The Dysfunctional Bladder Following Spinal Cord Injury: From Concept to Clinic

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Current Bladder Dysfunction Reports 2009, **4:**192–201
Current Medicine Group LLC ISSN 1931-7212

Lower urinary tract dysfunction is a common problem among individuals with spinal cord injury (SCI) that results from a disruption of coordinated control among the brain, spinal cord, and bladder. SCI initially induces areflexic bladder and urinary retention followed by the emergence of automatic micturition mediated by spinal reflex pathways. Experimental research has permitted insight into the pathophysiology of SCI and bladder dysfunction, thereby lending investigators the opportunity to discover therapeutic options. This review provides the reader with an overview of post-SCI bladder dysfunction and the use of currently available pharmacologic therapies to improve lower urinary tract dysfunction. It also highlights some of the promising treatment options on the horizon, such as bladder function restoration via tissue engineering and neurostimulation.

Introduction

The spinal cord is an intricate network of nerve fibers extending from the brainstem to the lumbosacral region. The human spinal cord has 31 pairs of spinal nerves that project out from ventral roots of the spinal cord as preganglionic fibers [1]. These preganglionic fibers synapse with postganglionic neurons located within target organs such as the skin, muscles, limbs, and other parts of the peripheral nervous system to permit the passage of ascending and descending nerve impulses between the brain and the rest of the body [1]. Not surprisingly, physical insult to the spinal cord results in disruption of motor and sensory control below the level of the injury. Moreover, the degree of ensuing neurologic deficit varies depending on the biophysical nature and anatomic level (ie, cervical, thoracic, or lumbar) of the initial traumatic insult to the spinal cord. Although validated classifications of spinal cord injury (SCI) exist, including the American Spinal Injury Association classification [2], SCI remains heterogeneous, with considerable interindividual variation and thus variability in clinical presentation.

The global annual incidence of SCI has been reported at 15 to 40 cases per 1 million individuals [3]. This incidence translates into about 10,000 to 12,000 SCI cases in North America each year. With improvements in medical and nursing protocols, SCI patients are afforded increased rates of survival and life expectancy [4]. In fact, the number of SCI survivors is dramatically more widespread than previously believed. According to a recent 3-year, population-based prevalence study co-sponsored by the Christopher and Dana Reeve Foundation and the Centers for Disease Control and Prevention and conducted by the University of New Mexico's Center for Development and Disability, an estimated 5,596,000 Americans (ie, 1 in 50) are living with paralysis [5]. About 1,275,000 people attribute their paralysis to SCI [5]—a number that is roughly five times greater than the 2008 prevalence estimate of 255,702 [6]. Notably, these findings suggest that SCI, a neurologic disorder previously considered a rare event, generates paralysis on roughly the same scale of magnitude as stroke (23% and 29% of the projected total American paralysis population, respectively) [5]. The implications of these revelations regarding SCI likely will require major adjustment to the agendas of research and clinical SCI programs to best meet the immediate needs of SCI survivors and allow for enhancements to SCI patients' quality of life (QoL)—that is, their ability to cope and adapt to their new SCI [7]. In a recent QoL survey involving 347 quadriplegic and 334 paraplegic participants, the highest priorities were given to bladder/bowel function, sexual function, restoration of normal sensation, and elimination of chronic pain [8].

Table 1. Methods to acquire spinal cord injury, and the biphasic pathobiological mechanisms contributing to lesion expansion

Methods to acquire acute spinal cord injuries	Primary injury mechanisms	Secondary injury mechanisms
Traffic accidents (motor vehicle, cycling, pedestrian)	Spinal cord compression	Systemic hypotension and spinal shock
Falls	Spinal cord contusion	Hemorrhage
Acts of violence	Spinal cord laceration	Disruption of spinal cord blood flow (persistent ischemia)
Recreational/sports accidents	Immediate cell death (necrosis)	Edema
Work-related accidents		Vasospasm
		Reperfusion
		Lipid peroxidation
		Free radical generation and reactive oxygen species
		Glutamate-mediated excitotoxicity
		Elevation in intracellular calcium
		Proteolytic enzyme (calpain and caspase) activation
		Elevated expression of proinflammatory cytokines
		Inflammation
		Delayed cell death (apoptosis)

Pathobiology of Spinal Cord Injury and Bladder Dysfunction

The pathobiology of SCI is believed to follow a two-phase process that involves an initial "primary injury," or blunt insult directed onto the spine, followed by "secondary injurious processes" driven by a delayed set of interwoven biochemical events (Table 1).

