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REVIEW ARTICLE

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Early interventions to prevent lower urinary tract dysfunction after spinal cord injury: a systematic review

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STUDY DESIGN: Systematic review.
OBJECTIVES: To synthetise the available scientific literature reporting early interventions to prevent neurogenic lower urinary tract dysfunction (NLUTD) after acute supra-sacral spinal cord injury (SCI).
METHODS: The present systematic review is reported according to the PRISMA guidelines and identified articles published through April 2021 in the PubMed, Embase, ScienceDirect and Scopus databases with terms for early interventions to prevent NLUTD after SCI. Abstract and full-text screenings were performed by three reviewers independently, while two reviewers performed data extraction independently. An article was considered relevant if it assessed: an in-vivo model of supra-sacral SCI, including a group undergoing an early intervention compared with at least one control group, and reporting clinical, urodynamic, biological and/or histological data.
RESULTS: Of the 30 studies included in the final synthesis, 9 focused on neurotransmission, 2 on the inflammatory response, 10 on neurotrophicity, 9 on electrical nerve modulation and 1 on multi-system neuroprosthetic training. Overall, 29/30 studies reported significant improvement in urodynamic parameters, for both the storage and the voiding phase. These findings were often associated with substantial modifications at the bladder and spinal cord level, including up/downregulation of neurotransmitters and receptors expression, neural proliferation or axonal sprouting and a reduction of inflammatory response and apoptosis.
CONCLUSIONS: The present review supports the concept of early interventions to prevent NLUTD after supra-sacral SCI, allowing for the emergence of a potential preventive approach in the coming decades.

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Spinal cord injury (SCI) incidence is estimated to be between 40 and 80 new cases per million population, meaning that every year, between 250,000 and 500,000 new people become para- or tetra paretic worldwide [1]. Spinal cord injury is associated with mechanical insults and secondary processes, including local hypoxia, ischaemia, oxidative stress, reactive gliosis, excitotoxicity and scarring [2, 3]. Endogenous repair mechanisms in the central nervous system (CNS), especially at the spinal cord level, are negligible, with innate plasticity unable to re-establish the original connectivity [4]. Reorganising pathways by sprouting, unmasking, or other compensatory mechanisms may contribute to the dysfunction that develops following SCI. Since several and complex neural circuits localised at the spinal cord level contribute to the coordinated activity of the bladder and the urethral sphincters, SCI often leads to neurogenic lower urinary tract dysfunction (NLUTD).

This dysfunction emerges as follow: acute supra-sacral SCI starts with an initial phase of "spinal shock" resulting in detrusor and sphincter areflexia, followed by the emergence of a spinal reflex occurring after several weeks, resulting in both storage and voiding phase dysfunction, including detrusor overactivity (DO), bladder compliance disorders (BCD) and detrusor-sphincter dyssynergia (DSD) [5]. The emergence of urinary incontinence and recurrent urinary tract infections are responsible for significant loss of quality of life [6]. Despite many advances regarding their prevention and management over the last three decades, the associated complications are still considered the leading cause of hospitalisation and the fifth cause of mortality in this population [5, 7]. For storage dysfunction, several treatments are available in a therapeutic escalation strategy in order to restore a low-pressure bladder reservoir, including antimuscarinics, β3-adrenergic agonists, intra-vesical botulinum toxin injections, as well as tibial nerve stimulation (TNS) and sacral nerve modulation (SNM), before considering augmentation cystoplasty or other urinary diversions [8, 9]. With respect to voiding dysfunction, even if α-blockers can be proposed, clean intermittent self-catheterisation (CISC) constitutes the standard of care and is often the only way to ensure regular, complete, and low-pressure bladder emptying [8, 9].

To our knowledge, current international recommendations only focus on the management of NLUTD without addressing any prevention steps [8, 9]. Several groups have recently reported various early interventions, using neurotransmission, inflammatory response, neurotrophicity, electrical nerve modulation or

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neuroprosthetic training, to prevent or attenuate NLUTD after SCI, allowing for the emergence of a potential preventive approach in the coming decades.

The purpose of the present systematic review was to synthesise the scientific literature focusing on early interventions to prevent the emergence of NLUTD after acute supra-sacral SCI.

METHODS

Information source and search strategy

The review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [10]. We identified articles published through April 2021 in the PubMed, Embase, ScienceDirect and Scopus databases with MeSH and non-MeSH terms for early intervention to prevent or attenuate NLUTD after SCI (Supplementary Table 1). In order to be exhaustive, publications identified from references were added to the final synthesis if they were considered relevant, and an updated search was performed in July 2021.

Eligibility criteria

Eligibility criteria were defined per PICOS: Patient (P), Intervention (I), Comparator (C), Outcome (O), Study Design (S). An article was deemed appropriate if it assessed: an in-vivo model of supra-sacral SCI (human or animal) (P), including a group undergoing an early intervention—before DO, BCD or DSD has emerged—to prevent and/or attenuate storage and/or voiding phase dysfunction (I), compared with at least one control group not undergoing any early intervention (C), and reporting clinical, urodynamic, biological and/or histological data (O). No restriction on study type was established (S).

Study selection and data extraction

Abstract and full-text screenings were performed by three reviewers independently (NV, DS, PLD). Disagreement was resolved by discussion with the help of a fourth reviewer (XB). Two reviewers performed data extraction independently (NV, XB), and a standardised form was used to extract data on study methodology, characteristics of in vivo model, early intervention performed, and clinical, urodynamic, biological as well as histological outcomes. Any discrepancy concerning data extraction was resolved by discussion.

Risk of bias assessment

To assess the risk of bias (RoB), reports were reviewed by two reviewers independently (NV, XB) using the SYRCLE (SYstematic Review Center for Laboratory animal Experimentation [11]) tool to assess studies focusing on animal models, and the ROBINS-I (Risk of Bias in Non-Randomised Studies—of Interventions [12]) tool to assess studies focusing on humans. Any disagreement concerning the RoB assessment was resolved by discussion.

Data synthesis

Data synthesis was performed through a structured presentation detailing step by step the main results associated with early interventions focusing on (1) neurotransmission, (2) inflammatory response, (3) neurotrophicity, (4) electrical nerve modulation, and (5) neuroprosthetic training.

RESULTS

Study selection

A total of 3792 abstracts were retrieved. After removal of duplicates and abstract screening, 48 articles were deemed eligible for full-text screening, of which 30 were included in the final synthesis (Fig. 1, Supplementary Table 2).

Risk of bias of included studies

Of the 29 studies focusing on animals, 17 had an unclear RoB, and only 7 had an overall low RoB (Fig. 2). For the one human study, overall RoB was low (Fig. 3).

Study characteristics

Of the 30 studies, 9 focused on neurotransmission (Table 1), 2 on inflammatory response, 10 on neurotrophicity (Table 2), 9 on electrical nerve modulation and 1 on multi-system neuroprosthetic training (Table 3).

Models included rats in 20 studies, mice in 4, dogs in 4, minipigs in 1 and humans in 1. SCI was performed between T2 and T12 by spinal cord transection (SCT) in 17 studies, by Hemi-transection (SCHT) in 1, by spinal cord compression (SCC) in 10 and both by transection and compression in 1. The study focusing on human SCI exclusively included AIS A traumatic lesions. Of the clinical outcomes of interest, 28 studies reported on urodynamic parameters, 5 on metabolic cages or bladder diary data, and 3 on contractility tests of ex-vivo bladder strips. Tissues were analysed in 25 studies, including bladder in 18, spinal cord in 12, and dorsal root ganglia in 2.

