, Frizon LA, Sabharwal NC, Xiao R, Hogue O, Lobel DA, et al. Rate of complications following spinal cord stimulation paddle electrode removal. Neuromodulation: Technology at the Neural Interface. 2018;21(5):513-9.

[28] Turner JA, Loeser JD, Deyo RA, Sanders SB. Spinal cord stimulation for patients with failed back surgery syndrome or complex regional pain syndrome: a systematic review of effectiveness and complications. Pain. 2004;108(1-2):137-47.

[29] Kumar K, Wilson JR, Taylor RS, Gupta S. Complications of spinal cord stimulation, suggestions to improve outcome, and financial impact. Journal of Neurosurgery: Spine. 2006;5(3):191-203.

[30] Pineda A. Dorsal column stimulation and its prospects. Surgical neurology. 1975;4(1):157-63.

474 **Legend**

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476 Table 1. Reported cases of severe spinal compression related to fibrous lead encapsulation
477 developing 3 to 17 years after electrode implantation

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