Primary injury to the spinal cord most frequently is a consequence of motor vehicle accidents, falls, acts of violence, or recreational sporting events [6]. The physical mechanism for which traumatic injury generates the actual spinal cord lesion can occur through dislocation of the vertebral column, disruption of the intervertebral disc, contusion, and/or compression of the spinal cord [3]. Rarely does the primary injury result in complete spinal cord transection. This is true even for those cases in which the patient is completely devoid of sensory and motor function below the level of injury. Instead, the initial traumatic event usually leaves an intact layer of neural tissue surrounding the penumbra of the lesion epicenter.

Following the primary injury, a cascade of secondary auto-destructive events are generated to yield a positive feedback loop of amplified pathology and functional deficit [9]. This process of secondary injury is thought to persist years after the SCI [9]. Post-SCI secondary injurious events include spinal cord ischemia–reperfusion, lipid peroxidation and membrane decomposition, glutamate-mediated excitotoxicity and ionic imbalance, generation of free radicals and reactive oxygen species, and extensive inflammation [10]. Secondary injury cascades also involve the activation and upregulation of proinflammatory cytokines, proteases, toxic metabolites, and neurotransmitters that cause rostral-caudal expansion of the lesion epicenter [11].

Secondary injury events following SCI negatively impact autonomic function [12]. Loss of urination control occurs as a result of uncoordinated efforts between the external urethral sphincter via somatic cortical control and smooth muscles lining the bladder via autonomic control [13]. Furthermore, although cervical and thoracic injuries may leave the spinal reflex control of micturition intact, connections with the pons are severed, resulting in a loss of one's ability to exert voluntary control to void. Thus, urinary control is dependent upon coordination among the brainstem, spinal cord, and bladder [14•].

Anatomy and Function of the Lower Urinary Tract

The urinary bladder and urethral sphincter act in reciprocal fashion. During urine storage, the bladder outlet is closed and the bladder smooth muscle is quiescent, allowing intravesical pressure to remain low over a wide range of bladder volumes [15•]. Sensory input is conveyed to the spinal cord through pelvic and hypogastric nerves. The afferent fibers carry impulses from tension receptors and nociceptors in the bladder wall to neurons in the dorsal horn of the spinal cord. These afferents include myelinated (A-δ fiber) or unmyelinated (C-fiber) axons [16]. Also, bladder afferent impulses activate a sacral-to-thoracolumbar intersegmental spinal reflex pathway, which triggers sympathetic firing to the bladder and subsequently inhibits bladder activity and contracts the bladder outlet. Furthermore, pudendal motoneurons are also activated by the bladder impulses to induce a contraction of the striated sphincter muscle [17••].