Neurotransmission

Muscarinic pathway. Biardeau et al. [13] and Temeltas et al. [14] assessed the effect of early pre [13]- and post-synaptic [14] inhibitions of the muscarinic pathway in SCT rats. Evaluating subcutaneous fesoterodine fumarate [13] and bladder wall injections of botulinum toxin A [14], they both reported a significant improvement in cystometric pressure parameters [13, 14], associated with a significant decrease in bladder fibrosis and hyperplasia [14]. Interestingly, Biardeau et al. [13] showed an effect persistent after a 72h wash-out period and hypothesised that the early administration of an antimuscarinic drug could act not only through an acute pharmacological effect but also by countering pathological modifications of muscarinic pathways, mainly at the M2 and M3 receptor level. Similarly, Temeltas et al. [14] reported better histological and cystometric outcomes after early injections (day 7) when compared with late injections (day 28), but the differences were not statistically significant.

Adrenergic pathway. Lee et al. [15] and Kadewaka et al. [16] assessed the effect of early α-adrenergic inhibition in SCT rats through intraperitoneal tamsulosin [15] or oral naftopidil [16]. Arguing that an α_{1D}-adrenergic receptor localised in the detrusor can promote acetylcholine secretion [15] and facilitate vasoconstriction [16] at the bladder level, the authors reasoned that inhibition of such receptors could improve the SCI-induced bladder remodelling. Even if Lee et al. [15] reported no significant modification in cystometric pressure parameters—with a urodynamic study performed only 1 week after SCI—they reported bladder strips contractility in the presence of M3 antagonist to be significantly decreased in tamsulosin-treated SCI rats. Furthermore, in tamsulosin-treated SCI rats, pERK1/2 and Rho-kinase expressions—associated with the activation of muscarinic receptors, particularly M2 receptors—were reported to be increased and decreased, respectively. Kadewaka et al. [16] reported an increase in bladder compliance and voiding efficiency associated with a decrease in urethral pressure in naftopidil-treated rats. They also reported a decrease early after SCI in upregulation of ischaemia and fibrosis markers and collagen concentration at the bladder level.

Nitrergic pathway. Kadewaka et al. [16] also assessed the effect of early oral tadalafil administration, a phosphodiesterase type 5 inhibitor, thought to improve bladder tissue oxygenation. When comparing treated SCT rats with non-treated SCT rats, the authors found a decrease in upregulation fibrosis markers and collagen

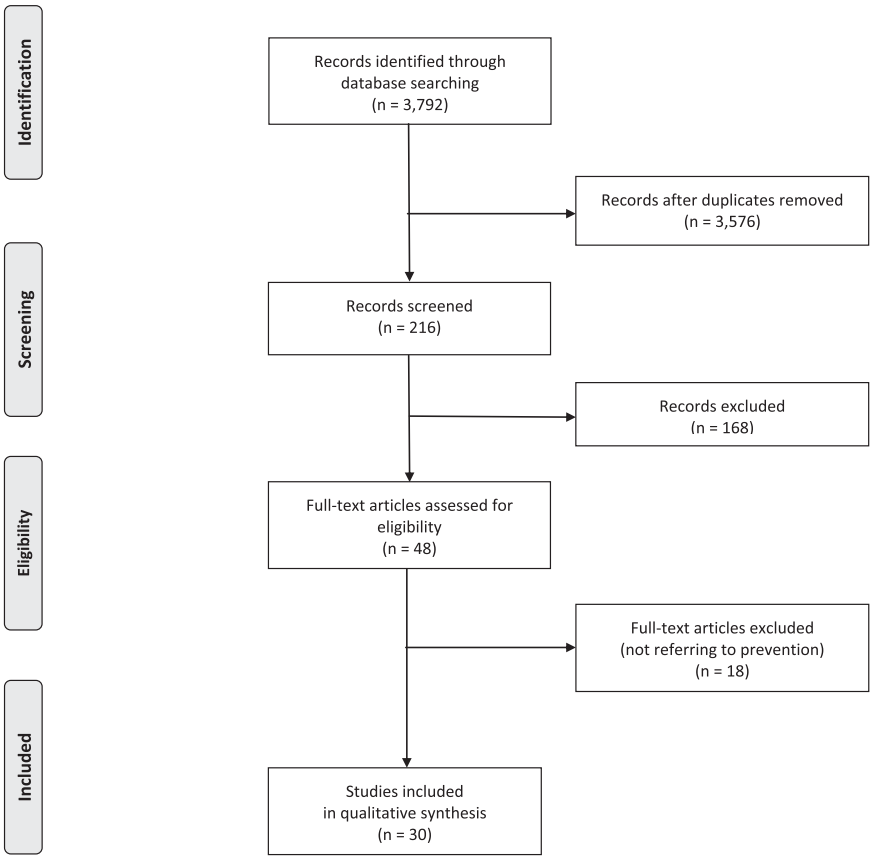
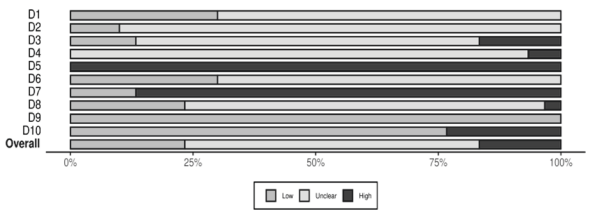


Fig. 1 PRISMA flow diagram.



Domains:
D1: Bias due to sequence generation.
D2: Bias due to baseline characteristics.
D3: Bias due to allocation concealment.
D4: Bias due to random housing.
D5: Bias due to blinding (performance).
D6: Bias due to random outcome assessment.
D7: Bias due to blinding (detection).
D8: Bias due to incomplete outcome data.
D9: Bias due to selective outcome data.
D10: Bias due to other source of bias.

Fig. 2 Risk of bias assessment—SYRCLE tool—Summary.

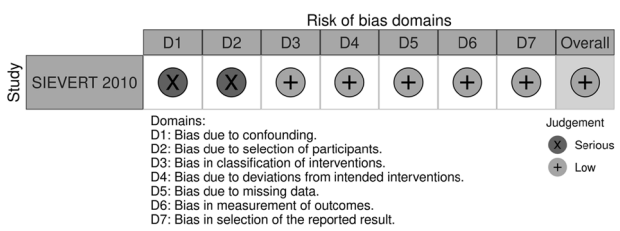


Fig. 3 Risk of bias assessment—ROBINS-I tool—Traffic-light plot.

concentration late after SCI, associated with an increase in bladder compliance.

Purinergic pathway. Munoz et al. [17] assessed the effect of early intrathecal instillation of P2X7R inhibitor in SCT rats. P2X7R is a purinergic receptor expressed in microglia that downplays proper tissue regeneration after SCI by enhancing inflammatory response and contributing to long-term scar formation. The authors showed a decrease in the number of non-voiding contractions (NVCs) associated with a decrease in microglial activation at the spinal cord level, and a concomitant decrease of urothelial P2X3—an ionotropic purinergic receptor involved in the transmission of bladder afferent activity—at the bladder level.

