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A Scoping Review of Epidural Spinal Cord Stimulation for Improving Motor and Voiding Function Following Spinal Cord Injury

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Objectives: To identify and synthesize the existing evidence on the effectiveness and safety of epidural spinal cord stimulation (SCS) for improving motor and voiding function and reducing spasticity following spinal cord injury (SCI). **Methods:** This scoping review was performed according to the framework of Arksey and O'Malley. Comprehensive serial searches in multiple databases (MEDLINE, Embase, Cochrane Central, Cochrane Database of Systematic Reviews, LILACS, PubMed, Web of Science, and Scopus) were performed to identify relevant publications that focused on epidural SCS for improving motor function, including spasticity, and voiding deficits in individuals with SCI. **Results:** Data from 13 case series including 88 individuals with complete or incomplete SCI (American Spinal Injury Association Impairment Scale [AIS] grade A to D) were included. In 12 studies of individuals with SCI, the majority (83 out of 88) demonstrated a variable degree of improvement in volitional motor function with epidural SCS. Two studies, incorporating 27 participants, demonstrated a significant reduction in spasticity with SCS. Two small studies consisting of five and two participants, respectively, demonstrated improved supraspinal control of volitional micturition with SCS. **Conclusion:** Epidural SCS can enhance central pattern generator activity and lower motor neuron excitability in individuals with SCI. The observed effects of epidural SCS following SCI suggest that the preservation of supraspinal transmission is sufficient for the recovery of volitional motor and voiding function, even in patients with complete SCI. Further research is warranted to evaluate and optimize the parameters for epidural SCS and their impact on individuals with differing degrees of severity of SCI. **Key words:** *bladder function, motor function, spasticity, spinal cord injury, spinal cord stimulation*

Introduction

Spinal cord injury (SCI) is a devastating central nervous system (CNS) insult that can lead to the permanent loss of sensory inputs and motor control. Over 2.5 million people in the world currently live with chronic SCI, and 250,000 to 500,000 individuals sustain new injuries each year worldwide.[1,2] The current annual economic burden of traumatic SCI in Canada is approximately $3.6 billion, of which $1.8 billion is associated with direct health care costs (SCI-BC). It is believed that most sensorimotor recovery occurs within the first 12 months following SCI,[3] with little additional recovery in individuals with severe chronic SCI (more than 12 months since injury) despite aggressive rehabilitation and pharmacologic treatments.[4] More recent research suggests this may not be true, with a meta-analysis

Supplementary material: This article contains supplementary digital material (eAppendix 1).

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of 20 studies published after 1992 to characterize neurological recovery in patients with complete injuries reporting an overall conversion rate from complete to incomplete SCI of 33.3% over a variable duration of time.[5] Loss of motor function in individuals with SCI impedes the independent performance of activities of daily living. Further, alterations in autonomic bladder function can lead to spinally mediated involuntary voiding reflexes, urinary retention, and medical complications such as urinary tract infections. These rank as important factors contributing to the reduced quality of life in individuals living with SCI.[6] Even partial restoration of these volitional functions provides significant improvement in the quality of life of persons living with SCI.[6,7]

Following an injury to the CNS, such as an SCI, uninjured structures and pathways can compensate for the functions of lost and injured tissue. Termed *neuroplasticity*, the process has been defined as "an adaptive reorganization of the neural pathways occurring after injury that acts to restore some of the lost function" or alternatively as "the CNS capacity to modify its morphological and functional properties as a response to environmental stimuli."[8,9] Following an SCI, neural reorganization includes the formation of new pathways in the spinal cord, reorganization processes, and changes in brain and spinal connectivity.[10] In animal models, axons from the motor cortex sprout and synapse on neurons that have maintained viable descending axons, thereby forming new circuits that can bypass partial lesions and mediate recovery.[11] There is also evidence of restored connectivity in tracts in the spinal cord following SCI.[12] Due to neuroplasticity, marked functional recovery occurs following experimental SCI, with as little as 10% of the axons spared.[13-15] Further, work by the research groups of Harkema, Courtine, Edgerton, and Hayton and others on animal models of rehabilitation that mimic clinical rehabilitation has been helpful to reveal the axonal changes underlying motor recovery.[16]

Evidence suggests that physical rehabilitation and locomotor training can facilitate plasticity-based recovery in individuals with incomplete SCI injuries.[17,18] Observed recovery, however, is minimal in complete SCI injuries. Beginning with the first case report in 2004 by Carhart et al.,[19] electrical stimulation of the spinal cord has shown the potential to further enhance the excitability of motor neurons and facilitate recovery post SCI. Enhancing the excitability of spinal neurons through the application of spinal cord stimulation (SCS) may enhance their responsiveness to local afferent input (e.g., step training) and spared supraspinal input; the latter even when it is clinically inapparent.[20] Animal models characterized by impaired upper motor neuron function following SCI have demonstrated the feasibility of facilitating motor function when epidural SCS is applied to anatomical landmarks with low activation thresholds, such as the entry point of the dorsal root fibers into the spinal cord.[21,22]

Given the growing body of literature addressing the potential role of epidural SCS in facilitating motor and bladder function following SCI, the objectives of this scoping review were to survey and synthesize the existing literature, identify knowledge gaps, and make recommendations for future research in this area. Furthermore, though some reviews on this topic have attempted to address these issues,[23] there is a lack of a systematic approach for understanding the pattern of epidural SCS and its impact on restoring motor and voiding function after SCI.

Methods

Arksey and O'Malley's "population, concept, context" approach[24] with modifications as suggested by Levac and colleagues was followed for this scoping review.[25,26] This scoping review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist[27] **(Figure 1**). Scoping reviews allow researchers to examine the extent, range, and nature of published research by using broad objectives and to summarize and disseminate key research findings while identifying gaps in the literature.[28] This type of methodology is especially useful when studying a complex concept with emerging evidence, such as epidural SCS for improving motor and voiding function following SCI. We used a review protocol, but we did not register it with PROSPERO.