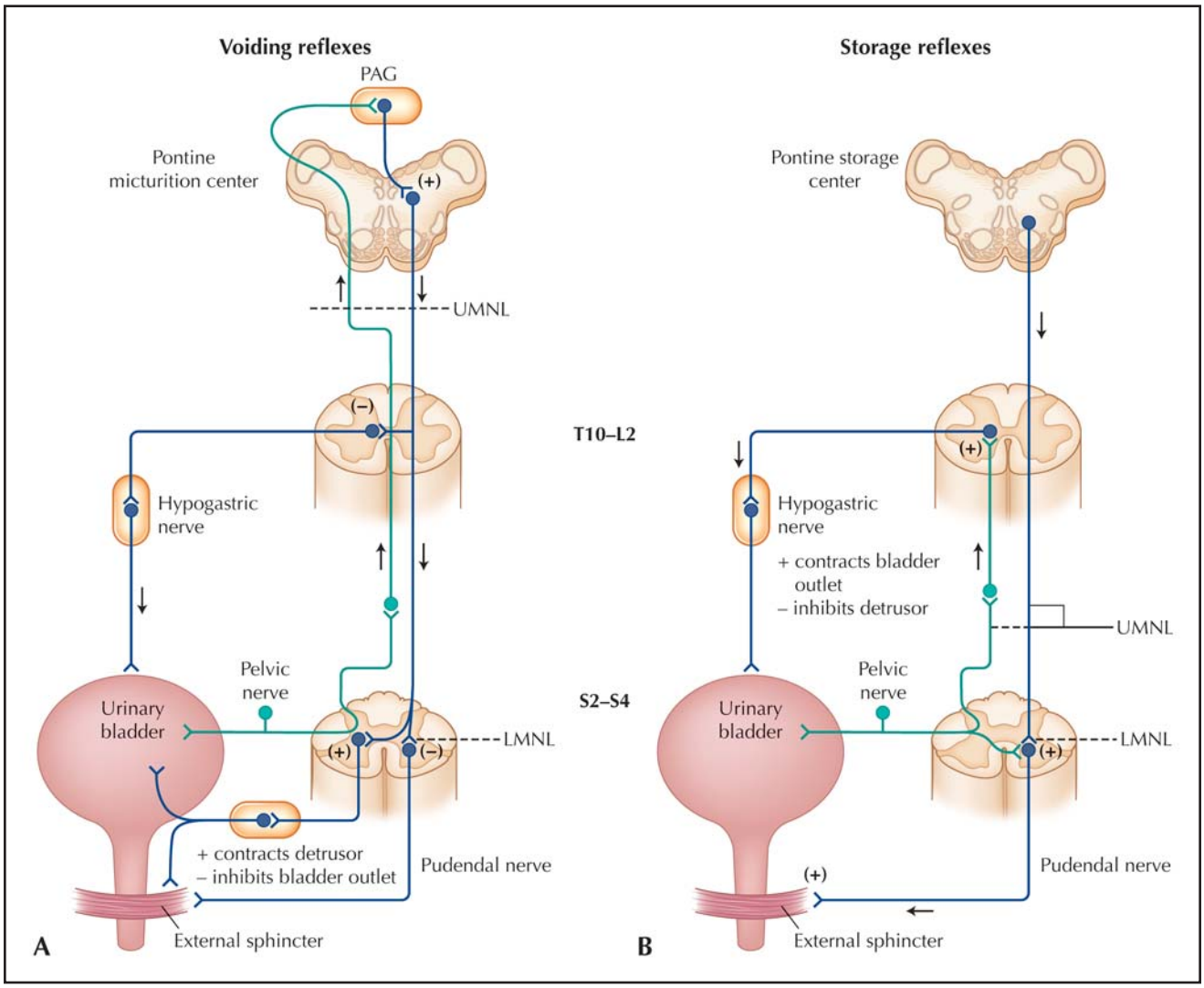


Figure 1. Voiding (**A**) and storage reflexes (**B**) of the bladder. In voiding reflexes, bladder mechanoreceptors activate the bladder–brain–bladder reflex to contact the bladder via parasympathetic pathway and inhibit the urethral sphincter via pudendal pathway. Storage reflexes are maintained by sympathetic and pudendal activation in response to bladder distention. Upper motor neuron lesions (UMNLs) correspond to spinal cord lesions above the sacral cord. Lower motor neuron lesions (LMNLs) correspond to lesions at the sacral level. *T10–L2* is the thoracolumbar junction. *S2–S4* represent anatomic levels within the sacral spinal cord. PAG—periaqueductal gray.

When bladder volume reaches the micturition threshold, afferent activity originating from the bladder mechanoreceptors triggers the micturition reflexes. These reflexes include activation of the parasympathetic pathways and inhibition of the sympathetic and somatic pathways, which leads to contraction of the bladder and simultaneous relaxation of the outlet [18].

Bladder afferents in the pelvic nerve synapse on neurons in the sacral spinal cord, which then send their axons rostrally to the micturition center in the dorsolateral pons. This center acts as an on/off switch activated by impulses from the bladder mechanoreceptors and also receives inhibitory and excitatory inputs from the brain. Descending input from the micturition center directly inhibits the pudendal motoneurons. Subsequently, the activity in the pudendal efferent pathway to the striated urethral muscles is suppressed to reduce outlet resistance (Fig. 1) [19].

During voluntary micturition, the initial event is a reduction of intraurethral pressure, which reflects a relaxation of the pelvic floor and the periurethral striated muscles followed by a detrusor muscle contraction and an opening of the bladder neck. Reflex inhibition of the smooth and striated urethral sphincter also occurs during micturition [20].

