Spinal cord stimulation for the restoration of bladder function after spinal cord injury

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Spinal cord injury (SCI) results in the inability to empty the bladder voluntarily, and neurogenic detrusor overactivity (NDO) and detrusor sphincter dyssynergia (DSD) negatively impact both the health and quality of life of persons with SCI. Current approaches to treat bladder dysfunction in persons with SCI, including self-catheterisation and anticholinergic medications, are inadequate, and novel approaches are required to restore continence with increased bladder capacity, as well as to provide predictable and efficient on-demand voiding. Improvements in bladder function following SCI have been documented using a number of different modalities of spinal cord stimulation (SCS) in both persons with SCI and animal models, including SCS alone or SCS with concomitant activity-based training. Improvements include increased volitional voiding, voided volumes, bladder capacity, and quality of life, as well as decreases in NDO and DSD. Further, SCS is a well-developed therapy for chronic pain, and existing Food And Drug Administration (FDA)-approved devices provide a clear pathway to sustainable commercial availability and impact. However, the effective stimulation parameters and the appropriate timing and location of stimulation for SCS-mediated restoration of bladder function require further study, and studies are needed to determine underlying mechanisms of action.

1. Introduction: In the United States, over 288,000 people live with spinal cord injuries (SCIs), and ~17,700 new cases of SCI are reported annually [1]. In addition to motor impairment, SCI causes autonomic and sensory deficits, including bladder dysfunction. In persons with SCI, bladder dysfunction includes neurogenic detrusor overactivity (NDO) and/or detrusor sphincter dyssynergia (DSD) [2]. NDO occurs as involuntary bladder contractions during filling and can occur at low volumes and lead to incontinence. DSD results from discoordinated simultaneous contraction of the detrusor and external urethral sphincter [3]. DSD leads to high bladder pressures, which may result in vesicoureteral reflux, leading to kidney damage [4, 5]. Mortality due to urological dysfunction has decreased in recent decades (3% of SCI deaths) due to increases in treatment options [1]; however, these treatment options are not well-tolerated by persons with SCI, and restoration of bladder function remains a challenge following SCI. The purpose of this review is to explore the current research regarding the use of spinal cord stimulation (SCS) as a therapy for bladder dysfunction after SCI.

Micturition requires coordination of the urinary bladder, whose role is urine storage, and the bladder neck, urethra, and urethral sphincters, which provide the outlet through which voiding occurs. These organs are under control of supraspinal, spinal, and peripheral innervation [6]. Low-pressure storage in the bladder relies on a lack of input from parasympathetic efferents, activity in sympathetic efferents, and the intrinsic properties of the detrusor muscle. To initiate a void, the external urethral sphincter is voluntarily relaxed, an increase in bladder pressure occurs, and passage of urine through the urethra triggers secondary reflexes that further aid in voiding. Following SCI, reflex sensitivity to sensory input from the bladder and periphery is significantly increased, and, in addition, descending input from micturition centres of the brainstem is disrupted [7]. These changes result in NDO and DSD. In the majority of persons with SCI, the spinal reflex mechanism for micturition remains intact (i.e. for SCI that occurs above the sacral cord); however, bladder emptying cannot be voluntarily initiated.

Medical complications due to bladder dysfunction are a substantial challenge in persons with SCI, and restoration of bladder function is consistently identified as a high priority [8–11]. Clean intermittent self-catheterisation, often in combination with anticholinergic medications, is presently the most effective method to treat bladder dysfunction resulting from SCI [12, 13] and is used by 45 and 40% of male and female patients with SCI, respectively [1]. However, this approach can be limited by impaired dexterity for catheterisation, intolerance or lack of effectiveness of anticholinergic drugs, high bladder pressures [14], persistent incontinence [15], and is still associated with frequent urinary tract infections [12, 16]. The side effects of anticholinergic medications include constipation, dry mouth, headaches, and blurred vision [17–20]. Thus, adequate and effective treatment of bladder dysfunction in persons with SCI remains a significant unmet need [21].