Framing the research question

A "population, concept, context" as proposed by Arksey and O'Malley[24] was used for defining the research question. The population of interest consisted of adults (18 years old and above) with SCI. The concept was the impact of epidural SCS, at cervical, low thoracic, and upper lumbar levels, on motor and/or voiding deficits and/or spasticity. The context was the clinical setting of dysfunctional motor and voiding abilities in individuals with SCI despite maximal medical care and rehabilitation and irrespective of the time elapsed since SCI. Exclusion criteria were comprised of animal studies, studies not in the English language, cadaveric studies, commentaries, or letters to editors. Studies were also excluded if they did not involve epidural SCS as the intervention for treatment of sequelae of SCI.

Searching the literature for relevant publications

A comprehensive search strategy was developed by two of the authors (K.M.M., A.B.) and a medical information specialist (M.E.) to capture all studies where SCS was used to improve motor function, reduce spasticity, and/or improve voiding ability in individuals with SCI. The following databases were searched: MEDLINE In-Process and Other Non-indexed citations, MEDLINE; Embase Classic+Embase; Cochrane CENTRAL, the Cochrane Database of Systematic Reviews (all via the Ovid platform); PubMed (non-MEDLINE records only), LILACS (PAHO); Scopus (Elsevier); the Web of Science Core Collection (Clarivate Analytics); and grey literature. The search concept components were made up of both controlled vocabulary and text word terms and synonyms for "motor" or "bladder" or "bowel" AND "spinal cord injury" AND "epidural stimulation". Database searches were limited to English language, human subjects, and adults, where possible. Lastly, the ProQuest Dissertations and Theses Global was searched for dissertations only. The reference lists of shortlisted papers were then reviewed for additional relevant publications, and informal searches using Google Scholar were performed to identify additional studies. Final search terms and combinations can be found in eAppendix 1.

Selecting and classifying the studies

Two authors screened all identified titles (N.D. and K.M.) and abstracts for eligibility based on the inclusion and exclusion criteria. Only studies published in the past 22 years (January 1, 2000, until April 28, 2022) were included in this review in order to focus on the most recent literature. Studies selected by either author were included in a full-text review. Disagreements regarding the inclusion of the articles were resolved by consensus.

Data charting and synthesis

Data extraction sheets were developed and pilot-tested. Data extraction was done independently by four authors (K.M., N.D., P.K., and Y.H.) for each of the studies selected for inclusion in the review. The following parameters were extracted: author, year of publication, type of study, number of study participants, participant demographics, details of the intervention including the SCS parameters (waveforms, types of stimulation electrodes), measured outcomes, therapies prior to SCS, and key results. Outcomes of interest included the effectiveness and safety of epidural SCS on motor function (strength, locomotion, spasticity) and bladder function (voiding efficiency). An assessment of study quality in terms of methodology was not performed. Results were described under the following headings: epidural SCS and recovery of motor function, epidural SCS and recovery of voiding function, SCS parameters, and adverse effects of epidural SCS. Potential opportunities for undertaking systematic reviews were also identified.

Results

A flow chart depicting the study selection process is shown in **Figure 1**. The initial search retrieved a total of 4422 articles. After applying the search parameters, 2321 were identified to undergo selection screening. We excluded 2307 publications because 1747 publications did not meet the inclusion criteria due to lack of relevance to our topic (e.g., focus on SCI but not on SCS, SCS for non-SCI patients, non-SCS neuromodulation, pediatric patients, etc.) or type of the manuscript (editorials, letters to the editor, etc.), or they met the exclusion criteria because they pertained to animal experiments or were commentaries or opinion pieces (560 publications). Thirteen case series met our inclusion criteria. These publications included 88 individuals with AIS grade A to D SCI with cervical or thoracic levels of injury varying from

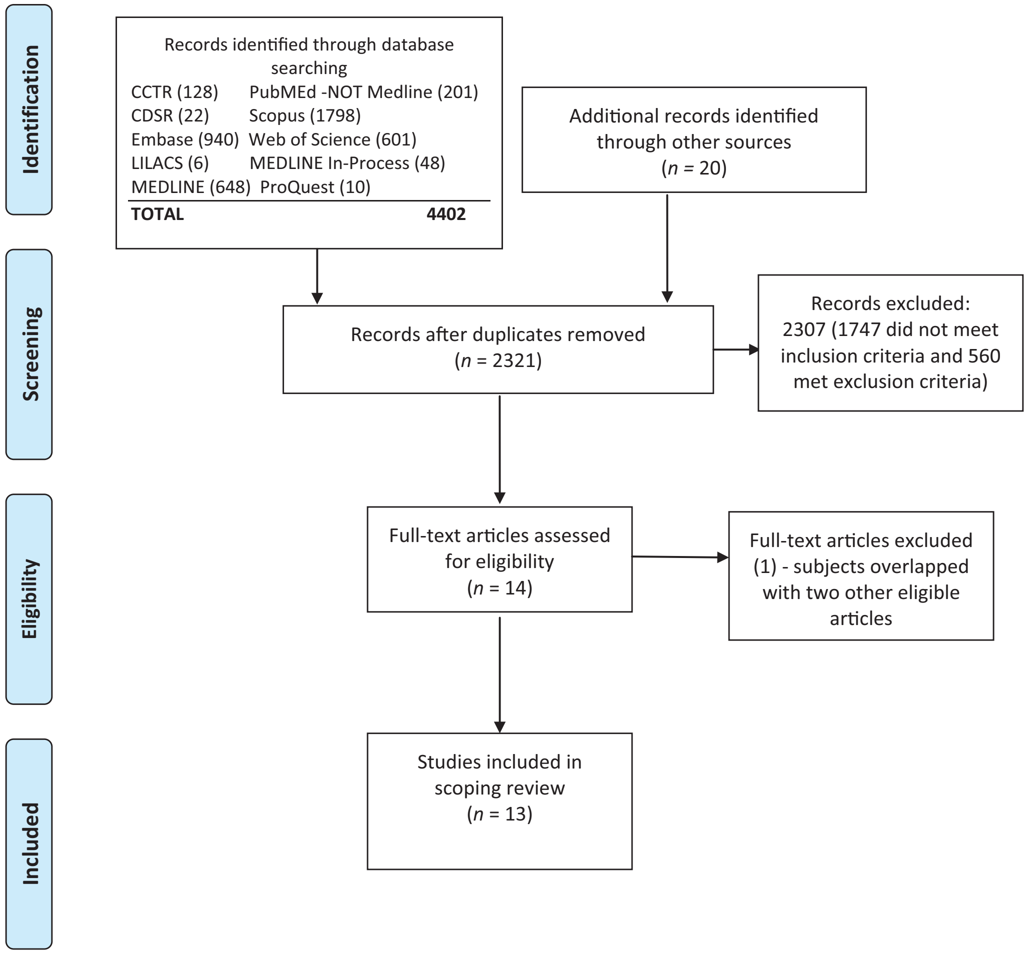

Figure 1. PRISMA flow diagram for the scoping review.