In the human bladder smooth muscle, only two muscarinic receptor subtypes (M2 and M3) have been identified. Although the M2 receptor is the most dominant subtype in the bladder, the contraction of the bladder is believed to result primarily from activation of M3 receptors [21•]. Voiding reflexes are mediated by myelinated (A-δ fiber) bladder afferents, which activate a supraspinal micturition reflex in the brainstem. Unmyelinated (C-fiber) bladder afferents are also present, but they are in a quiescent state and do not respond to bladder distention [15•].

Effects of Spinal Cord Injury on Voiding

SCI mediates damage to spinal tracts involved in central control of the lower urinary tract (LUT) and leads to simultaneous activation of parasympathetic neurons innervating the detrusor and somatic neurons innervating the external urethral sphincter to cause varying degrees of detrusor–sphincter dyssynergia (DSD) [13].

The effects of SCI on the LUT depend on the level, duration, and completeness of the cord lesion. With regard to anatomic level, injuries occurring above the conus medullaris cause an overactive or upper motor neuron lesion pattern of damage affecting LUT, bowel, and sexual functions [13]. Conal injuries include those affecting the conus medullaris of the spinal cord and cause a mixed lesion to LUT, bowel, and sexual functions with a resultant overactive or acontractile picture [13]. Cauda equina injuries generally cause an acontractile or lower motor neuron lesion picture affecting LUT, bowel, and sexual functions [13].

Upper motor neuron lesions are seen in most patients with SCI and initially lead to a phase of spinal shock followed by a recovery phase, during which neurologic changes emerge. In the shock phase, the bladder becomes flaccid and areflexic; however, the activity of the external sphincter recovers rapidly after SCI [22]. Thus, urinary retention develops, and patients may need intermittent or continuous catheterization to eliminate urine. Following the shock phase, voiding reflexes start to reappear after 2 to 12 weeks, a phenomenon that is involuntary to reflex bladder contractions. These reflexes generate low vesical pressure initially, but over time, bladder contractions become more powerful and produce involuntary contractions. Because of resulting DSD, the bladder partially empties, and postvoiding residual volume increases over time. Bladder hyperreflexia and DSD lead to high intravesical pressure with or without vesical-ureteral reflux, which leads to impairment of renal functions. In the lower motor neuron lesion type of SCI, the bladder and its outlet become flaccid; hence, bladder capacity and compliance are increased [15•].

Injuries above T6 produce autonomic dysreflexia, which is characterized by an arterial pressor effect in response to stimuli such as bladder and rectal distention. These stimuli produce an exaggerated sympathetic response that leads to very high levels of blood pressure and bradycardia via vagal stimulation. This could be life threatening and may cause cerebral hemorrhage or seizures [23].

Impact of Bladder Dysfunction on Spinal Cord Injury Patients

Urinary incontinence is very common and problematic for SCI patients. The general symptoms of impaired bladder emptying are a feeling of fullness in the bladder area, straining to void, hesitancy, interrupted or diminished stream, double voiding, incomplete emptying, lower abdominal discomfort, dribbling, and recurrent urinary tract infections (UTIs) [24]. Chronic renal failure as a result of SCI-induced bladder dysfunction, severe urinary retention, and UTI was once viewed as a leading cause of death in patients with SCI [25]. Despite current medical practices, which have effectively reduced the incidence of post-SCI renal failure deaths below 5% [26], urologic complications continue to account for most of the morbidity and 10% to 15% of deaths within the SCI population and are associated with significant reduction in the SCI patients' QoL [27]. With regard to increased bladder-related morbidity in SCI patients, UTIs resulting from neurogenic bladder, incomplete voiding, elevated intravesicular pressure, catheter use, and frequent exposure to antibiotics have been implicated as underlying contributing mechanisms to increased morbidity.

With no cure in place to fully restore autonomic function, carefully adjusted bladder management is required over the course of the SCI patient's life. For instance, shortly after SCI, patients with neurogenic bladders frequently receive urethral catheters to facilitate voiding. With increasing continence as the time following SCI progresses, catheterization is applied intermittently in combination with rehabilitation [25]. For SCI patients who can resume an active lifestyle, bladder management may then include condom drainage into a leg bag or wearing a diaper [25]. Ideally, the ultimate goal of managing the neurogenic bladder is to preserve urinary function and enhance patient independence and QoL [7].

