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

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1 Title: **Complications of epidural spinal stimulation: Lessons from the past and alternatives**
2 **for the future**

3

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

5

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21

22 **Abstract**

23 **Study Design:** Systematic Review

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

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

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

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

44

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

46

47 **Keywords:** neuromodulation, spinal cord, epidural interface, complications, transcutaneous

48 stimulation

49

50 **Introduction**

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

73 spinal stimulation as chronic neuropathic pain management performed in the United Kingdom's
74 National Institute of Health and Clinical Excellence, has shown that the therapy is cost-effective
75 [5]. The Incremental Cost Effectiveness Ratio calculated over a 15-year horizon demonstrated high
76 economic benefits mostly referred to the improved health and productivity of the subjects, that
77 have been quantified as 35 times more significant than the cost of the therapy itself, even including
78 the incidence of complications. At the same time, similar analysis on the benefit to cost ratio from
79 the studies recovering motor control using SCS is not available to date, but it would likely show a
80 smaller ratio given that the recovery of independent motor function is rather small, requires
81 intensive therapy, and is limited so far by a person's need for continuous assistance during
82 ambulation.

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

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

119 epidural bleeding, which causes hematoma and accidental compression of the spinal cord¹⁹.
120 Research into the underlying causes and risk factors for adverse effects of invasive SCS is therefore
121 paramount to maintain high levels of therapeutic efficiency, decrease complication rates, reduce
122 the need for costly surgeries for electrode revision or scar removal, and improve clinical and
123 functional outcomes. The current perspective paper focuses on the implanted electrode
124 encapsulation and its negative impact on effective and sustainable spinal cord stimulation (SCS).

125

126 **Complications of implanted electrodes**

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

132 Among hardware-related problems, lead migration was previously reported as one of the
133 most common risks of SCS, with a variable incidence spanning 13 to 22%, with a higher
134 prevalence for implants in the cervical spine, where the degree of motion of vertebrae is greater
135 [SA35, 36]. Lead migration often requires a new surgical procedure for repositioning or replacing
136 the electrode. However, two recent retrospective studies, analyzing SCS systems implanted from
137 2008 to 2011, found that lead migration requiring repositioning of the systems occurred in only in
138 1.4 to 2.1 % of over a hundred of analyzed cases, a much lower incidence rate than previously
139 reported, possibly accounting for hardware and technique improvement, including revised
140 published guidelines by SCS manufacturers on proper fascial anchoring and the use of strain-relief
141 loops [SA37]. Noteworthy, older studies have compared the migration rates of percutaneous leads

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

148 Additional complications originate from an acute biological response to the implant.
149 Infection is one of the major complications with incidences of 5% and requiring antibiotic
150 treatment and even device removal and reinstallation after healing from sepsis [26, SA32-33]. This
151 is a higher value compared to other implantable electronic devices, such as cardiac pacemakers,
152 which have an incidence of infection of about 0.5 to 2.2% [SA40]. For SCS, superficial or
153 subcutaneous infections at the incision site are more common than deep tissue infections with
154 abscesses over the spine. Although meningitis rarely occurred, an intradural abscess resulting in
155 paralysis has been reported [SA41]. Pain in the region around the stimulator has also been
156 registered in 5 to 10% [26, SA32-33]. During surgical or blind percutaneous insertion of
157 electrodes, accidental dural puncture, epidural hematoma, as well as blunt trauma to the cord, have
158 been documented, causing the onset of paraplegia in the 30 days following SCS implantation for
159 2% of individuals analyzed [42].

160

161 **Tolerance to SCS**

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

165 43, 44]. Although an increase in pulse amplitude might circumvent the problem for a while [SA45-
166 47], the tolerance phenomenon still often mitigates SCS efficacy if therapy is continued. This
167 phenomenon can develop as early as a few months after implantation and as late as 10 to 15 years
168 following implantation [29, SA48]. Although, psychological affective factors might also
169 contribute to a tolerance to the analgesic effects of SCS [SA46], there is some evidence that
170 suggests the development of tolerance over time results from dropped charges related to the deposit
171 of high impedance biological material progressively encapsulating the electrode after implantation
172 [SA46, 49]. The extent of fibrous tissue growth around the electrode has been positively correlated
173 to impedance increases in studies with cochlear implants [SA50-51]. It is doubtful that tolerance
174 reflects only structural and conductive changes on the surface of the implanted material and can
175 be solved by merely substituting the system. Tolerance originates from more profound changes at
176 the interface between the contact electrode and the underlying tissues. An immune-mediated
177 foreign body response is determined by the implant's materials and causes both the aggregation of
178 mononuclear macrophages and the encapsulation of the device in a collagenous envelope [SA52].
179 The picture can be further worsened by the local toxicity of metal particles dissolved by the long-
180 term corrosion of electrodes [SA53]. All these events can activate fibroblasts, with a consequent
181 fibrotic growth around the electrode that causes a shallow mechanical depression of the spinal cord
182 regions under the array [SA52]. Moreover, perturbations on the surface of the cord result both in
183 the localized activation of glial cells, and in epidural fibrosis, which can be associated with dural
184 thickening or even superficial scarring, that eventually alter the charge transfer to the surrounding
185 neural structures [SA54].