Glutamatergic pathway. Wang et al. [18] assessed the effect of a replication-defective herpes simplex virus vector of kynurenine aminotransferase (HSVrd KAT II) administered through an early bladder wall injection in SCT rats. The N-methyl-D-aspartate receptor (NMDAr), found in the lumbosacral spinal cord, is an ionotropic glutamatergic receptor that has been reported to play an essential role in the micturition reflex pathway. In parallel, kynurenic acid, synthesis of which is catalysed by KAT II, acts as an endogenous non-competitive antagonist at the glycine site of the glutamate NMDAr and has been reported to directly influence the micturition reflex. With KAT II protein and mRNA levels significantly increased at the L6-S1 spinal cord level, the authors found a significant decrease in maximum voiding pressure and maximum urethral closure pressure, associated with an increase in voiding efficiency in treated SCT rats when compared with non-treated SCT rats. They hypothesised that transport of KAT II to Onuf's nucleus and then to L6-S1 parasympathetic preganglionic neurons could reduce the urethral pressure by blocking NMDAr,

Table 1. Characteristics of studies focusing on neurotransmission.

First author Year Reference	In-vivo model	Level of SCI Type of SCI	Intervention Mode of administration	Groups (delay after SCI)	Clinical and urodynamic outcomes (delay after SCI)	Biology and tissue analysis outcomes (delay after SCI)
Muscarinic pathway						
BIARDEAU 2017 Ref. [13]	Rats	T10 Transection	Fesoterodine Sub-cutaneous	3 non-SCI 6 SCI 6 SCI + Fesoterodine 0.12 mg/kg (d0) 6 SCI + Fesoterodine 0.18 mg/kg (d0) 6 SCI + Fesoterodine 0.12 mg/kg (d0) + 72 h WO 6 SCI+ Fesoterodine 0.18 mg/kg (d0) + 72 h WO	Metabolic cages (d21, 28, 35) Voided volume; Voiding frequency Urodynamic-awake-supra-pubic (d42) Baseline pressure; Intermicturition pressure; Treshold pressure; Maximum pressure; Bladder capacity; Voided volume; Post-void residual volume	
TEMELTAS 2005 Ref. [14]	Rats	T9-T10 Transection	Onabotulinum-A toxin Bladder wall injection	6 non-SCI 6 SCI 5 SCI + Onabotulinum-A toxin 2-3U (d7) 5 SCI + Onabotulinum-A toxin 2-3U (d28) 5 SCI + vehicle (d28)	Urodynamic-anesthetized-urethral (d0, d42) Baseline pressure; Opening pressure; Frequency and Amplitude of NVC Bladder capacity	Bladder tissue (d42) Fibrosis; Epithelial desquamation; Hyperplasia
Adrenergic pathway						
KADEKAWA 2017 Ref. [16]	Rats	T9-T10 Transection	Naftodipil/Tadalafil Oral	6/8 non-SCI 6/8 SCI + vehicle (d7) 6/8 SCI + Naftopidil 20 mg/kg/day (d7) 6/8 SCI + Tadalafil 2 mg/kg/day (d7)	Urodynamic-anesthetized urethral/supra-pubic (d14, 28, 56, 84) Bladder capacity; Intercontraction interval; Maximum voiding pressure; Baseline pressure; Number of NVC; Voided volume; Post-void residual volume; Urethral pressure	Bladder (d7,14, 28, 56, 84) Weight Collagen (type 1,3); Elastin TGF-β1; HIF-1α; VEGF
LEE 2014 Ref. [15]	Rats	T10 Transection	Tamsulosin Intra-peritoneal instillation	12 non-SCI 12 SCI 21 SCI + Tamsulosine 0.1 mg/kg (d0)	Urodynamic-awake-supra-pubic (d7) Baseline pressure; Maximunl pressure; Voided volume; Voiding frequency Ex-vivo bladder strips contractility (d7) Acetylcholine ± M2 antagonist and M3 antagonist	Bladder (d7) ERK1/2; pERK1/2; rho-kinase
Nitrinergic pathway						
KADEKAWA 2017 Ref. [16]	Rats	T9-T10 Transection	Naftodipil/Tadalafil Oral	6/8 non-SCI 6/8 SCI + vehicle (d7) 6/8 SCI + Naftopidil 20 mg/kg/day (d7) 6/8 SCI + Tadalafil 2 mg/kg/day (d7)	Urodynamic-anesthetized urethral/supra-pubic (d14, 28, 56, 84) Bladder capacity; Intercontraction interval; Maximum voiding pressure; Baseline pressure; Number of NVC; Voided volume; Post-void residual volume; Urethral pressure	Bladder (d7,14, 28, 56, 84) Weight Collagen (type 1,3); Elastin TGF-β1; HIF-1α; VEGF
Purinergic pathway						
MUNOZ 2017 Ref. [17]	Rats	T8-T9 Transection	P2X7R inhibitor Intrathecal instillation	6 non-SCI 6 SCI 6 SCI + vehicule (d0) 6 SCI + P2X7R antagonist (d0)	Urodynamic-anesthetized-supra-pubic (d28) Maximum voiding pressure; Duration of intra-luminal pressure HFO Frequency of NVC; Voided volume	Bladder (d28) P2X3R Spinal cord (d28) P2X7R
Glutamatergic pathway						
WANG 2017 Ref. [18]	Rats	T10 Transection	HSVrd KAT II Urethral wall injection	12 SCI + vehicle (d7) 12 SCI + HSVrd (d7) 12 SCI + HSVrd KAT II (d7)	Urodynamic-anesthetized-supra-pubic (d21) Maximum urethral closure pressure; Number and amplitude of NVC; Maximum voiding pressure Bladder capacity; Voided volume; Voiding efficiency; Time to first NVC; voiding time	Spinal cord (d28) KAT II Actin Ratio of KAT II/actin KAT II mRNA

Table 1. continued

First author Year Reference	In-vivo model	Level of SCI Type of SCI	Intervention Mode of administration	Groups (delay after SCI)	Clinical and urodynamic outcomes (delay after SCI)	Biology and tissue analysis outcomes (delay after SCI)
GABAergic pathway						
MIYAZATO 2010 Ref. [19]	Rats	T9-T10 Transection	HSV GAD Bladder wall injection	*Experiment 1* 10 SCI (d7) 8 SCI + HSV LacZ (d7) (control) 10 SCI + HSV GAD (d7) *Experiment 2* 5 SCI + HSV GAD (d7) Intrathecal GABA-r antagonist during UDS *Experiment 3* 4 SCI + HSV LacZ (d7) (control) 4 SCI + HSV GAD (d7)	*Experiment 1* Urodynamic-awake-urethral/supra-pubic (d28) Baseline urethral pressure; Urethral pressure at the peak of bladder contractions; Interval and Amplitude of bladder contractions; Baseline intra-vesical pressure *Experiment 2* Urodynamic-awake-urethral/supra-pubic (d28) *Before/After Intrathecal GABA receptor antagonist* Baseline urethral pressure; Urethral pressure at the peak of bladder contractions; Interval and Amplitude of bladder contractions; Baseline intra-vesical pressure	*Experiment 3* Dorsal root ganglia (d28) GAD mRNA
TRPV1 desensitisation						
OLIVEIRA 2019 Ref. [20]	Rats	T8-T9 Transection	Resiniferatoxin Bladder instillation	4 sham SCI 4 SCI control 4 SCI + vehicle (d0) 8 SCI + vehicle (d3 and d9) 4 SCI + Resiniferatoxin 50 nM (d0) 8 SCI + Resiniferatoxin 50 nM (d3 and d9) 4 SCI sham + vehicle (d3 and d9) 4 SCI sham + Resiniferatoxin 50 nM (d3 and d9)	Urodynamic-anesthetized-supra-pubic (d28) Frequency and Amplitude of NVC; Baseline and Peak pressure of NVC	Bladder (d28) TRPV1; CGRP; GAP43 Spinal cord + dorsal root ganglia (d28) CGRP; GAP43 Dorsal root ganglia culture (d28) Quantification of neurite branching; Quantification of total neurite length ATF3;
THOMAS 2007 Ref. [21]	Rats	T9-T10 Transection	Capsaicin Sub-cutaneous	6 SCI 5 SCI + capsaicin (d-4 and d5) 6 SCI + capsaicin (d28)	Urodynamic-awake-supra-pubic (28) Intercontraction intervals; Voiding pressure; Number of NVC; Voiding efficiency; External urethral sphincter EMG (d28) (In 2 SCI rats)	