A large number of approaches using electrical stimulation have been pursued to restore bladder function following SCI [22]. Prior efforts to provide commercial devices to restore bladder function, e.g. 'the Brindley system,' marketed as Vocare by NeuroControl Corp, met with commercial failure in the U.S. [23]. Further, the present commercially available systems using sacral nerve stimulation (Medtronic Interstim and Axonics Sacral Neuromodulation) to treat overactive bladder and urinary retention are not generally effective for treating NDO [24–26]. As well, posterior tibial nerve stimulation has only modest effects, and there are few data in persons with NDO resulting from SCI [27]. The National Institute of Biomedical Imaging and Bioengineering SCS Consortium determined autonomic dysfunction after SCI, such as the bladder, bowel, and sexual function, to be a primary target for future research on epidural SCS [28]. As described below, there is accumulating evidence that SCS may have beneficial effects on bladder function following SCI [29–31].

2. Spinal cord stimulation

2.1. Epidural stimulation: Epidural SCS includes an electrode array placed in the epidural space of the spinal canal connected by a subcutaneous lead wire to a battery-powered implanted pulse generator, the output of which can be programmed by a clinician. Importantly, the effects of SCS can be assessed using a temporary, percutaneously-placed electrode during a trial phase,

and thus, the therapeutic impact can be documented prior to committing to a surgically-implanted device. Epidural SCS is well-established as a treatment for neuropathic pain [32], and, in addition to effects on bladder function in persons with SCI, epidural SCS shows promise in the recovery of locomotion [29, 33, 34] and bowel and sexual function [35, 36].

2.2. Transcutaneous stimulation: While epidural SCS requires an invasive surgical procedure, transcutaneous electrical SCS uses electrodes placed on the skin above the lower thoracic and lumbosacral vertebrae and can be controlled by either clinicians or users outside of the clinic. The lack of invasive surgery required for transcutaneous SCS, in addition to reduced cost, increases the appeal of this potential therapy. Transcutaneous SCS demonstrated promise in restoration of function of the upper- and lower-extremities [37, 38], locomotor function [30, 39, 40], and trunk control [41]. Transcutaneous magnetic SCS utilises a magnetic field created by passing a time-varying current through a coil to generate an electric field that can cause non-invasive stimulation. Transcutaneous magnetic stimulation appears to be painless and is typically well-tolerated, including in persons with allodynia and cutaneous hypersensitivity [42]. Magnetic SCS has seen minimal use in persons and animal models of SCI; however, magnetic SCS has demonstrated effectiveness in the restoration of respiratory function [43, 44], gastric function [45], and antinociception [46].

3. Restoration of bladder function with SCS after SCI

3.1. In clinical research participants with SCI: Epidural SCS is an emerging approach to improve bladder function in individuals with SCI. SCS, in combination with rehabilitation (step training), produced remarkable gains in voluntary motor function in persons with SCI [29, 47–49]. In a single case study, Harkema *et al.* [29] reported unexpected gains in bladder function per clinical assessments after activity-based training and epidural SCS, including gaining the ability to void voluntarily with minimal residual volume. To examine further the impacts of activity-based training and epidural SCS on bladder function, Herrity *et al.* conducted bladder mapping in an individual with motor-complete SCI. They quantified the effective stimulation parameters for reflexive voiding at 30 pulses per second (pps), which resulted in the lowest residual volumes. Four additional SCI research participants underwent epidural SCS across a range of parameters, and stimulation over the L5/S1 cord at 30 pps produced increases in voiding efficiency from approximately 0–5% without SCS to approximately 10–70% with SCS; however, bladder capacity remained unchanged [31].

It remains unclear whether improvements in bladder function following epidural SCS and accompanying step training were mediated directly by SCS or resulted from the locomotor training that was enabled by SCS. There is an interaction between the spinal networks controlling hindlimb locomotor function and those controlling the bladder [40, 50–52], and there is documented benefit to bladder function following step training in the absence of SCS [53, 54].