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

189

190 **Histological Findings in Fibrous Encapsulations**

191 Despite the rarity of negative published results in the field of SCS, there have been at least
192 20 reported cases of severe spinal compression related to fibrous lead encapsulation developing 3
193 to 17 years after electrode implantation (Table 1, mean onset = 7 ± 5 years) [SA43, 55, 56].
194 Oftentimes, these cases began as tolerance, eventually resulting in the development of neurological
195 deficits, such as myelopathy [SA43, 57], worsened spasticity [SA45], and increased paralysis
196 [SA43, 45, 56, 58]. In all 20 reported cases, delicate surgical procedures on the spinal cord to
197 remove the whole electrode and the scar tissue that surrounded it inside the epidural space were
198 necessary, sometimes in response to tolerance [SA43, 45, 47, 55-57, 59-64]. Also, in some reported
199 cases, analysis of the extracted scar tissue revealed the presence of excessive fibrosis around the
200 electrode itself – both for paddle electrodes implanted via laminectomy and those implanted
201 percutaneously into the epidural space [29, SA43, 48]. Still, the vast majority of published clinical
202 reports about failures and complications of SCS unfortunately do not comment on end-term tissue
203 and array conditions. Rather, a more detailed exploration of electrode-associated fibrous tissue
204 comes primarily from the few animal studies that have explored this issue. Notably, histological
205 examination of cortical epidural implants has revealed an overgrowth of connective tissue [SA54,
206 65] and an aggregation of cortical microglia in a resting state morphology in the first week after
207 implantation [SA52] that is followed in the subsequent week by the accumulation of a layer of
208 astrocytes [SA66]. Further studies have documented the presence of granulomatous tissue and a

209 nonspecific chronic inflammatory reaction [SA57] characterized by multinucleate macrophages
210 (giant cells) aggregating in response to the foreign body and engulfing the implant [SA61].
211 Underlying dural thickening and fibrous implant encapsulation has also been seen in experimental
212 animal models within the first month after implantation of cortical epidural arrays [SA54, 65].
213 This fibrous envelope consists of both fibroblasts and Collagen I, with the “collagenous” tissue
214 located in the distal part of the implanted array mimicking healthy dura mater while the more
215 proximal region contains “cellular” tissue with increased inflammatory cell activity [SA52]. The
216 thickness and density of cortical neural tissue, however, does not seem to change appreciably, even
217 with long-term array implantation [SA52]. There has been a number of documented cases of
218 fibrous masses developing in humans in association with SCS, often requiring electrode
219 explantation or revision due to some combination of tolerance and/or neurological deficits (Table
220 1). Moreover, many of said cases have reported histological findings similar to those seen in
221 animals, including dense fibroconnective tissue, variable non-specific inflammatory infiltrates,
222 multinucleated giant cells, noncaseating granulomas indicative of a foreign body reaction [SA45,
223 55-58, 61, 67]. Furthermore, in a recent clinical report [SA68], histologic examination of the
224 fibrous tissue around the electrode used for SCS revealed granulomatous inflammation and
225 phagocytic reaction of neutrophils and macrophages due to a metallic irritation of the dura mater.
226 Putatively, metallosis due to the deposition of metal debris on the dura mater was secondary to the
227 corrosion of the protective silicon and urethane coating around the lead of the SCS paddle
228 electrode. Uncovering of the silicon and urethane coating was likely caused by the micromotion
229 and friction between the electrode and the dura mater.

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

233

234 **Approaches for avoiding fibrous encapsulation**

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

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

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

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

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

304

305 **Transcutaneous SCS**

306 Recently, several research groups have demonstrated the feasibility of non-invasive,
307 transcutaneous SCS to neuromodulate excitability at multiple spinal levels, ranging from the
308 cervical to the coccygeal segments, and facilitating both motor [SA98-105] and autonomic
309 [SA106-107] functions. These findings provide some evidence that human spinal networks feature
310 the critical level of motor task-specific automaticity, which can be exploited using both invasive
311 and non-invasive spinal neurostimulation. Further, they can effectively function even in the lack
312 of supraspinal excitatory drive. Electrophysiological [SA108-110] and computational [SA111-
313 113] studies demonstrated that the structures, stimulated electrically by epidural or transcutaneous
314 SCS, are primarily afferent fibers of the posterior roots. Additionally, many other neural structures
315 can be directly impacted by the electrical field, including axons, synapses, neuronal cell bodies,
316 and glial cells [2]. As such, both invasive and non-invasive spinal neuromodulation may engage
317 spinal interneural networks via synaptic projections, as well as antidromic activation of ascending
318 fibers in the dorsal columns [SA105, 114-116]. Currently, the dominating hypothesis is that the
319 mechanisms through which invasive and non-invasive SCS can improve motor function after
320 paralysis include activation of residual, longitudinal fibers across and below the level of injury,
321 which were functionally silenced during SCI, and emerging responsiveness of spinal networks to

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

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

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

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

363

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367

368 **Conflicts of interest statement**

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

371

372 **Authors' contributions**

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

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385

386

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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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