Ref: refers to on-line supplement (Supplementary Table 2).
SCI spinal cord injury, *NVC* non-voiding contraction, *ERK1/2* extracellular signal-regulated kinases 1/2, *pERK1/2* phosphorylated extracellular signal-regulated kinases 1/2, *TGF-β1* transforming growth factor beta 1, *HIF-1α* hypoxia inducible factor 1 alpha, *VEGF* vascular endothelial growth factor, *GABA* gamma-aminobutyric acid, *EMG* electromyogram, *HSVrd* replication-defective herpes simplex virus vector, *GAD* glutamic acid decarboxylase, *UDS* urodynamic study, *KAT II* kynurenine aminotransferase, *P2X3* P2X purinergic receptor 3, *P2X7* P2X purinergic receptor 7, *TRPV1* Transient receptor potential vanilloid 1, *GAP43* growth-associated protein 43, *CGRP* calcitonin gene-related peptide, *ATF3* activating transcription factor 3.

Table 2. Characteristics of studies focusing on inflammatory response and neurotrophicity.

First author Year Reference	In-vivo model	Level of SCI Type of SCI	Intervention Mode of administration	Groups (delay after SCI)	Clinical and urodynamic outcomes (delay after SCI)	Biology and tissue analysis outcomes (delay after SCI)
Inflammatory response						
SHUNMUGAVEL 2015 Ref. [22]	Rats	T9-T10 Compression	GSNO Oral	12 SCI 10 SCI + vehicle (h1) 10 SCI + GSNO (h1)	Urodynamic-anesthetized-supra-pubic (d2, 14) Intercontraction intervals; Voiding pressure Number of voidings; Voided volume	Urinanalysis (d2, 14) Weight; Protein; Osmolality Bladder (d2, 14) Weight; Detrusor morphology ICAM-1; iNOS; TUNEL-positive cells Kidney (d2, 14) ICAM-1; iNOS; TUNEL-positive cells
DAVID 2014 Ref. [23]	Mice	T8 Compression	TLR9 inhibitor Intrathecal instillation	X non-SCI X SCI + vehicle (d1) X SCI + TRL9 inhibitor (CpG ODN 2088), (d1)	Evaluation of bladder function Weight of urine voided (every 12h) Water intake (every 48h)	Urinanalysis (d7, 14, 28) Ketones; Bilirubin; Protein, Nitrites; Leucocytes; pH Bladder (d28) Bladder weight and volume; Bladder wall thickness Kidney (d28) Glomerulopathy; Interstitial inflammation; Fibrosis Spinal cord (d28) Lesion volume; Spared white and grey matter
Neurotrophicity						
Axonal growth inhibitors antagonists						
MOTHE 2020 Ref. [24]	Rats	T8-T9 Compression	Elazanumab Intra-veinous	8 SCI 10 SCI + Elazanumab 25 mg/kg (h0) 9 SCI + Elazanumab 25 mg/kg (h3) 8 SCI + Elazanumab 25 mg/kg (h24) 9 SCI + hIgG (h0) (control)	Voiding ability Ability to void on its own And without requiring manual pressure And during 3 consecutive days	Bladder (d84) Thickness of the detrusor muscle layer Spinal cord (d84) Percentage of lesion area Anterograde axonal tracing with BDA Immunostaining NeuN; 5-HT; BDA
SCHNEIDER 2019 Ref. [25]	Rats	T8 Transection	Anti-Nogo A antibodies Intrathecal instillation	17 non-SCI 17 incomplete SCI + vehicle (d0) 16 incomplete SCI + Anti-Nogo A (d0) 10 complete SCI + vehicle (d0) 11 complete SCI + Anti-Nogo A (d0)	Urodynamic-awake-supra-pubic + External urethral sphincter EMG (d7,14,21,28) Maximum detrusor pressure; Bladder compliance Maximum flow rate; Voiding time; Voided volume External urethral sphincter EMG analysis	Spinal cord Percentage of spared white matter; CRF; Glycinergic interneurons; GABAergic nterneurons; Glutamatergic interneurons
Neurotrophic factors						
WADA 2020 Ref. [26]	Mice	T8-T9 Transection	BDNF inhibitor Sub-cutaneous	29 SCI 16 SCI + anti-BDNF antibodies (d7) 16 SCI + anti-BDNF antibodies (d27)	Urodynamic-awake-supra-pubic (d10,20,30) Bladder capacity; Number of NVC; Treschold pressure; Maximum voiding pressure; Voided volume; Post-void residual volume; Voiding efficiency; Notch-like periods *(synergistic activity between the bladder and the external urethral sphincter)*	Bladder (d2, 14) BDNF
WADA 2018 Ref. [27]	Mice	T8-T9 Transection	NGF inhibitor Sub-cutaneous	10 SCI 10 SCI + anti-NGF for 7 days (d21) 8 SCI + anti-NGF for 14 days (d21)	Urodynamic-awake-supra-pubic + External urethral sphincter EMG (d28) Bladder capacity; Number of NVC; Treschold pressure; Maximum voiding pressure; Voided volume; Post-void residual volume; Voiding contraction time EMG activity duration	Bladder (d28) NGF TRPA1; TRPV1; P2X3 Spinal cord (d28) NGF
MITSUI 2004 Ref. [28]	Rats	T8-T9 Compression	Fibroblasts expressing BDNF/NT3 Intrathecal instillation	6 non-SCI 11 SCI + vehicle (d9) 12 SCI + Fb-BDNF/NT3 (d9)	Urodynamic-awake-supra-pubic (d56) Maximum voiding pressure; Frequency of NVC; Bladder capacity; Voided volume; Post-void residual volume;	Spinal cord (d56) Volume of normal spinal cord 5-HT; CRF; GAP43; CGRP VR-1; DβH; synaptophysin
CHUNG 2015 Ref. [30]	Rats	T8 Transection Compression	Inosine Intra-peritoneal instillation	5 SCI (transection) + vehicle(d0) 4 SCI (transection) + Inosine (d0) 6 SCI (compression) + vehicle (d0) 5 SCI (compression) + Inosine (d0)	Urodynamic-awake-supra-pubic (d42) *(d98 if intervention = d56)* Frequency and Amplitude of NVC; Compliance; Peak pressure; Voided volume	Bladder (d42) SYP; NF200; TRPV1; VAChT