Meglio *et al.* [55] reported improvements in bladder spasticity and capacity, as well as decreased residual volumes with epidural SCS without activity-based training in six of seven research participants with SCI. Detrusor tone, assessed as basal bladder pressure, decreased from an average of 17 mmHg before stimulation to 8 mmHg with SCS, while bladder capacity increased from an average of 145 to 218 ml after SCS. Similarly, Darrow *et al.* reported improvements in bladder function as measured by the Neurogenic Bladder Symptom Score (NBSS) with epidural SCS in two female patients with SCI. One participant reported a 45% reduction in NBSS scores for the storage and voiding subdomain, and the other participant reported a 100% reduction in the NBSS score for the incontinence subdomain [35]. Moreover, Walter *et al.* reported urinary tract and bowel modulation, including changes in detrusor pressure (before stimulation: ∼5 cm H_2O; during stimulation: ∼5–13 cm H_2O) and pelvic floor electromyography (EMG) (before stimulation: ∼40 mV; during stimulation: ∼40–120 mV), in an SCI participant during stimulation with multiple different parameters (pulse widths: 300, 330, 390, and 450 μs; frequency: 25, 30, 40, and 45 Hz; intensity: 4, 6, and 7 V) [36]. Additionally, Schieferdecker *et al.* reported an 86% decrease in daily incontinence, 49% reduction in residual urine volumes, and 36% increase in the quality of life scores in persons with SCI undergoing epidural SCS at 10 kHz [56].

There are multiple commercial systems that employ epidural SCS to treat chronic pain (Abbott, Boston Scientific, Medtronic, Nevro), and this same Food And Drug Administration (FDA)-approved hardware could be employed to treat bladder dysfunction in persons with SCI, thereby creating a pathway to sustainable commercial availability and impact. Indeed, persons with SCI indicate a willingness for spinal cord-based implants, provided that a sensory rhizotomy is not required [57]. Thus, this approach has exceedingly strong potential for translation and commercialisation, a key consideration to making innovative therapies available to persons with SCI [58, 59].

In addition to implanted epidural approaches, non-surgical transcutaneous electrical and magnetic SCS produced improvements in bladder function in persons with SCI. Transcutaneous SCS at 1 Hz over the T11 spinal cord in six participants with SCI generated improvement in voiding efficiency from 27 to 51% and improved detrusor-sphincter coordination, as well as decreased residual volumes of urine in the bladder from 214 ml before SCS to 176 ml after SCS [37]. Moreover, stimulation applied at 30 Hz increased bladder capacity from 171 to 253 ml and improved detrusor-sphincter coordination. In one participant, transcutaneous SCS at 1 Hz over the T11 spinal cord allowed initiation of volitional voiding, resulting in a voiding efficiency of 37%; the participant was unable to voluntarily void prior to application of SCS [60]. In a proof-of-concept study, Niu *et al.* [61] examined the effects on bladder function of transcutaneous magnetic SCS in five clinical participants with SCI. After 16 weeks of transcutaneous magnetic SCS, all five participants were able to initiate volitional voiding. During the 16-week assessment period, each subject underwent SCS at both 1 and 30 Hz frequencies. Voided volumes increased from 0 cc/day before treatment to 1120 cc/day after 16 weeks of treatment, and bladder capacity increased from 244 ml before treatment to 404 ml after 16 weeks of treatment. The participants reported a decrease in daily self-catheterisation after 16 weeks of SCS therapy, and an increase occurred in the quality of life scores, as well.

Nashold *et al.* reported using intraspinal stimulation at S1–S2 through implanted electrodes to allow 4 persons with paraplegia to cease use of bladder catheters. Voided volumes ranged from 80 to 210 ml, while residual volumes ranged from 100 to 280 ml [62]. Using the same intraspinal paradigm, Carlsson and Fall reported an increase in bladder function in a person with paraplegia, who, with three successive stimulation sequences, could empty his bladder with minimal residual volume. After 7 years of using SCS for bladder emptying, the user fully developed the micturition reflex and was no longer reliant on SCS for voiding [63].

3.2. In animal models: Similar improvements in bladder function are observed in animal models of SCI with multiple modalities of SCS, both with and without activity-based training. To examine the effects of epidural SCS and step-training on bladder function, Gad *et al.* used a T8 spinal transection female rat with 6-weeks of step-training and epidural SCS between the L2 and S1 cord (1, 5, and 40 Hz stimulation frequencies). In acute measures of the effects of epidural SCS, 1 Hz was most effective for voiding, and voiding was completed within 90 s. Additionally, chronic step-training, in conjunction with epidural SCS, resulted in increased spontaneous voiding [30]. In a separate study, Gad *et al.* again used a T8 transection and epidural SCS between the L2 and

S1 spinal cord, as well as peripheral stimulation, to assess varying frequencies (1, 5, and 40 Hz) and amplitudes on bladder outcomes. EMG recordings from both the external urethral sphincter and the hindlimb muscles showed an overlap of spinal networks involved in both locomotor function and voiding, which can be further explored to determine stimulation parameters that can positively affect both locomotor and bladder function [40]. These studies corroborate the results from epidural SCS with activity-based training in persons with SCI, and further support that epidural SCS and activity-based training increase the excitability of spinal neural networks to enhance viscero-somatic interactions.