C2 to T10. Because of the relatively small number of researchers in this field, we were aware of the possibility of results from the same participants being reported in more than one publication. We ensured outcomes of each participant were reported only once in our review. The included studies are summarized in **Tables 1** and **2**. The details of the search strategy for MEDLINE are provided in eAppendix 1.

Epidural SCS and recovery of motor function

Eighty-three participants from a total of 12 studies demonstrated a variable degree of improvement in volitional motor function.[7,22,29-38]

Six studies reported improvements in volitional lower limb muscle activity with epidural SCS,[22,30,32,34,36,37] but ambulation was not evaluated as an outcome in these studies. In one study, four out of seven participants developed sustained volitional movement, even in the absence of active stimulation, following long-term exposure to epidural SCS (5-21 hours/day for a mean of 255 days), and volitional power improved over time with epidural SCS.[34] Another study ($n = 2$) reported the immediate restoration of volitional movement with the initiation of epidural SCS.[30]

Three studies reported the recovery of varying degrees of standing or ambulation.[29,35,38] In one study of individuals with chronic paraplegia ($n = 4$), two participants with AIS A were able to stand without any external assistance except for balance. Two participants with AIS B used elastic cords fixed to a standing frame to assist with hip extension.[35] Angeli et al.[29] reported that two individuals (both AIS B) achieved over-ground walking after 278 sessions (85 weeks) and 81 sessions (15 weeks), respectively, of epidural SCS combined with gait training. All four participants in their study achieved independent

Table 1. Study and participant characteristics of publications including in the scoping review

Author year **Age of participants** **AIS/spasticity grade of participants**	**SCI level**	**Time since injury**	**Implant details and stimulation location stimulation parameters**
Murg 2000[32] Age, years: 28.8 (range: 18-57) Frankel grade of spinal cord function: A (*n*=6) B (*n*=4) C (*n*=3)	C (*n*=8) T (*n*=5)	44.5 (range: 16-97) months	Quadripolar electrode at T11-L1 levels Freq: 5 Hz PW: 210 µs A: Increased in 0.5V increments from 0 to 10 V
Pinter 2000[33] Age, years: 28.1 (range: 18-24) AIS A = 5 AIS B = 2 AIS C = 1	C5-6 (*n*=3) T3-6 (*n*=5)	41.5 (range: 19-94) months	Quadripolar electrode at T11-L1 levels Freq: 5 Hz PW: 210 µs A: Increased in 0.5V increments from 0 to 10 V
Jilge 2004[22] Age, years: 27.6 (range: 24-33) AIS A = 4 AIS B = 1	C4/5 (*n*=1) C5/6 (*n*=1) T4/5 (*n*=1) T10 (*n*=1) T7 (*n*=1)	4.8 (range: 2-7) years	Quadripolar electrode array at T11-L1 levels to stimulate L1-S1 Freq: 5-60 Hz PW: 210-450 µs A: 1-10 V
Sayenko 2014[37] Age, years: 26.33 (range: 23-32) AIS A = 1 AIS B = 2	C7 (*n*=1) T2 (*n*=1) T4 (*n*=1)	3.27 (range: 2.2-4.2) years	16-electrode (5-6-5) paddle lead array at T11-L1 level to stimulate L1-S2 Freq: 2 Hz PW: 210 µs A: 0.5-10 V
Dekopov 2015[31] Age, years: 35.68 (range: 17-56) Ashworth (Spasticity) Scale: 3 (*n*=7) 4 (*n*=10) 4.5 (*n*=1) 5 (*n*=1)	NR	NR	Quadripolar electrode at T10-T12 level Freq: 100-130 Hz PW: 120-300 µs A: 1.5-4 V
Rejc 2015[35] Age, years: 27 (range: 24-33) AIS A = 2 AIS B = 2	C7 (*n*=1) T2 (*n*=1) T4 (*n*=2)	3.03 (range: 2.2-4.2) years	16-electrode (5-6-5) paddle lead array at T11-L1 levels to stimulate L1-S1 Freq: 5-50Hz PW: NR A: 1-9 V

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Table 1. Study and participant characteristics of publications including in the scoping review *(cont.)*

Lu 2017[7] Age, years: NR AIS B = 2	C5 (*n*=1) C6 (*n*=1)	NR	16-electrode array at C5-T1 levels Freq: 2-40 Hz PW: 210 µs A: 0.1-10 mA
Angeli 2018[29] Age, years: 25.75 (range: 22-32) AIS A = 2 AIS B = 2	C5 (*n*=1) T1 (*n*=1) T4 (*n*=2)	2.9 (range: 2.5-3.3) years	16-electrode (5-6-5) paddle lead array to stimulate L1 to S1-2 Freq: 2 Hz PW: NR A: NR
Herrity 2018[6] Age, years: 31 (*n*=1), NR (*n*=4) AIS A = 3 AIS B = 2	C5 (*n*=1) NR (*n*=4)	3.3 years (*n*=1) 6.5±1.9 years (*n*=4)	16-electrode (5-6-5) paddle lead array at T11-T12 levels to stimulate L1-S1 Freq: 5, 15, 30, 45, 60 Hz PW: 450 µs A: 0.1 V increments < motor response threshold
Wagner 2018[38] Age, years: 36.6 (range: 28-47) AIS C = 1 AIS D = 2	C4 (*n*=1) C7 (*n*=2)	4.7 (range: 4-6) years	16-electrode (5-6-5) paddle lead array at T11-L1 levels to stimulate L1-S1 Freq: 20 - 100 Hz PW: NR A: 2.2-8 mA
Darrow 2019[30] Age, years: 48 and 52 AIS A = 2	T4 T8	5 and 10 years	16-electrode (5-6-5) paddle lead array at T12 level Freq: 2 Hz PW: 450 µs A: 0-10 mA
Pino 2020[34] Age, years: 42 (±11.4) AIS A = 6 AIS B = 1	T4 (*n*=2) T5 (*n*=3) T8 (*n*=3)	7.7 (range: 3.05-16.83) years	16-electrode paddle lead array at T11-T12 levels to stimulate L2-S2 Freq: NR PW: NR A: NR
Rejc 2020[36] Age, years: 27.1 (range: 21-61) AIS A = 6 AIS B = 7	C2 (*n*=1) C4 (*n*=6) C5 (*n*=2) C6 (*n*=1) C7 (*n*=1) C8 (*n*=1) T1 (*n*=1)	5.5 (range:3.1-8.6) years	16-electrode (5-6-5) paddle lead array at L1-L2 level to stimulate lumbosacral spinal cord segments Freq: NR PW: NR A: NR