Table 2. continued

First author Year Reference	In-vivo model	Level of SCI Type of SCI	Intervention Mode of administration	Groups (delay after SCI)	Clinical and urodynamic outcomes (delay after SCI)	Biology and tissue analysis outcomes (delay after SCI)
				6 SCI (compression) + vehicle (d56) 3 SCI (compression) + inosine (d56)	Ex-vivo bladder strips contractility (d42) Phenylephrine; Carbachol; Electrical field stimulation; α,β- methylene-ATP	
MURE 2004 Ref. [29]	Mice	T8 Compression	DHEA Sub-cutaneous + Oral + Lesion site	12 SCI + vehicle (d0) 12 SCI + DHEA (d0) 10 sham SCI + vehicle (d0) 6 sham SCI + DHEA (d0) 10 SCI + vehicle (d0) 10 SCI + DHEA (d0)	Voiding ability Ability to void in response to external stimuli; Or Ability to void spontaneously	Bladder (d42) Thickness of the detrusor muscle layer Number of neuclei in the detrusor Collagen type I and III Spinal cord (d42) Area of spared white matter
Neural precursor cells						
MITSUI 2011 Ref. [31]	Rats	T8-T9 Compression	NRP/GRP + NBQX Intrathecal instillation	10 SCI 10 SCI + NRP/GRP (d9) 10 SCI + NBQX (d0) + NRP/GRP (d9)	Metabolic cages (d-1, 7, 14, 21, 28, 35, 42, 49, 56) Voided volume per micturition Urodynamic-awake-supra-pubic (d56) Maximum voiding pressure; Frequency of NVC; Bladder capacity; Voided volume; Post-void residual volume;	Spinal cord (d56) Volume of normal spinal cord Projection patterns at L6-S1
MITSUI 2005 Ref. [33]	Rats	T8-T9 Compression	NRP/GRP Intrathecal instillation	6 non-SCI 10 SCI 10 SCI + NRP GRP (d9)	Metabolic cages (d-1, 7, 14, 21, 28, 35, 42, 49, 56) Voided volume per micturition Urodynamic-awake-supra-pubic (d56) *Before/After Intrathecal Tamsulosin* Maximum voiding pressure; Frequency of NVC; Bladder capacity; Voided volume; Post-void residual volume	Spinal cord (d56) Volume of normal spinal cord Projection patterns at L6-S1 MAP2; RIP; NeuN; GFAP; nestin: SYP
MITSUI 2003 Ref. [32]	Rats	T8-T9 Compression	EG6 *immortalised neural stem cells* Intrathecal instillation	6 SCI + vehicle(d9) 6 SCI + EG6 cells BrdU labelled(d9)	Metabolic cages (d14, 28) Voided volume per micturition Urodynamic-awake-supra-pubic (d28) Intra-vesical pressure; Bladder capacity; Voided volume; Post-void residual volume;	Spinal cord (d56) BrdU immunoreactive-cells

Ref: refers to on-line supplement (Supplementary Table 2).

SCI spinal cord injury, *GSNO* S-Nitrosoglutathione, *ICAM-1* intercellular adhesion molecule 1, *iNOS* inducible nitric oxide synthase, *TUNEL* terminal deoxynucleotidyl transferase-mediated biotinylated UTP nick end labelling, *TLR9* toll-like receptor 9, *hIgG* human immunoglobulin G, *TLR9* toll-like receptor 9, *BDA* biotinylated dextran amine, *5-HT* 5-hydroxytryptamine, *CRF* corticotropine releasing factor, *BDNF* brain-derived neurotrophic factor, *EMG* electromyogram, *NGF* nerve growth factor, *TRPA1* transient receptor potential cation channel A1, *TRPV1* transient receptor potential vanilloid 1, *P2X3* P2X purinergic receptor 3, *NT3* Neurotrophin 3, *GAP43* growth-associated protein 43, *CGRP* calcitonin gene-related peptide, *VR1* vanilloid receptor type 1, *DβH* dopamine-beta-hydroxylase, *NVC* non-voiding contraction, *SYP* synaptophysin, *NF200* neurofilament 200, *TRPV1* Transient receptor potential vanilloid 1, *VAChT* anti-vesicular acetylcholine transferase, *DHEA* dehydroepiandrosterone, *NRP* neuronal restricted precursor, *GRP* glial restricted precursor, *NBQX* 2,3-dihydroxy-6-nitro-7 sulfamoylbenzo(f)quinoxaline, *MAP2* microtubule-associated protein-2, *RIP* receptor interacting-protein, *GFAP* glial fibrillary acidic protein, *BrdU* 5-bromo-2-deoxyuridine.

Table 3. Characteristics of studies focusing on electrical nerve modulation and multi-system neuroprosthetic training.

First author Year Reference	In-vivo model	Level of SCI Type of SCI	Intervention Mode of administration	Groups (delay after SCI)	Clinical and urodynamic outcomes (delay after SCI)	Biology and tissue analysis outcomes (delay after SCI)
Electrical nerve modulation						
Pudendal nerve modulation						
KELLER 2019 Ref. [34]	Minipigs	T11-T12 Compression	Nerve modulation Pudendal, unilateral Sacral S3, unilateral	3 SCI 4 SCI + PNM 10 Hz (d7) 4 SCI + SNM 10 Hz (d7)	Urodynamic-awake-urethral + peri-anal skeletal muscle EMG (d7, then every week until d112) Detrusor overactivity; Maximum voiding pressure Compliance; Bladder capacity Intravesical pressure Leak point pressure; Electromyographic activity	Bladder (d112) Wall thickness Wall composition and structure
LI 2013 Ref. [35]	Dogs	T9-T10 Transection	Nerve modulation Pudendal	3 SCI 3 SCI + PNM 5 Hz (d1)	Urodynamic-anesthetized-urethral (d0, 30, 90) Number of NVC; Bladder Compliance; Bladder capacity	Bladder (d90) Collagen fibres; Elastin fibres
CHEN 2012 Ref. [36]	Dogs	T9-T10 Transection	Nerve modulation Pudendal	4 SCI + PNM 5 Hz *during UDS* (d30) 4 SCI + PNM 5 Hz *during UDS* (d180)	Urodynamic-anesthetized-urethral (d30, 180) Number of NVC; Bladder Compliance; Bladder capacity	Bladder (d90) Collagen fibres; Elastin fibres
Sacral nerve modulation						
KELLER 2019 Ref. [34]	Minipigs	T11-T12 Compression	Nerve modulation Pudendal, unilateral Sacral S3, unilateral	3 SCI 4 SCI + PNM 10 Hz (d7) 4 SCI + SNM 10 Hz (d7)	Urodynamic-awake -urethral + peri-anal skeletal muscle EMG (d7, then every week until d112) Detrusor overactivity; Maximum voiding pressure Compliance; Bladder capacity Intravesical pressure Leak point pressure; Electromyographic activity	Bladder (d112) Wall thickness Wall composition and structure
LEE 2019 Ref. [37]	Rats	T9-T10 Compression	Nerve modulation Sacral S2-S3, bilateral	7 non-SCI 7 SCI + sham SNM (d7) 7 SCI + SNM 20 Hz (d7)	Urodynamic-anesthetized-urethral (d35) Interval between bladder contractions; Maximum voiding pressure; Number of NVC; Maximum NVC pressure	
SHI 2015 Ref. [38]	Rats	T9-T10 Transection	Nerve modulation Sacral S1, unilateral	1 SCI + SNM *during 6 h* (d7) 1 SCI + SNM *during 6 h* (d12) 1 SCI + SNM *during 6 h* (d15) 1 SCI + SNM *during 6 h* (d18) 1 SCI + SNM *during 6 h* (d20) 1 SCI + SNM *during 6 h* (d27) 1 SCI + SNM *during 6 h* (d36) 1 SCI + SNM *during 6 h* (d42)	Urodynamic-anesthetized-urethral (before and after 6-h SNM) Interval between bladder contractions; Bladder contractions duration; Peak bladder pressure; Number of NVC	
HASSOUNA 1992 Ref. [39]	Dogs	T10 Transection	Nerve modulation Sacral, bilateral	6 chronic SCI + intermittent catheterisation 6 chronic SCI + undwelling catheterization	Cystography Vesico-ureteral reflux Intra-venous pyelography Degree of hydronephrosis Urodynamic-awake-urethral	Blood parameters Creatinine; Urea