In spinally intact adult and aged rhesus macaques, Gad *et al.* mapped the responses in the lower urinary tract to transcutaneous SCS and showed activation of both the external urethral sphincter and the detrusor muscle [64]. Moreover, Havton *et al.* showed activation of the detrusor, external urethral sphincter, and pelvic floor muscles using transcutaneous SCS over either the L1/L2 or L3/L4 spinal cord in intact rhesus macaques. While voiding flow rate, detrusor contraction duration, and peak bladder pressures remained unchanged, voiding efficiency increased from 18% before SCS to 33% with SCS, and residual urine volumes decreased [65]. These studies suggest that transcutaneous SCS is a viable method for modulating the function of the lower urinary tract, and the results are consistent with the improved bladder function resulting from transcutaneous SCS in human SCI participants. Further, Guiho *et al.* found it was possible to increase both bladder and rectal pressures concomitantly using epispinal-intradural SCS in an intact pig, suggesting a mechanism through which both bladder and bowel dysfunctions could be addressed after SCI [66].

In addition to epidural and transcutaneous SCS, intraspinal and trans-spinal SCS approaches have been examined in animal models of SCI. Pikov *et al.* utilised intraspinal (dorsal horn) stimulation of the sacral spinal cord to examine bladder function following T12 transection SCI in the cat. Intraspinal stimulation at the S1 spinal cord proved most effective for bladder contractions and external urethral sphincter relaxation, which resulted in voiding in 15 out of 22 cats [67]. Furthermore, Ahmed utilised trans-spinal direct current SCS over the L2–L5 in spinally contused mice, which initiated voiding in mice without the voiding reflex. There were significant increases in external urethral sphincter activity, maximum bladder pressure, pudendal-EUS reflex amplitude, and voided volumes. Although there was no decrease in the number of non-voiding contractions, there was a lower detrusor overactivity/cystometry ratio with trans-spinal SCS. Overall, trans-spinal SCS enhanced the voiding reflex, and the results indicated there was a carry-over effect of increased pressure after stimulation was ended [68]. In neurologically intact cats, Grill *et al.* reported evoked bladder pressures by microstimulation in the intermediolateral region, pericanalicular grey, and the dorsal aspect of the sacral spinal cord, with larger bladder pressures evoked by microstimulation in the S2 segment [69]. Similarly, Tai *et al.* reported large-amplitude bladder contractions and voiding evoked by microstimulation of the S2 lateral ventral horn or the ventral funiculus in intact and chronic SCI cats, although voiding was incomplete with high residual volumes [70].

3.3. Mechanism of action: While the mechanisms through which SCS modulates bladder function remain unclear, it is hypothesised that SCS increases the excitability of appropriate spinal cord centres, and therefore, the excitability of the spinal reflexes necessary for proper bladder function [31]. SCS activates both afferent and efferent pathways [71], and thus, both peripheral sensory and supraspinal drivers of volitional function may be enabled through SCS [72]. In this regard, SCS likely allows the micturition circuitry in the sacral cord to respond appropriately to residual descending input from supraspinal micturition centres, enabling increases in storage and voiding reflexes, as well as volitional sphincter control.

It appears that transcutaneous approaches may share similar mechanisms to epidural approaches [47, 73, 74]. While epidural SCS may provide more targeted and focused stimulation, computer modelling of both epidural and transcutaneous SCS showed neuronal activation of targeted populations with both stimulation methods [75]. Computer simulations suggest posterior root fibres are stimulated both as they enter the spinal cord and exit the spinal canal. Further, effects of subthreshold polarisation of presynaptic axon terminals [76] and post-synaptic neurons [77] are well documented in the brain and produce profound effects on neuronal input–output functions [78]; similar mechanisms appear to operate in the spinal cord [79]. Therefore, subthreshold SCS may reduce the responsiveness of spinal reflex circuits to the increased sensory input from the bladder, which occurs following SCI, and thereby reduce NDO and DSD.