Current Pharmacologic Therapies

Incontinence caused by neurogenic detrusor overactivity

Overactive bladder (OAB) is a syndrome resulting from inappropriate bladder contractions during the bladder filling stage as a consequence of an overactive detrusor muscle. The irregularly high frequency of OAB has been defined as greater than eight attempts per day to empty the bladder coupled with a strong desire to urinate [28]. Anticholinergics, also referred to as antispasmodics or antimuscarinics, work by blocking the neurotransmitter acetylcholine at muscarinic cholinergic receptors, through which efferent parasympathetic nerve impulses evoke detrusor contraction. Anticholinergics are the first-line treatment class for OAB. Six anticholinergic drugs are currently marketed for the treatment of OAB: oxybutynin, tolterodine, propiverine, trospium, darifenacin, and solifenacin [29]. These anticholinergic drugs, as well as the α-1–adrenergic receptor (α-1 AR) agonist doxazosin, the γ-aminobutyric acid (GABA) agonists diazepam and baclofen, the neurotoxins, botulinum toxin type A (BTX-A), and vanilloid compounds capsaicin and resiniferatoxin (RTX) are discussed in greater detail subsequently and presented as validated therapies for bladder dysfunction in Figure 2.

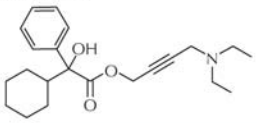
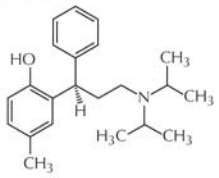
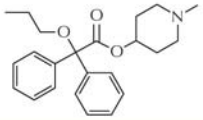
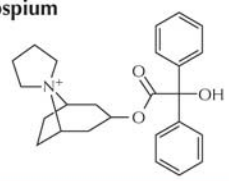
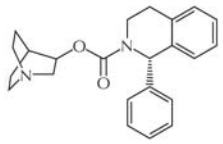
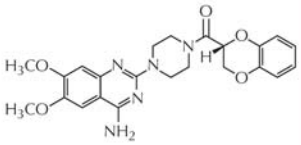
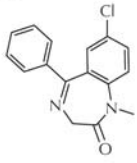
Drug name	Indication	Drug class/mechanism of action	Formulation/ administration route	Adverse effects
Oxybutynin 	Overactive bladder	Anticholinergic/ muscarinic receptor blocker	Oral immediate release and extended release, catheter-mediated installation, transdermal patch, topical gel	Dry mouth, constipation, vision impairment, confusion, cognitive dysfunction, tachycardia
Tolterodine 	Overactive bladder	Anticholinergic/ competitive muscarinic receptor blocker (M3 selective)	Oral immediate release and extended release	Dry mouth, upset stomach, headache, constipation, dry eyes, drowsiness
Propiverine 	Overactive bladder	Anticholinergic/ muscarinic receptor blocker and calcium channel antagonist	Intravenous injection, oral	Dry mouth
Trospium 	Detrusor hyperreflexia	Anticholinergic/ muscarinic receptor blocker	Oral	Dry mouth, constipation, upset stomach, headache, dry eyes, dizziness, blurred vision, drowsiness
Solifenacin 	Overactive bladder	Anticholinergic/ muscarinic receptor blocker	Oral	Dry mouth, blurred vision, constipation
Doxazosin 	Detrusor–sphincter dyssynergia	α-1–Adrenergic receptor blocker/antihypertensive drug that lowers blood pressure	Oral	Dizziness, drowsiness, light-headedness, headache, constipation, loss of appetite, dry mouth, tiredness, stuffy nose, blurred vision, dry eyes, trouble sleeping
Diazepam 	Detrusor–sphincter dyssynergia	Benzodiazepine/$GABA_A$ agonist with spasmolytic actions	Oral, intravenous, intramuscular	Sedation, central nervous system depressant, confusion

Figure 2. Validated pharmacologic therapies for the management of bladder dysfunction following spinal cord injury. GABA—γ-aminobutyric acid.