Table 3. continued

First author Year Reference	In-vivo model	Level of SCI Type of SCI	Intervention Mode of administration	Groups (delay after SCI)	Clinical and urodynamic outcomes (delay after SCI)	Biology and tissue analysis outcomes (delay after SCI)
				6 chronic SCI + SNM 20–60 Hz (long-term experiment)	(every week during 1 m, then every month during 5 m) Return of detrusor activity Maximum intra-vesical pressure Spontaneous voiding Bladder capacity	
LI 1992 Ref. [40]	Dogs	T10 Transection	Nerve modulation Sacral	5 SCI + intermittent catheterization (IC) (d0) 5 SCI + IC (d0) followed by SNM (w4–6) 5 SCI + SNM (d0) 5 SCI + SNM (d0) followed by IC (w4–6)	Cystography Vesico-ureteral reflux Bladder neck; Bladder contour Intra-venous pyelography Degree of hydronephrosis Urodynamic-anesthetized-urethral (m6–8) (every week during 1 m, then every month during 5–7 m) Amplitude and Duration of bladder contractions Bladder capacity Post-void residual volume Ex-vivo bladder strips contractility (m6-8) Urecholine	Bladder (m6–8) Acetylcholine content
SIEVERT 2010 Ref. [41]	Humans	T2-T11 Traumatic ASIA A	Nerve modulation Sacral S3, bilateral	6 SCI 10 SCI + SNM, bilateral (m2.9; 0.8–4.5)	Three-day Bladder diary (m3, 6) Bladder capacity Urinary incontinence Urinary tract infections Quality of life-Auto-questionnaires (m3, 6) Video-Urodynamic-awake-urethral + peri-anal skeletal muscle EMG (m3, m6, then every 6 monts) Detrusor overactivity Compliance Bladder capacity Electromyographic activity	
Multi-system neuroprosthetic training						
HORST 2013 Ref. [42]	Rats	T7 + T11 Bilateral hemi-section	Multi-system neuroprosthetic training (MSNT program)	4 non-SCI 4 SCI + Partial MSNT program (d7) *(Epidural stimulation alone)* 4 SCI + Complete MSNT program (d7) *(Epidural stim. + Locomotor training + 5-HT + dopamine)*	Urodynamic-anesthized-urethral (d56) Number of NVC; Bladder capacity; Leak point pressure;	Blood analysis (d56) Creatinine; Cystatin C Bladder (d56) Detrusor thickness PGP-9.5; NPY; NF200; TH; VAChT

Ref: refers to on-line supplement (Supplementary Table 2).
SCI spinal cord injury, *EMG* electromyogram, *PNM* pudendal nerve modulation, *SNM* sacral nerve modulation, *NVC* non-voiding contraction, *UDS* urodynamic study, *PGP-9.5* protein gene product 9.5, *NPY* Neuropeptide Y, *NF200* neurofilament 200, *TH* tyrosine hydroxylase, *VAChT* anti-vesicular acetylcholine transferase.

influencing neurotransmitter levels in the L6-S1 spinal cord and even desensitising C-fibre afferents.

GABAergic pathway. Miyazato et al. [19] assessed the effect of HSVrd Glutamic acid decarboxylase (GAD) administered through an early bladder wall injection in SCT rats. GAD is an enzyme that catalyses the decarboxylation of glutamate to GABA and contributes to maintaining the significant physiological supply of GABA. Hypofunction of inhibitory GABAergic neuronal activity in the spinal cord after SCI has been suspected of contributing to the genesis of DSD and DO. The authors reported a significant association between GAD mRNA increased expression in L6-S1 dorsal root ganglia (DRG) and a voiding urethral pressure decrease. Meanwhile, they did not identify associated differences regarding bladder activity and baseline urethral pressure. The intrathecal administration of a GABA antagonist almost completely reversed the decrease in the voiding urethral pressure. The authors hypothesised that GABA synthesis in bladder afferent pathways could inhibit Onuf's nucleus that innervates the external urethral sphincter (EUS) via the suppression of C-fibre bladder afferent activity to decrease DSD.

TRPV1 desensitisation. Two studies assessed the effect of early administration of resiniferatoxin [20] or capsaicin [21] in SCT rats, using subcutaneous administration [21] or bladder [20] instillation. Capsaicin and resiniferatoxin, one of its derivatives, are ultrapotent desensitising agonists of the transient receptor potential vanilloid-1 (TRPV1) known to be increased in urothelial cells and nerve fibres in the case of neurogenic DO. The authors reported an increased bladder capacity [20] and a decrease in the number of NVCs [21], with some of the rats presenting with complete suppression of DO [21]. However, Thomas et al. reported no significant improvement in the intercontraction interval, voiding pressure or voiding efficiency, or in EUS activity during both NVCs and voiding bladder contractions. Oliveira et al [20] showed after bladder instillation of resiniferatoxin decreased expressions of TRPV1, calcitonin gene-related peptide (CGRP)—two markers of peptidergic fibres—and growth-associated protein 43 (GAP43)—a marker of sprouting nerve fibres—at the bladder level, with no modification of CGRP and GAP43 expression or in the number of activating transcription factor 3 (ATF3) positive nuclei—a marker of neuronal stress—in the L5-S1 DRG. The authors hypothesised that the early administration of vanilloid therapy might mitigate the development of high intra-vesical pressures, in a long-lasting manner. It might prevent C-fibre afferents becoming hyperexcitable [21] by inhibiting peptidergic fibres at the bladder level [20], without inducing damage to the DRG neurons [20].

Inflammatory response

Shunmugavel et al. [22] assessed the effect of early oral administration of S-Nitrosoglutathione (GSNO) in SCC rats. GSNO, an endogenous nitrosylating agent, has anti-inflammatory properties. Since it has been reported to ameliorate inflammatory sequelae observed in the bladder and renal tissues after SCI, the authors postulated that GSNO would improve the recovery of micturition dysfunction by reducing the bladder tissue inflammation associated with SCI. They reported that GSNO-treated SCI rats regained significant micturition control compared to vehicle-only SCI rats. They also found a significant decrease in bladder weight, proteinuria, urine osmolality, and immune cell infiltration and collagen deposition at the bladder level. They also reported a decrease in iNOS and ICAM-1 (mediator of inflammation expression) at the bladder and kidney level, associated with a decrease of TUNEL-positive cells at the bladder level, indicating a decrease in the apoptotic process.

David et al. [23] assessed the effect of early intrathecal instillation of the Toll-like Receptor 9 (TR9L) inhibitor in SCC mice. TLR9 is a receptor expressed in the immune system cells that triggers signalling cascades, leading to a pro-inflammatory cytokine response. The authors reported a significant decrease in urinary retention associated with decreased bladder weight, bladder volume and bladder wall thickness. At the spinal cord level, they reported the white matter to be significantly more spared.