Note: A = amplitude; AIS = American Spinal Injury Association Impairment Scale; C = cervical; EMG = electromyography; Freq = frequency; NR = nor reported; NRS = numerical rating scale; PR = pulse rate; PW = pulse width; SCI = spinal cord injury; T = thoracic.

Table 2. Outcomes assessed, therapies tried prior to spinal cord stimulation, and key results of the publications included in the scoping review

Author Year	Outcomes assessed	Therapies tried prior to SCS	Key results
Pino 2020[34]	Volitional movement	Medications used for spasticity, for example, baclofen and oxybutynin (individuals asked to stop using these following enrollment in the study).	• Four out of 7 patients developed evidence of sustained volitional movement, even in the absence of active stimulation after undergoing chronic epidural SCS. • Significant increases in volitional power found between those observed to spontaneously move without stimulation and those unable ($p < .0005$). • Likelihood of recovery of spontaneous volitional control correlated with Ashworth spasticity scores prior to the start of SCS ($p = .048$). • Volitional power progressively improved over time ($p = .016$).
Darrow 2019[30]	Volitional muscle activity Autonomic function: bowel function, bowel-bladder synergy	One individual had 60 hours of rehabilitation in 6 months prior to study while the other individual had none within 6 months prior to study.	• Bowel-bladder synergy (i.e., improvements in bowel and bladder function due to shared mechanisms) improved in both individuals while restoring volitional urination. • Volitional movement was restored immediately.
Wagner 2018[38]	Voluntary control of walking	NS	• Motor neuron activation maps with hotspots indicating areas of stimulation for body mechanics, ensuring weight acceptance, propulsion, and swing were created. Targeted SCS effectively activated the regions embedding these hotspots. • Subjects could walk hands-free when provided with hip support in gravity-assist mode after 1-3 months. Two subjects regained independent walking while 35% of their body weight was supported against gravity and the third subject needed a walker to progress over ground with SCS. • Spatiotemporal selective stimulation was better than continuous stimulation to establish adaptive locomotor control in paralyzed muscles.

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Table 2. Outcomes assessed, therapies tried prior to spinal cord stimulation, and key results of the publications included in the scoping review *(cont.)*

Author Year	**Outcomes assessed**	**Therapies tried prior to SCS**	**Key results**
Angeli 2018[29]	Independent swing and stepping on treadmill Independent over-ground walking	Activity-based physical therapy (intense locomotor training with manual assistance by trainers)	• Two patients (both AIS B) achieved over-ground walking after 278 sessions of epidural stimulation and gait training over a period of 85 weeks and 81 sessions over a period of 15 weeks, respectively. • All four patients achieved independent standing and trunk stability. • Walking possible only with SCS turned on and with subject's intent to walk. • One patient had a hip fracture during training and another patient had drainage from surgery site that lasted less than a week.
Herrity 2018[6]	Autonomic function: bladder capacity, detrusor pressure Changes in bladder control	3 months of activity-based locomotor training	• Voiding efficiency increased from 68.5% to 87.5% with SCS. • Lowest post-void urinary bladder residual volume was at 30 Hz stimulation. • Caudal part of paddle lead (L5/S1 • region) used to stimulate pelvic parasympathetic outflow. • Stimulation parameters used in three of the four additional participants never demonstrated voiding efficiency greater than 50% (one as low as 10% indicating that the results are highly patient-specific).
Lu 2017[7]	Voluntary motor control performance Volitional hand contractions	160 sessions of activity-based recovery training	• Following ABRT-eSCS, there was a significant improvement in bladder capacity relative to baseline, maintaining significance at follow-up. • Significant reduction in detrusor pressures at post-training point in ABRT-eSCS group. • Significant improvement in bladder capacity at post-training and follow-up in ARBT-eSCS compared to post-usual care group.

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Table 2. Outcomes assessed, therapies tried prior to spinal cord stimulation, and key results of the publications included in the scoping review *(cont.)*

Author Year	Outcomes assessed	Therapies tried prior to SCS	Key results
Rejc 2015[35]	Motor output (EMG) for full weight-bearing standing	NS	• Improved hand strength (approximately three-fold) and volitional hand control in the presence of epidural stimulation. • Maximum force values were observed at 10 and 20 Hz. • Frequency of 20 Hz at 0.7, 1.0, and 1.3 mA was chosen for further investigation, due to less tonic contraction and more overall voluntary hand control at this frequency of stimulation.
Dekopov 2015[31]	Decrease in muscle tone based on Ashworth Scale	80 sessions of locomotor training (combined stand and step training with stepping comprising the majority of minutes)	• Electrode configurations with cathodes placed in the caudal portion of the array, and more caudally than the anodes, at relatively higher frequencies (25–60 Hz) induced continuous EMG activity, higher level of activation of leg muscles, and better standing behavior. • EMG pattern of several muscles changed from continuous to rhythmic as the stimulation amplitude increased at higher stimulation frequencies. • Subjects with AIS A were able to stand without any external assistance except for balance. Subjects with AIS B used elastic cords fixed to the standing frame to assist with hip extension.
Sayenko 2014[37]	Bilateral evoked potentials from leg muscles (knee and ankle muscles)	Antispastic medications Botulinum injections Rehabilitation therapy	• 3 to 5 stimulation sessions (30 minutes each) per day • Decrease in the muscle tone was observed in most cases in the spinal spasticity group: the Ashworth score decrease from 3.71 ± 0.61 before the operation to 2.26 ± 0.56 after the operation ($p < .001$).