Oxybutynin

Oxybutynin, a smooth muscle relaxant that works to improve bladder dynamics through suppression of detrusor hypertonicity and hyperreflexia, is the standard to which other therapies for OAB are compared [30,31]. The combination of clean intermittent catheter use with oxybutynin has provided effective management of detrusor hyperreflexia [32] by removing the high-pressure, uninhibited detrusor contractions and urinary leakage while preventing high-pressure bladder storage and emptying [30]. Although oral oxybutynin is efficacious for treating OAB symptoms, dose-related side effects, including dry mouth, constipation, vision impairment, confusion, cognitive dysfunction, and

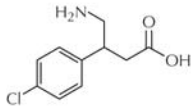
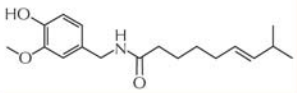
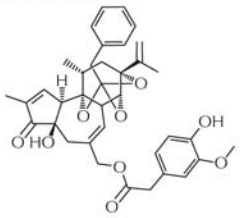
Drug name	Indication	Drug class/mechanism of action	Formulation/ administration route	Adverse effects
Baclofen 	Detrusor–sphincter dyssynergia	Benzodiazepine/$GABA_B$ agonist with spasmolytic actions	Oral, intrathecal infusion	Less sedation than diazepam
Botulinum toxin type A	Neurogenic detrusor overactivity	Neurotoxin with ability to inhibit acetylcholine release from cholinergic motor neuron terminals causing paralysis	Injection	Occasionally headache, light-headedness, fever, abdominal pain, diarrhea
Capsaicin 	Detrusor overactivity	Vanilloid compound that initially excites and desensitizes C-fiber afferent bladder neurons	Intravesical injection	Acute pain and burning
Resiniferatoxin 	Detrusor overactivity	Ultrapotent vanilloid analogue of capsaicin that initially excites and desensitizes C-fiber afferent bladder neurons	Intravesical injection	Less acute pain and burning than capsaicin

Figure 2. *(Continued)*

tachycardia, collectively limit utility of this drug due to discontinuation [28]. To improve patient compliance and tolerability, alternate delivery systems for oxybutynin were developed and include a once-daily extended-release formulation and a transdermal system.

Tolterodine

Tolterodine represents a newer competitive muscarinic antagonist with demonstrated efficacy against OAB. In a double-blind, parallel-group, multinational phase 3 study, 293 OAB patients were randomly assigned to receive tolterodine (2 mg twice daily), oxybutynin (5 mg three times daily), or placebo [33]. The results demonstrated that relative to oxybutynin, the tolterodine dosing regimen provided comparable clinical efficacy with a reduced intensity of dry mouth [33]. Thus, the principal investigators of the study concluded that tolterodine therapy offers superior tolerability that can permit patients with OAB to continue prescribed treatment [33].

Propiverine

Propiverine is a calcium antagonist with moderate antimuscarinic effects that work in the face of OAB via spasmolytic effects on the bladder [31]. A retrospective observational cohort study was recently carried out with 255 children and adolescents with neurogenic detrusor overactivity to compare the efficacy, tolerability, safety, and clinical effectiveness of propiverine against that of oxybutynin [34]. The results suggest that propiverine is at least as effective as oxybutynin for reducing detrusor pressure in individuals with neurogenic detrusor overactivity but also yields fewer adverse events [34]. Further study within a prospective, randomized, placebo-controlled clinical trial will be necessary to corroborate this retrospective conclusion.

Trospium

Trospium, an anticholinergic drug available in Europe for more than 20 years, recently gained US Food and Drug Administration approval for treatment of OAB with symptoms of urge incontinence, urgency, and frequency [35]. A hydrophilic derivative of atropine with the ability to antagonize acetylcholine, trospium is a useful agent against OAB [35]. Its proposed mechanism of action is competitive antagonism of acetylcholine stimulation of muscarinic M1, M2, and M3 receptor subtypes on the smooth muscle of the urinary bladder to effectively reduce the tension and contractility of the bladder [35].

In a randomized, double-blind, multicenter trial involving 95 patients with SCI and detrusor hyperreflexia, trospium (20 mg twice daily + one dose of placebo) was shown to provide similar therapeutic efficacy to oxybutynin (5 mg three times daily); however, the percentage of patients who reported adverse events or discontinued

treatment was lower for the trospium treatment group, thereby indicating its superiority over oxybutynin [36].

Solifenacin

Solifenacin is a newer muscarinic M3 receptor antagonist developed for the treatment of OAB [37]. Radioligand binding analysis for solifenacin demonstrated that the greatest equilibrium dissociation constants were associated with the M2 muscarinic subtype [37].