Neurotrophicity

Axonal growth inhibitors antagonists. Mothe et al. [24] and Schneider et al. [25] assessed the effect of early antagonization of axonal growth inhibitors using intravenous administration of elazanumab [24], a human monoclonal antibody targeting Repulsive Guidance Molecule (an RGMa), and intrathecal administration of anti-Nogo A [25] in SCC and SCT rats, respectively. RGMa is a potent inhibitor of axonal growth that has been reported to be rapidly upregulated after injury of the central nervous system. In contrast, myelin-enriched membrane protein Nogo-A, a potent nerve fibre growth inhibitory protein, has been reported to be implicated in the low level of spontaneous neuronal regeneration after SCI. The authors reported an earlier spontaneous voiding ability [24] associated with a decrease in bladder wall hypertrophy [24], a decrease in EUS EMG activity [24], as well as a significant decrease of maximum bladder pressure during voiding [25]. Mothe et al. [24] also found more remarkable tissue preservation at the spinal cord level, characterised by reduced lesion areas associated with increased perilesional neuronal sparing as well as serotonergic and corticospinal axonal plasticity. Schneider et al. [25] found higher densities of fibres originating from the pontine micturition centre in the lumbosacral grey matter, and a decreasing number of inhibitory interneurons in lamina X. The authors hypothesised that early and temporary neutralisation of the neurite growth inhibitory factor Nogo-A might contribute to the reconfiguration of bladder control at spinal and supraspinal levels.

Neurotrophic factors. Two studies assessed the effect of early inhibition of neurotrophic factors in SCT mice, using oral administration of brain-derived neurotrophic factor (BDNF) [26] and nerve growth factor (NGF) [27] inhibitors. Although both reported a significant decrease in cystometric pressure parameters [26, 27], BDNF inhibition only reduced NVCs in a late phase following SCI, while NGF inhibition acted earlier after SCI. Furthermore, while BDNF inhibitors improved voiding dysfunction [26], NGF inhibitors did not modify EUS EMG activity [27]. After NGF-inhibitor treatment, NGF expression was decreased at the bladder and the spinal cord level, while TRPA1 and TRPV1 expressions—predominantly found in C-fibre afferent pathways—were significantly decreased in L6/S1 dorsal root ganglia (DRG) [27]. The authors concluded that short- to long-term BNDF inhibition could improve voiding dysfunction associated with DSD, while a long-term BNDF inhibition was required to reduce the later-phase development of C-fibres-dependent DO. On the other hand, NGF inhibition could precociously slow down TRPV1 upregulation, attenuate C-fibres activation and thus prevent the early emergence of DO.

Mitsui et al. [28] assessed the effect of early intrathecal administration of fibroblasts (Fb) expressing BDNF and Neurotrophin 3 (NT3) in SCC rats. According to the authors, BDNF and NT3 act as neurotrophic factors on specific neurons of the central and peripheral nervous system, helping to support the survival of existing neurons, and encouraging growth and differentiation of new neurons and synapses. The authors reported a significant decrease in voiding pressure and in the number of NVCs. The density of small dorsal root axons increased in the superficial layers of the dorsal horn in non-treated SCI rats but not in Fb-BDNF/NT3-treated SCI rats, suggesting inhibition of sprouting of primary afferents by Fb-BDNF/NT3. Synaptophysin immunoreactivity in the lumbosacral dorsal horn was similar in treated and non-treated SCI rats, consistent with restoring synaptic density after SCI in both groups—probably through different pathways. The authors

concluded that Fb-BDNF/NT3 transplants could contribute to organisation of spinal circuitry after SCI.

Mure et al. [29] and Chung et al. [30] assessed the effect of early administration of neurotrophic facilitators, including administration of dehydroepiandrosterone (DHEA) [29] in SCC mice and inosine [30] in SCC/SCT rats. DHEA as a neuroactive steroid could act as a modulator of neurotrophic factor receptors and has previously been shown to promote neurological recovery after SCI. As a purine nucleoside with neurotrophic properties, inosine has been shown to promote corticospinal tract fibres sprouting and improve motor function in pre-clinical models of SCI. Mure et al. [29] reported a faster recovery of autonomic bladder control in DHEA-treated SCI mice while Chung et al [30] reported a significant decrease in the frequency of NVC in inosine-treated SCC/SCT rats and a significant decrease in the amplitude of NVCs in inosine-treated SCT rats. After DHEA administration [29], change in function was associated with a of collagen type3-type1 ratio similar to that seen in sham-operated animals. At the same time, after inosine administration [30], bladder analysis showed an increased expression of the pan-neuronal marker SYP and Aδ-fibre marker NF200 and a decreased expression of the C-fibre marker TRPV1. Mure et al. [29] concluded that DHEA could prevent NLUTD after SCI through its neuroprotective and neuroactive properties, including glucocorticoid and cyclooxygenase-2,12 inhibition or even act directly on the bladder tissue through the androgen and estrogen metabolism. In addition, Chung et al. [30] concluded that inosine could prevent DO through modulation of sensory neurotransmission.

Neural precursor cells. Mitsui et al. assessed in three distinct studies [31–33]. the effect of early intrathecal implantation—at the lesion site in SCC rats—of restricted neuronal precursor (NRP) and glial restricted precursor (GRP) alone [33] or combined with 2,3-dihydroxy-6-nitro-7 sulfamoylbenzo(f)quinoxaline (NBQX) [31] as well as early intrathecal implantation of EG6 immortalised neural stem cells [32]. Microinjection of NBQX has been shown to significantly decrease the amount of tissue loss following SCI through inhibition of AMPA/Kainite receptors contributing to the excitotoxicity mediated tissue damage that ensues within minutes following traumatic SCI. NRP/GRP alone [33] or in combination with NBQX [31] was reported to increase voided volume per micturition and improve cystometric pressure parameters, including a decrease in micturition pressure and the number of NVCs. On the other hand, EG6 cells [32] were reported to decrease the post-void residual volume and increase voiding efficiency without impacting voided volume or DO. NRP/GRP-treated and NBQX-treated SCI rats [31–33] presented with increased sprouting, regeneration or sparing of descending projections to the lumbosacral cord associated with a decrease in the size of the lesion.

Similarly, these rats [31, 33] showed a decrease in the sprouting of primary afferents in the lumbosacral cord. Furthermore, in NBQX + NRP/GRP-treated SCI rats [33], the density of serotonergic, noradrenergic, and corticotrophin-releasing factor-positive fibres was increased, while the density of axons in the dorsal horn appeared normal. The authors concluded that neural stem cell transplantation could prevent NLUTD by providing local protection consisting of increased sparing/sprouting of descending pathways, thus preventing sprouting by dorsal root axons.

Electrical nerve modulation

Pudendal nerve modulation. Three studies assessed the effect of early 5–10 Hz pudendal nerve modulation (PNM) in SCI minipigs [34] and dogs [35, 36]. They all reported a significant decrease in the number of NVCs and a significant increase in bladder capacity and compliance. Interestingly, Chen et al. [36] assessed this effect at different time points (early: day 30, delayed: day 180) and found?? significant changes after early PNM treatment compared to baseline, while no significant change was found after delayed PNM treatment. They also noted the presence of fewer collagen fibres associated with more elastin fibres in early PNM-treated compared with delayed PNM-treated SCI dogs. Keller et al. [34] directly compared 10 Hz PNM to 10 Hz SNM and noted a significant increase in bladder capacity associated with a significant decrease in voiding pressure and DSD in SNM-treated minipigs compared to PNM-treated and non-treated SCI minipigs. Although structural results revealed SCI-typical fibrotic alterations in both SNM and PNM-treated SCI minipigs, SNM-treated SCI minipigs showed a better-balanced distribution of smooth muscle to connective tissue, with a trend towards reduced progression of bladder wall scarring.