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Table 2. Outcomes assessed, therapies tried prior to spinal cord stimulation, and key results of the publications included in the scoping review *(cont.)*

Author Year	Outcomes assessed	Therapies tried prior to SCS	Key results
Jilge 2004[22]	Muscle twitch pattern through EMG recording Suppression of spasticity Limb extension	NS	• SCS resulted in stimulation of multiple muscles at higher stimulation intensities. • Bilateral hip/knee flexion and plantar flexion were observed. • Magnitude of potentials in most muscles was dependent on location of stimulation site. • During localized stimulation, magnitude of response increased in a more linear fashion and either reached a plateau or had tendency to decrease at higher stimulation intensities. • Wide-field stimulation resulted in a more generalized pattern of activation between proximal and distal muscles.
Murg 2000[32]	Muscle twitch pattern and recruitment order through poly EMG recording	NS	• Extension of the lower limbs was initiated using epidural SCS at frequencies between 5-15 Hz, intensity 4-10 V, and a pulse width of 210 microseconds. • Continued stimulation actively maintained the extended position.
Pinter 2000[33]	Levels of spasticity in lower limbs before and during stimulation	NS	• Threshold stimulus of epidural electrodes placed over the medial posterior portion of lumbar cord segments induced bilateral muscle twitch responses. • Twitch amplitudes, but not latency times, varied with stimulus strength. • polyEMG recording of muscle twitches accurately differentiated between upper and lower lumbar cord segments. • Recruitment order and amplitude of muscle twitches depended on the site of stimulation of the lumbar spinal cord – stimulating cathode over the upper (response from quadriceps and/or adductor muscles) or the lower (response from tibialis anterior and triceps surae) lumbar cord segments.

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Table 2. Outcomes assessed, therapies tried prior to spinal cord stimulation, and key results of the publications included in the scoping review *(cont.)*

Author Year	Outcomes assessed	Therapies tried prior to SCS	Key results
Rejc 2020[36]	Volitional movement EMG recordings during leg flexion and ankle dorsiflexion	Baclofen at mean daily dose of 62.5 (25 ± 100) mg up to 5 times/day (*n*=8) Tizanidine (*n*=3) Tetrazepam (150 mg/day (*n*=1)	• Six patients showed a marked and two patients a moderate reduction in spasticity with long-term continuous stimulation. • SCS electrode was located over the upper lumbar cord segment (L1, L2, L3) with the frequency of stimulation 50 ± 100 Hz and amplitude within 2 ± 7 V. • More affected patients required stronger stimuli and/or higher frequencies. • Antispastic medication was discontinued in all patients but one (reduced baclofen from 125 mg to 50 mg) as soon as continuous stimulation was in place.
			• None of the research participants were able to modulate the baseline EMG activity of lower limb muscles by volitionally attempting to generate lower limb flexion or ankle dorsiflexion when SCS was not present. • All individuals were able to generate meaningful volitional motor output (generation of force and movement, and/or activation of primary muscles involved in the movement attempt) when SCS was present. • Motor responses were detected on average for 2.7 ± 1.4 motor tasks out of the four tested for each individual (range: 1-4) when SCS on.

Note: ABRT-eSCS = activity-based recovery training – epidural spinal cord stimulation; EMG = electromyography; NS = not specified; SCS = spinal cord stimulation.

standing and trunk stability. Moreover, walking was possible only with epidural SCS turned on and with the participant's intent to walk. In another study of incomplete SCI (one individual with AIS C SCI, two individuals with AIS D SCI), two participants regained independent walking with 35% of their body weight supported against gravity and the third participant needed a walker to progress over ground with SCS.[38]

Improved hand grip strength (approximately three-fold) and volitional hand control were observed in the presence of cervical epidural SCS in a small case series of two individuals with tetraplegia.[7] Stimulation at a frequency of 20 Hertz (Hz) was found to be favorable due to less tonic contraction and more overall voluntary hand control.

Epidural SCS and decrease in spasticity

Two studies with 27 participants reported a decrease in spasticity with epidural SCS.[31,33] In addition, Pino and colleagues[34] observed that a greater degree of spasticity at baseline increased the probability of volitional movement in the lower limbs in response to epidural SCS. In another study, antispastic medication was discontinued in all patients but one (reduced baclofen from 125 mg to 50 mg) as soon as continuous epidural SCS was in place.[33]

Epidural SCS and recovery of voiding function

Two small studies have reported improved supraspinal control of volitional micturition.[6,30] The study by Herrity and colleagues[6] (n = 5) reported an increase in voiding efficiency (the percentage volume of urinary contents expelled by the end of voiding as compared to the start of voiding) from 68.5% to 87.5% with epidural SCS. The lowest post-void urinary bladder residual volume was noted after 30 Hz stimulation. The caudal section of the paddle lead (overlying lumbosacral junction) was used to stimulate pelvic parasympathetic outflow. In another study (n = 2) of epidural SCS, Darrow and team[30] observed improved voluntary control of voiding in both AIS A participants and improved bowel-bladder synergy (i.e., improvements in bowel and bladder function due to shared mechanisms).

SCS parameters utilized in the studies

In the reviewed studies, epidural SCS was administered from the fifth cervical to the first thoracic vertebral body levels for the upper limbs[7] and from the eleventh thoracic to the first lumbar levels (to stimulate from the first lumbar to the second sacral nerves) for the lower limbs [7,22,29-38] and bladder.[6,30] The majority of the studies used a 16-electrode paddle lead array (5-6-5 arrangement of electrodes in three columns) for stimulation.