4. Challenges and future directions: As the mechanisms of action of SCS remain to be determined, the identification of optimal or even appropriate stimulation parameters and their translation between animal models and humans remains challenging, and the interaction between locomotor function and autonomic function after SCI is unclear. It remains to be determined if the same stimulation parameters can be used for the treatment of multiple dysfunctions (i.e. locomotor recovery versus restoration of bladder function) or if different stimulation parameters will be required. Additionally, there remains a gap in translating preclinical studies, all but one of which used complete spinal transection, to clinical applications, where the majority of injuries are incomplete. The goal of determining successful parameters for SCS requires the use of a more clinically relevant injury model, such as spinal cord contusion.

Moreover, in both animal models and human research participants, the most effective stimulation parameter may vary from subject-to-subject, and stimulation parameters that have been configured for one aspect of micturition (e.g. storage) may not be effective for another (e.g. efficient voiding) [31, 67]. Therefore, the mapping of responses to SCS is necessary to determine the optimal or even appropriate stimulation site(s) and parameters for the restoration of continence and efficient emptying, and the results should also help to increase understanding of mechanisms of action [28, 33]. Future studies of the effects of SCS on bladder function should include the evaluation of electrophysiological biomarkers that could be used to determine the most effective stimulation location and parameters without the necessity for exhaustive functional assessments. As well, these studies should determine the specific anatomical pathways that are activated by different sites and parameters of SCS. The determination of specific stimulation parameters for the restoration of target functions or the development of a method to determine appropriate parameters at the level of individual users would result in significant clinical impact.

The mitigation of bladder dysfunction in persons with SCI who underwent activity-based training in conjunction with epidural SCS suggests a role for vesico-somatic interactions, which may be enhanced through epidural SCS. It is important to consider the role of activity-based training in conjunction with SCS on bladder function versus epidural SCS alone, as activity-based training may not be a feasible therapeutic option for the entirety of the SCI population. Studies examining bladder function in SCI individuals with epidural SCS treatment alone may represent a wider therapeutic target throughout the SCI population. Finally, the outcomes in studies of both persons with SCI and SCI animal models examining the use of SCS for the treatment of bladder dysfunction are variable. There is little consistency in reported outcome measures, and appropriate controls are often lacking. Thus, challenges exist with comparisons between SCS paradigms and translation from animal models to human applications. Overall, the field would greatly benefit from a standardised battery of control and

outcome measures to be reported in future studies analysing the effects of SCS on bladder function after SCI.

Given the current hypotheses of the mechanism of action of SCS involving central activation and excitation of the micturition circuitry induced by SCS and subsequent promotion of plasticity at the level of the spinal cord, the long-term effects of SCS on bladder function should be examined in both animal models and persons with SCI. These studies should quantify short-term carry-over effects, long-term alterations in bladder function using both behavioural observations and cystometry, and long-term efficacy of specific electrode placements, configurations, and stimulation parameters.

Altogether, the number of persons with SCI who have been evaluated for alterations in bladder function with SCS is small, and the clinical significance and efficacy of SCS for the restoration of bladder function remain unclear. Small study sizes, other concomitant interventions, heterogeneity of the participants and interventions, and the small numbers of long-term studies make it difficult at present to determine therapeutic efficacy. Nonetheless, the paucity of other appropriate therapies and promising initial results point to the importance of continued efforts to advance SCS for the restoration of bladder function after SCI.

5. Conclusions: Urological complications are a leading cause of morbidity in persons with SCI, and impaired bladder function results in decreased quality of life, lower life satisfaction, and limits social contact [80, 81]. Not surprisingly, restoration of bladder function is consistently identified as a high priority for persons with SCI [8, 10, 11]. Current approaches to treat bladder dysfunction are inadequate, and novel approaches are required to restore continence with increased bladder capacity, as well as provide predictable and efficient on-demand voiding [12, 21]. Current studies in both animal models and persons with SCI examining the effects of epidural and transcutaneous SCS on bladder function suggest that these approaches are indeed viable methods for decreasing NDO and DSD, along with increasing volitional voiding, voided volumes, bladder capacity, and quality of life. Importantly, SCS is well-developed and commercially available for treating chronic neuropathic pain [82]. There are multiple commercial systems that employ SCS, and this same FDA-approved hardware could be employed to treat bladder dysfunction in persons with SCI, thereby creating a pathway to sustainable commercial availability and sustained impact.

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7 References

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