Sacral nerve modulation. Five studies assessed the effect of early 10–60 Hz SNM in animals [34, 37–40]. For SCI minipigs [34] and rats [37, 38], the authors found a significant improvement in DO, including a decrease in the frequency and maximum pressure of NVCs, associated with an increase in the time between contractions and the duration of contraction. In the Shi et al. [38] study, SNM was proven to be able to decrease DO regardless of the delay between SCI and implantation. However, the authors reported SNM to be particularly effective when implanted 2–4 weeks after SCI, at the end of the spinal shock phase and before the development of DO. For SCI dogs, Hassouna et al. [39] and Li et al. [40], on the basis of particularly elaborate studies, reported the delay before the return of DO after spinal shock to be significantly decreased in NMS-treated SCI dogs, when compared to SCI dogs managed with indwelling or intermittent catheterization, with SNM reported to ensure complete voiding up to 8 months [40].

Sievert et al. [41] assessed the effect of early SNM in supra-sacral post-traumatic AIS A SCI humans. In early SNM-treated SCI patients, the authors noted the persistence of low bladder pressure (<30 cmH2O) without any NVCs or bladder compliance disorders throughout the filling phase, without any pelvic activity, during a mean follow-up period of 26 (range 5.4–38.9) months. The bladder diaries revealed a mean catheterised volume of 582 ml (range 480–650 ml). The participants, who did not receive an antimuscarinic or botulinum toxin before their last evaluation, did not report involuntary urine leakage. On the contrary, despite taking antimuscarinics, the non-treated SCI patients were reported to present with lower bladder capacity (mean 208 ml; range 57–314 ml) and higher bladder pressure (>30 cmH2O). Furthermore, they reported mean catheterised volumes of 294 ml (range, 105–390 ml), with more frequent CISC and a more frequent use of urinary condoms because of urinary incontinence. The authors concluded that early SNM implantation in SCI patients might dramatically change NLUTD management, as it could prevent DO and urinary incontinence and provide standard bladder capacity.

Multi-system neuroprosthetic training

Horst et al. [42] assessed the effect of a multi-system neuroprosthetic training (MSNT) program in bilateral T7 + T11 SCHT rats. The MSNT program included an electrochemical stimulation (epidural S2-L1 electrical stimulation associated with serotonergic and dopamine agonists administration) and locomotor treadmill-based training. MSNT has been previously reported to trigger a massive reorganisation of descending and intra-spinal pathways in SCI rats. The authors reported a significant decrease in the number of NVCs while bladder capacity increased 3-fold in complete MSNT SCI-rats and 7-fold in partial MSNT SCI-rats. Bladder morphology was similar in complete MSNT SCI and non-SCI rats, while partial MSNT SCI rats exhibited detrusor hypertrophy characterised by increased detrusor thickness and decreased connective tissue to smooth muscle ratio. The authors also reported that nerve density was significantly increased in complete MSNT SCI rats while it was significantly decreased in partial MSNT SCI rats. The proportion of NF200-positive afferent nerves was significantly decreased in complete MSNT SCI rats compared to partial MSNT SCI and non-SCI rats, while NPY-positive fibres density was significantly decreased in partial MSNT SCI rats.

DISCUSSION

To our knowledge, the present systematic review is the first to synthesise the scientific literature focusing on early interventions to prevent the emergence of NLUTD after acute supra-sacral SCI. Since NLUTD remains the leading cause of hospitalisation and the fifth largest cause of mortality after SCI [7]—despite multiple advances in NLUTD management over the last three decades—its prevention should be considered a priority by the scientific community.

Even if we have regularly specified throughout the manuscript the role of neurotransmitters and their receptors involved in the micturitional reflex pathway [43, 44], the present review should not be considered an attempt to precisely describe the complex mechanisms underlying the genesis, consolidation and prevention of LUTD after SCI. It should rather be seen as a guide for clinical studies to prevent NLUTD in this specific population.

We can regret the lack of studies focusing on the prevention of LUTD after SCI in humans. Animal models, mostly rodents, have been widely used in the last two decades in the literature focusing on LUTD after SCI. The validity of these models was reinforced a decade ago by Andersson et al. [45] who participated in the standardisation of the practice of urodynamic in rodent models, and by Dietz and al. [46] who more recently emphasised the importance of translational basic research in rodent SCI models.

The high number of studies (29/30) reporting significant improvement in urodynamic parameters clearly supports the concept of a preventive approach, aiming to interfere in the uncontrolled spinal pathways reorganisation occurring below the level of SCI—at least in some animal models. Early post-SCI interventions were mostly reported to inhibit C-fibres hyperexcitability and promote neuroplasticity, including the promotion of sprouting, regeneration or sparing of descending projections to the lumbosacral cord as well as the inhibition of sprouting of primary afferents in the lumbosacral cord. However, methodological heterogeneity of the included studies in terms of rationals, design, in-vivo model studied, outcomes considered, as well as their frequent unclear or even high RoB—prevent us from drawing any definitive conclusion on the best strategy to promote. Although all the proposed approaches deserve to be explored in humans, some of them will be difficult to implement in the early phase of SCI, given the time-consuming, complex and invasive care that will be needed. For these reasons, we feel that some orally administered drugs (antimuscarinic, α-blocker and phosphodiesterase type 5 inhibitor) and electrical nerve modulation seem the most mature candidates for medium-term application in humans. With 9 studies reported here, including 1 in humans, electrical nerve modulation is the therapeutic approach with the longest history and greatest visibility, with SNM and TNS—two minimally invasive therapies—already considered as second-line therapies to treat NLUTD [8, 9]. This finding is supported by recent findings suggesting that manipulation of neuronal activity can drive plasticity-related growth mechanisms and increase collateral sprouting, thereby enhancing the functional effect of axonal remodelling [47]. Furthermore, while electrical stimulation has long been known to enhance regeneration of peripheral axons [48], it has been reported recently that electrical modulation can also enhance CNS plasticity in rodent models, and modulate and strengthen spared circuitry in individuals with SCI [49]. However, given the limited data available in humans, it is impossible to propose electrical nerve modulation therapies as a preventive approach for SCI-related NLUTD in clinical practice. Clinical trials, such as the TASCI research protocol (transcutaneous tibial nerve stimulation in patients with acute spinal cord injury to prevent neurogenic detrusor overactivity) proposed by Birkhäuser [50] et al., are mandatory to confirm the value of such a preventive strategy in SCI humans, in both the short and long term.

CONCLUSION

The present systematic review supports the concept of early interventions to prevent NLUTD after SCI, allowing for the emergence of a potential preventive approach. Electrical nerve modulation should be considered as the most mature strategy for medium-term application in humans.

DATA AVAILABILITY

All references cited in the manuscript are available on PubMed.

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AUTHOR CONTRIBUTIONS

NV was responsible for designing the review protocol, writing the protocol and report, conducting the search, screening potentially eligible studies, extracting and analysing data, interpreting results, updating reference lists, creating 'Summary of findings' tables and writing the report. XB contributed to designing the review protocol, writing the protocol and report, conducting the search, screening potentially eligible studies, extracting and analysing data, interpreting results, updating reference lists, creating 'Summary of findings' tables and writing the report. PLD and DS contributed to conducting the search and screening potentially eligible studies. PV and SDW contributed to designing the review protocol and provided feedback on the report.

COMPETING INTERESTS

The authors have no conflicts of interest to declare. XB has received compensation as a member of the scientific advisory board of Medtronic.

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