In vitro analysis of the antimuscarinic actions of solifenacin demonstrated that they were more potent than those of propiverine but less potent than those of tolterodine, oxybutynin, darifenacin, and atropine [37]. Conversely, in vivo analysis of solifenacin and oxybutynin demonstrated that each antimuscarinic drug increased the maximum bladder capacity in a dose-dependent manner and decreased the maximum intravesical pressure at comparable concentrations [37]. More recently, solifenacin treatment was demonstrated as a significant improvement over oxybutynin immediate release in bladder diary and validated QoL parameters [38].

Therapies to improve detrusor–sphincter dyssynergia

Doxazosin

The bladder neck and proximal urethra, where impaired sphincter relaxation may be responsible for voiding difficulty and the large amount of residuals, contain α-1 ARs. Doxazosin is an α-1 AR blocker with antispastic ability [39]. In a recent study exploring the effectiveness of combined doxazosin (4 mg/d) with baclofen, a GABA agonist (15 mg/d), patients with DSD demonstrated the ability to improve micturition [39].

GABA agonists

Diazepam and baclofen belong to the benzodiazepine family, a group of drugs that depress the central nervous system through agonist actions on GABA receptors within presynaptic and postsynaptic sites [40]. The actions of these drugs effectively inhibit the contractility of smooth muscles in the periphery, but the mechanism of this inhibitory action has not been clarified [40]. Although several studies have shown the application of GABA agonists as beneficial in controlling DSD, safety concerns continue to limit the use of this drug class in patients with SCI [41].

Neurotoxin treatments

BTX-A and the vanilloid compounds capsaicin and RTX are used to treat bladder dysfunction. Intramuscular detrusor BTX-A injection (200–300 U of BTX-A toxin injected into the detrusor muscle at 20–30 sites [10 U/mL per site]) is believed to improve neurogenic detrusor overactivity via selective antagonism of acetylcholine-mediated detrusor contraction [42]. BTX-A is commercially available and may also be effective in the management of DSD and pelvic floor spasticity [42]. Intravesically administered capsaicin, a vanilloid receptor agonist and natural component of spicy foods, alleviates detrusor overactivity via activation of vanilloid receptor subtype 1 within small- and medium-sized dorsal root ganglion neurons of the bladder and corresponding desensitization of C-fiber afferent bladder neurons [43]. Capsaicin-sensitive vanilloid receptor subtype 1–expressing fibers are extremely abundant within the urinary bladder mucosa and in the muscular layer. Adverse effects associated with capsaicin use include acute pain and burning sensations. RTX is an ultrapotent vanilloid analogue of capsaicin that offers comparable efficacy with reduced side effects [44].

Novel Therapeutic Approaches

Vascularization and innervation of engineered bladder

Given the loss of coordination among the brain, spinal cord, and bladder, efforts to regenerate or bioengineer correct connections within the micturition pathway may facilitate restoration of bladder function. However, such strategies require reinstallment of blood supply and innervation to permit physiologic function and survival. Several approaches of vascularization have been investigated, including omental wrap, seeding of endothelial progenitor cells, and prevascularization of the scaffold, in addition to the use of several enhancing factors, such as vascular endothelial cell growth factor, fibroblast growth factor, and platelet-derived growth factor. Schultheiss and colleagues [45] described an original technique for increasing the vascular supply of decellularized porcine small intestine submucosa seeded with smooth muscle cells and urothelial cells. These authors showed that implanted scaffolds seeded with endothelial progenitor cells developed into capillary networks to provide arterial and venous pedicles that turned into iliac vessels. This result is a promising step in developing adequate vasculature within engineered bladders [45].

Cell therapy for urethral sphincter insufficiency

Bladder tissue engineering involves harvesting autologous cells from the bladder, in vitro expansion, matrix seeding, and implantation back into the bladder. Bladder smooth muscle cells and bone marrow mononuclear cells have shown very promising results for bladder tissue engineering. However, controversy still surrounds their value, especially when used in large numbers [46]. Autologous muscle precursor cell (MPC) transfer for treating intrinsic rhabdosphincter insufficiency has been the focus of many researchers. However, the primary obstacle associated with the use of autologous MPC transfer is the very low survival rate of these cells. To overcome this challenge, researchers have explored several approaches, including: 1) using selected MPCs with a stem cell phenotype, 2) injecting a large number of MPCs, and 3) injecting MPCs without prior cultivation.