In the study by Sayenko and colleagues,[37] bilateral hip and knee flexion and plantar flexion were observed in participants with epidural SCS. The magnitude of electromyography (EMG) potentials (range, 0.5-10 V) in most muscles was dependent on the location of the stimulation site, and it was calculated by measuring the area under the curve across each component. During localized stimulation, the magnitude of response increased in a generally linear fashion and either reached a plateau or had a tendency to decrease at higher stimulation intensities. However, overall, epidural SCS resulted in the stimulation of multiple muscles at higher stimulation intensities.[37] Electrode configurations with cathodes (negative electrodes) placed in the caudal portion of the stimulating array, and more caudally than the anodes (positive electrodes), at relatively higher frequencies (25–60 Hz) induced continuous EMG activity, increased activation of leg muscles, and better standing behavior.[35] The EMG pattern of several muscles changed from continuous to rhythmic as the stimulation amplitude increased at higher stimulation frequencies.[35]

Findings by Murg and colleagues[32] strongly suggest that posterior roots and not posterior columns of the lumbar spinal cord were stimulated by epidural SCS. Threshold stimulus of epidural electrodes placed over the medial posterior portion of lumbar cord segments induced bilateral lumbar cord segments muscle twitch responses. The EMG recording of muscle twitches accurately differentiated between upper and lower lumbar cord segments. Recruitment order and amplitude of muscle twitches depended on the site of stimulation of the lumbar spinal cord. Placement of the stimulating cathode over the upper lumbar cord induced a response from the quadriceps and/or adductor muscles, while placement over the lower lumbar cord induced a response from tibialis anterior and triceps surae.

Extension of the lower limbs was initiated using epidural SCS at frequencies between 5 and 15 Hz, intensity 4–10 volts (V), and a pulse width of 210 microseconds. Continued stimulation actively maintained the extended position.[22] On the other hand, the lowest post-void bladder residual volume was noted with 30 Hz stimulation.[6]

In two studies that included 27 participants with spasticity,[31,33] the frequency of epidural SCS required to reduce spasticity was reported to be 100 Hz or higher. In the study by Pinter and team[33] (n = 8), six patients showed a marked reduction and two patients a moderate reduction in spasticity with long-term continuous stimulation. The electrode was located over the upper lumbar cord segment (overlying L1, L2, L3) with the frequency of stimulation 50 ± 100 Hz and amplitude within 2 ± 7 V. After three to five stimulation sessions (30 minutes each) per day, a decrease in muscle tone was observed in most cases. The Ashworth spasticity score decreased from 3.71 ± 0.61 before the operation to 2.26 ± 0.56 after the operation ($p < .001$).

Adverse effects of epidural SCS

There were two reported complications related to epidural SCS in the reviewed studies. In one study, one participant sustained a hip fracture during training, and another participant experienced drainage from the surgical site that lasted less than a week.[29]

Discussion

This review synthesizes the current literature supporting the efficacy of epidural SCS for improving motor control, facilitating neurological recovery (including standing and walking), and enhancing voiding in individuals with chronic SCI.

Eleven studies reported improved motor function with epidural SCS administered at the lower thoracic and upper lumbar (T10-L2) vertebral levels for the lower limbs, whereas one study reported improvement with epidural SCS applied to the C5-T1 vertebral levels for the upper limbs. SCS frequencies in the 5–40 Hz range were found to improve muscle tone and voluntary movement. In two studies that included 27 patients with spasticity, epidural SCS at 100 Hz or higher was associated with a reduction in spasticity. One study reported an improvement in voiding efficiency of over 60% achieved with a SCS frequency of 30 Hz. However, reporting and publication biases cannot be ruled out because all the publications included in this review were supportive of the use of epidural SCS in participants with SCI with no reports of significant failures.

Role of epidural SCS in improving volitional motor function

Epidural SCS involves the surgical implantation of a small array of electrodes into the epidural space. It was originally developed in 1967 to treat chronic pain.[39] The studies included in this review support epidural SCS as a promising intervention to enhance volitional motor control in individuals with SCI. However, the outcomes of interest with respect to volitional motor function varied in the included studies. Whereas earlier studies tended to explore electrophysiological (e.g., EMG-based) outcomes,[22,32] the more recent publications assessed standing, stepping, and ambulation[29,38] (**Table 2**). Several mechanisms of motor recovery with epidural SCS have been proposed to explain these findings. These include large diameter afferent activation leading to increased net excitability of caudal circuits, recruitment of spared descending fibers, and, potentially, segmental disinhibition.[40] It has been proposed that epidural SCS not only enables the brain to exploit spared but functionally silent descending pathways in order to produce movements of paralyzed limbs but also improves the ability of the spinal cord to translate task-specific sensory information into the muscle activity that underlies standing and walking.[38]

Wagner and colleagues[38] used spatial stimulation instead of continuous stimulation and suggested that activation of spinal proprioceptive pathways with epidural SCS modulated cortical excitability that accelerated motor movement. They proposed targeted epidural SCS effectively activating the regions embedding hotspots of motor neurons needed to reproduce walking (weight acceptance, propulsion and swing). Epidural SCS has also been postulated to activate motor neurons by recruiting proprioceptive circuits within the posterior roots of the spinal cord. This has been translated into SCS protocols that target individual posterior roots to access the motor neuron pools located in the spinal cord segment innervated by each root.[41] Other proposed mechanisms of motor recovery post-implantation of epidural SCS include the excitation or reactivation of interneurons and motor neurons below the level of injury, which in turn contributes to axonal regeneration or sprouting induced from activity-dependent mechanisms over the ensuing months.[40] Remodeling of synaptic connections among spinal inhibitory and excitatory interneurons projecting to motor neurons and reorganization of other descending inhibitory mechanisms are additional potential mechanisms for motor recovery with SCS.[29]

Following epidural SCS, the recovery of volitional activity in individuals with SCI has been attributed to the modulation of the intrinsic circuitry caudal to a spinal cord lesion. In the absence of epidural SCS, electrical activity in the descending outputs has been shown to fall below the threshold for action potential propagation and activation of motor pools.[40] Long-term activity-based training after SCI has been found to translate volitional movement attempts into actual muscle actions when done in conjunction with epidural SCS.[29] Eventually, independent volitional movements, including lower limb movements and standing, without using epidural SCS have been achieved even in patients with motor complete SCI.[29]

However, in the study published by Rejc et al.,[36] all 13 individuals with chronic motor complete SCI were able to demonstrate meaningful volitional lower motor control with epidural SCS within 2 to 3 weeks after surgical implantation, prior to any training. This raises the possibility that it may not be essential to combine intensive motor training with epidural SCS in patients with SCI to achieve motor recovery. Due to the lack of supraspinal input, the continuous stimulation from an implanted epidural device plays an important role in enhancing intrinsic sensory information processing. Harkema et al.[20] utilized the sensory input from epidural SCS to control and modulate spinal circuitry for standing and manually facilitated stepping. Sayenko and colleagues[37] noted this could be achieved even at lower intensities to affect selective motor pools, if carefully localized stimulation was applied. In addition, they observed that weight-bearing itself while standing acted as a sensory stimulus that contributed to the reorganization of spinal circuitries. An interesting finding showed that using lower intensities led to involvement of low-threshold afferent structures, whereas with higher intensities, antidromic effect was observed as more efferent structures were recruited. Consequently, wide-field stimulation results in a more generalized pattern of activation between proximal and distal muscles.[37]

Spasticity in individuals with SCI can also be reduced with the application of epidural SCS. Pinter and colleagues[33] described two different epidural SCS stimulation sites depending on the severity of spasticity. If the lesion was incomplete with mild spasticity, they found it suitable to stimulate below the level of the lesion. Meanwhile, for individuals with severe lower limb spasticity, selective upper lumbar dorsal root stimulation using higher amplitudes or frequencies was deemed to be more appropriate. Participants with severe motor impairments required stronger stimuli and/or higher frequencies. The reduction in spasticity with epidural SCS appears to be of a smaller magnitude as compared to the effect of intrathecal baclofen (ITB). Sayenko and colleagues[37] reported a decrease in the mean Ashworth score from 3.71 ± 0.61 to 2.26 ± 0.56 following the use of SCS in participants with SCI, whereas a review on the effect of ITB in this population reports a reduction in this score from 3.1 to 4.5 at baseline to 1.0 to 2.0 following the use of ITB.[28] However, these findings need to be validated in larger studies, and comparative studies between ITB and epidural SCS for reducing spasticity are required. **Table 3** summarizes the proposed mechanisms of epidural SCS in individuals with SCI.

Role of SCS in facilitating voiding

Neuromodulation for the treatment of neurogenic lower urinary tract dysfunction (NLUTD) in patients with SCI is under rapid development. The epidural SCS settings used by Herrity and

Table 3. Proposed mechanisms of action of spinal cord stimulation for improving motor and voiding function in individuals with spinal cord injury

Site of action	Mechanisms of action
Afferent neuronal traffic	Activation of primary afferent fibres and, indirectly, spinal interneurons (CPG)
Spinal cord	Modulation of spinal cord excitability
Supraspinal	• Engagement of residual supraspinal control, facilitating the excitability of motor neurons in response to supraspinal input • Ascending input from SCS modulates cortical and subcortical motor regions
Multiple sites	Remodelling of spared circuitry

colleagues[6] and Harkema and colleagues[20] were comparable. Both studies reported improvement in bladder control. Because the latter study was mainly focused on locomotor outcomes (standing), voiding efficiency was observed as an additional benefit with the use of epidural SCS settings that focused on achieving volitional motor control. This configuration targeted caudal segments with a frequency of 15 Hz and an amplitude of 8 V.[20] Both studies targeted sacral segment stimulation distal to the lumbar stimulation that is commonly used for lower limb motor recovery. Herrity and colleagues[6] also used the caudal end of the electrode array for mapping of bladder function and found significantly improved bladder function with a higher voiding efficiency and the lowest post-void residual volume, at a frequency of 30 Hz with fixed intensity and pulse width (450 microseconds). It is important to note that in this study, stimulation parameters used in three of the four additional participants never demonstrated voiding efficiency greater than 50%, with one as low as 10% indicating that the results were very participant-specific. However, the improvement in voiding efficiency in one participant from 68.5% to 87.5% in this study is promising because the post-epidural SCS value was close to the standard threshold of 90%.[42]

Investigators have also argued in favor of on-demand epidural SCS for triggering the voiding phase of micturition in individuals with SCI. Epidural SCS may prime the spinal cord to ultimately modulate the excitability of spinal reflexes particularly crucial for efficient voiding. In incomplete SCI, continuous sacral nerve stimulation was found to be more effective for improving bladder capacity and incontinence. This was attributed to preserved spino-bulbospinal pathways that are lacking in complete SCI.[6] Herrity and colleagues[6] also suggested targeting lower neural levels, second to the fourth sacral segments, to directly target the sacral micturition center to further improve voiding efficiency. Although they observed voiding efficiency up to 87.5% from stimulating level L1-S1, they encourage the use of multiple configurations (e.g., two different frequencies run concurrently to assess if both stages of micturition will be affected) for various systems. They highlighted that altering the stimulation spinal level, even by one segment, or lengthening the electrode array may affect the positive benefits demonstrated. Finally, SCS can also have an impact on the bladder storage capacity. Although there are concerns about the settings best for voiding efficiency being suboptimal for bladder storage.[6] Darrow and colleagues[30] did report improvement in bladder storage capacity in one but not the other participant with SCI in their study following the use of SCS. Similarly, Herrity and colleagues[6] reported an overall positive and persistent effect of SCS on bladder emptying in patients with SCI, but more research is required to evaluate improvements in bladder function over time when SCS is turned off.