The practicality of MPC transfer to improve sphincter tone in neurogenic urinary incontinence is also an

area of active research. Using a porcine animal model, one group showed that injection of autologous MPCs developed an innervated and functional microtubule in an electrocautery-induced sphincter injury. Furthermore, these myotubules had cholinergic receptors connected to nerve endings after 1 month, demonstrating connection with urethral nerves [47]. Although this may appear very promising, clinical value and long-term outcome remain undetermined.

Restoration of complete bladder function by neurostimulation

Nerve stimulation using implantable devices has proven to be an effective modality for the control of bladder dysfunction [48]. During the past few decades, several approaches have focused on developing technologies using nerve stimulation to provide full control of bladder function after SCI. These approaches include the following: 1) sacral anterior root stimulation for emptying the paralyzed bladder, 2) sacral root stimulation for suppressing detrusor hyperreflexia, 3) conditional neuromodulation for automatic control of reflex incontinence, 4) sacral posterior and anterior root stimulator implantation, 5) selective stimulation of sacral roots to prevent DSD, and 6) sacral anterior and posterior intrathecal root stimulation implantation [49].

DSD resulting from bladder hyperreflexia remains a significant challenge to overcome regardless of the chosen neuromodulation strategy (ie, neuromodulation of the sacral root via anterior or posterior stimulators, or selective stimulation techniques). In the near future, technology innovation may enable improved design of implantable devices with more sensitive and intelligent sensors to improve bladder function after SCI.

Conclusions

Normal voluntary control of the bladder is dependent on the coordinated actions of the brainstem, spinal cord, and bladder. SCI damages the spinal tracts involved in central control of the LUT, often leading to simultaneous activation of parasympathetic neurons innervating the detrusor and somatic neurons innervating the external urethral sphincter. Bladder dysfunction was once a leading cause of mortality following SCI; however, thanks to improvements within medical and nursing protocols, the incidence of mortality during the first year after SCI has decreased substantially. However, the recent population-based prevalence study that was co-sponsored by the Christopher and Dana Reeve Foundation and the Centers for Disease Control and Prevention suggests that the prevalence of SCI is grossly underestimated [5]. This fact implies that the societal burden of SCI and its associated complications, including bladder dysfunction, are also underestimated. Thus, efforts to identify therapies to improve neurologic function following SCI are critically needed.

In addition to the therapeutic approaches discussed in this article, many clinical trials investigating neuroprotective and/or neuroregenerative translational strategies have the potential to positively impact post-SCI bladder dysfunction. These promising translational approaches include the following: 1) the off-patent neuroprotective tetracycline derivative minocycline (an investigator-driven phase 1/2 study conducted at the University of Calgary in Canada); 2) the off-patent benzothiazole anticonvulsant sodium channel antagonist riluzole (an investigator-driven, phase 1 multicenter trial within North American Clinical Trial Network centers across Canada and the United States); 3) the neuroregenerative anti-Nogo antibody ATI355 (a phase 1 multicenter trial within Canada and Europe sponsored by Novartis [Basel, Switzerland]); and 4) the *Clostridium botulinum*, C3 transferase ρ-antagonist, Cethrin (a phase 1 multicenter trial sponsored by Alseres Pharmaceuticals [Hopkinton, MA] conducted within Canada and the United States recently concluded and showed Cethrin to be safe; a larger phase 2 trial is the subject of current planning).

Concurrent with efforts to identify novel treatments with increased therapeutic efficacy, SCI researchers should heed the recommendations of the American Spinal Injury Association to incorporate a combination of objective urodynamic outcome measures to assess sensation during filling, detrusor activity, and sphincter function [13]. Additionally, subjective patient-reported outcome measures such as the Medical Outcome Study 20-Item Short Form, OAB Questionnaire, OAB Satisfaction Questionnaire, and patient-completed bladder diaries may provide added value by permitting clinical investigators to determine the ability of an investigational drug to improve the patient's QoL [50]. However, use of these subjective outcome measures necessitates determination of appropriate assessment intervals to allow treatment effects to be measured, sufficient training of study personnel to standardize survey delivery and data collection, and suitable selection of patient-related outcome measurement tools to provide optimal correlation with objective urodynamic measures [50].

Disclosure

No potential conflicts of interest relevant to this article were reported.

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