It should be recognized that despite the need to undergo epidural SCS implantation surgery, potential multisystem gains (including autonomic control of cardiovascular, respiratory, bowel, sexual, and temperature regulation) of epidural SCS could translate to improved quality of life following SCI.[6,20]

Future research on epidural SCS for individuals with SCI

SCS configurations

Identification of appropriate epidural SCS targets (spinal cord levels that need to be stimulated) and parameters suited to improve locomotion, spasticity, and voiding in individuals with SCI need to be determined. Varying combinations of frequency, amplitude, current strength, pulse width, and differing waveforms may have differential effects on the supraspinal descending pathways that modulate motor function and micturition. As an example, increased stimulation frequencies have been shown to change the EMG pattern from continuous to a rhythmic locomotor-like pattern with increasing amplitude. However, at a higher amplitude of 5.0 V and stimulating frequency at 25 Hz and 50 Hz, unstable standing behaviors were observed in individuals with SCI in one study.[35] The recent study by Formento et al.[43] on the antidromic effect of epidural SCS on proprioception suggests an ideal stimulation configuration consisting of high frequency but low amplitude stimulation. This epidural SCS setting will recruit fewer afferents (due to lower amplitude); however, the repeated recruitment with high frequency stimulation may compensate for this and lead to a summation of excitatory postsynaptic potentials (EPSPs) in the motor neurons. However, this modulation of bursts of stimulation may counter the antidromic effects of epidural SCS on proprioception. Newer modes of epidural SCS stimulation could provide assisted impulse augmentation in a coordinated fashion to antagonist neuronal pathways for facilitation and reproduction of pre-SCI pattern of locomotion in an individual living with paraplegia or tetraplegia.

Further studies should also determine the long-term sustenance of epidural SCS effects and their impact on bowel and sexual function. Abdominal muscle activation has been demonstrated to occur with epidural SCS.[35] Herrity et al.[6] suggested examining the relationship between lower limb and abdominal muscle activation and the contraction of the bladder musculature and sphincter system. Future research should also explore whether one SCS device with multiple concurrent programs or epidural SCS combined with other neuromodulation modalities such as sacral nerve stimulation can address motor deficits, spasticity, voiding, and autonomic dysfunction in cohorts with SCI. We are aware of ongoing efforts that address some of these objectives.[44]

SCS as a co-intervention with rehabilitation

The impact and role of combining epidural SCS with varying intensities of motor training in individuals with SCI also need to be evaluated. Rhythmic efferent activity can be achieved with manually facilitated stepping, but added benefit will likely be derived with epidural SCS, as stimulation of neuronal circuits with high intensities can stimulate dorsal columns and other spinal structures alike.[6] Despite the documented improvement in volitional motor function with the application of epidural SCS after SCI, continuous epidural electrical stimulation has been proposed to be not as effective without rehabilitation.[43] In a case report of an individual with chronic sensory-incomplete motor-complete SCI, the participant was initially unable to bear weight following 170 sessions of locomotor training (over 26 months) that incorporated stand training. He later regained the ability to bear weight when intensive task-specific stand training was combined with epidural SCS.[20] In addition, rhythmic oscillating locomotor patterns were observed with EMG when the manual facilitation of stepping was combined with SCS. These patterns were absent without epidural stimulation because muscle activity was not sufficient for unassisted stepping.

Previous studies have demonstrated that during training, the repetition of specific hind limb tasks brought about long-lasting spinal pathway plasticity. The promotion of plasticity and/or reactivation of silent neural circuitry are mechanisms by which the combination of epidural SCS with intensive task-specific training[20] or activity-based rehabilitation[35] are thought to improve volitional function and extend the duration of full weight-bearing standing in individuals with SCI. Further, in patients with clinically motor complete SCI, co-intervention with epidural SCS and locomotor training was found to improve autonomic functions, temperature regulation, and sexual functions.[6] Further, a recent study by Kandhari and colleagues[45] reported the impact of activity-based neurorehabilitation with epidural spinal submotor threshold stimulation over a period of 12 to 16 hours/day in enabling simultaneous global recovery of sensorimotor and autonomic functions in 10 patients with complete motor paralysis due to SCI.

Adverse effects of SCS

An important issue to recognize in this scoping review was the lack of reliable data on safety and possible complications with epidural SCS. This is not surprising and probably due to the lack of large number of participants in the publications since the majority were case series or reports. Reported complications following initiation of epidural SCS in individuals with SCI were hip fracture in one individual and postoperative discharge from surgical site in another. From the published experience of epidural SCS to treat chronic pain conditions, possible more severe complications include infection, foreign body reaction, lead migration, cerebral spinal fluid leak, and epidural hematoma. Larger studies and longer follow-up periods with a systematic approach to monitoring for adverse effects are needed to establish the safety profile of epidural SCS in individuals with SCI.

Limitations of this scoping review

Though we did not perform a formal assessment of the quality of included publications, a limitation of the literature on this topic is the quality of the existing literature. Identified studies consisted of case reports and case series, with small cohort sizes, entailing a high risk of publication bias. The lack of large, good quality prospective controlled trials limits the strength of evidence and the accompanying conclusions that can be drawn regarding the efficacy and benefits that can be ascribed to epidural SCS in individuals with SCI. With the newer epidural SCS modes, such as high frequency and burst that are associated with paresthesia free stimulation, it may be possible to blind participants and investigators to allocated treatment in randomized controlled studies, thereby reducing observer and reporting biases. In addition, the relationship of the physiologic changes observed with epidural SCS to daily activities, societal participation, and ultimately quality of life remains unclear. Future high-quality studies that compare epidural SCS to other active or placebo interventions are urgently needed before epidural SCS can be recommended for widespread adoption in day-to-day clinic practice. It is also worth noting that only English publications were included in this review.

Conclusion

The existing literature suggests epidural SCS may have the potential to aid the recovery of motor function, improve voiding efficiency, and reduce spasticity following complete and incomplete SCI. However, large, definitive clinical randomized trials with concealment of treatment allocation are needed to rigorously assess the benefits and adverse effects of epidural SCS in participants with SCI that have been identified by the case series and case reports included in this scoping review. Further, we need to identify the optimal epidural SCS parameters for improving locomotion and voiding and reducing spasticity in participants with with complete and incomplete SCI. Future studies should also assess and incorporate outcomes establishing the relationship between the physiologic effects of epidural SCS and the completion of daily activities, participation in societal activities and roles, and ultimately quality of life.

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Conflicts of Interest

The authors declare no conflicts of interest.

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