Pharmacologic Management of Neurogenic Lower Urinary Tract Dysfunction

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Introduction

Normal lower urinary tract function is dependent on precise neural control of storage and emptying of urine. Any alteration of this complex coordination from a neurologic lesion can result in neurogenic lower urinary tract dysfunction (NLUTD), with the extent and location of the neurologic lesion affecting the type and severity of dysfunction.

A prior chapter has described, in -depth, the neurophysiology of micturition, but it will be briefly reviewed below to provide context for the effects of pharmacologic management of neurogenic bladder. Prior to an in-depth exploration of the pharmacologic treatment options, goals of management and assessment of NLUTD will be discussed to offer a complete understanding of the scope of this issue.

Neurologic Control of Micturition

Lower urinary tract function is controlled by the autonomic (parasympathetic and sympathetic) and somatic nervous systems. Parasympathetic pathways are responsible for bladder emptying, while sympathetic nerve activation is involved in bladder storage. Parasympathetic preganglionic nerves originate in the sacral spinal cord, travel in the pelvic nerve, and synapse with parasympathetic postganglionic neurons in the pelvic plexus. Parasympathetic postganglionic neurons release acetylcholine, which binds to M2 and M3 receptors located within the detrusor muscle, to stimulate contraction. Although M2 receptors are present in higher density, M3

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receptors are the principal receptors involved in mediating bladder contraction and are the target of antimuscarinic drugs [1]. Parasympathetic pathways to the urethral sphincter cause relaxation during voiding through release of the inhibitory neurotransmitter, nitric oxide [2].

Sympathetic preganglionic nerves exit the thoracolumbar spinal cord and pass through the hypogastric nerve to synapse with nicotinic receptors on sympathetic postganglionic neurons. Sympathetic postganglionic nerves release norepinephrine to act on adrenergic receptors in the lower urinary tract and facilitate bladder storage. Specifically, norepinephrine acts on β-adrenergic receptors (β1, β2, β3) located within the bladder body to promote relaxation and α1-adrenergic receptors in the bladder base and proximal urethra causing smooth muscle contraction. Bladder relaxation is primarily induced through stimulation of β3 adrenergic receptors and is the target of mirabegron, a β3 agonist, in the treatment of detrusor overactivity [3].

The somatic pudendal nerve originates from Onuf's nucleus in the sacral spinal cord and releases acetylcholine which acts on nicotinic receptors to induce contraction of the striated urinary sphincter and pelvic floor musculature [4].

The pontine micturition center (PMC), also known as Barrington's nucleus, is the regulation center for voluntary control of the bladder and is located in the rostral brainstem. Neurons from the PMC project in descending spinobulbospinal pathways to the intermediolateral cell column of the sacral spinal cord. Activation of this pathway causes urethral relaxation and activation of pelvic parasympathetic nerves and inhibits the sympathetic and pudendal effects on the urethral outlet to promote bladder emptying [5].

During bladder storage, the raphe nuclei of the central nervous system (CNS) send serotonergic inputs to the sympathetic and parasympathetic nerves with resultant inhibition of reflex bladder contractions. A serotonin and norepinephrine reuptake inhibitor has been shown to both increase sphincter activity and decrease bladder contractions in an animal model [6].

On a cellular level, interstitial cells of Cajal (ICCs) are located just below the urothelium within the lamina propria and with the detrusor muscle of the bladder [7]. ICCs act as pacemakers and trigger contractions of adjacent smooth muscle cells, as well as interact with cholinergic and sensory nerve endings [8]. This allows ICCs to act as a channel of information between the autonomic system and sensory nerves with the detrusor muscle. Any disturbance in the ICC signaling may alter detrusor contraction and cause detrusor overactivity and/or may alter bladder sensation and cause bladder pain.

In addition to ICCs, purinergic receptors are present within the lamina propria and may have a role in detrusor overactivity. Adenosine triphosphate released from urothelial cells during filling can stimulate purinergic receptors and help mediate normal detrusor contraction directly [9]. Bladder biopsy specimens from patients with neurogenic detrusor overactivity (NDO) showed higher rates of atropine-resistant contractions compared to stable bladder specimens. These contractions were ameliorated by a purinergic receptor blocker, suggesting not only a direct influence of ATP on NDO but also the possibility for alternative drug developments

[10]. The role of ICCs and purinergic receptors highlights the idea that the urothelium has a function in modulating bladder activity.

Lastly, it is also important to remember that neurologic lesions can be partial and/or multiple, creating the opportunity for multiple combinations of neurologic effects that may not precisely correlate with the location of the lesion(s). Also, neural plasticity following injury can occur, inducing structural and functional changes, over time [11]. Clinically, this can result in evolving neurologic deficits. The neurologic findings present at an initial encounter can alter over time, and continuous and vigilant care is needed.

Goals of Management

Early diagnosis and treatment are paramount to avoiding long-term complications of the neurogenic bladder. Protection of upper tract function is the primary concern with continence being an important, yet secondary, matter. Upper tract preservation is dependent upon maintaining a low-pressure reservoir (detrusor pressure below 40 cmH_2O, compliance greater than 12.5 cmH_2O/mL), complete emptying, and reducing the risks of urinary tract infection [12, 13]. More recent data in children with myelodysplasia suggested that detrusor leak point pressure <20 cmH_2O may be a more sensitive measurement of the risk of upper tract damage [14]. Patients with continuous versus intermittent DSD had an increased incidence of upper urinary tract abnormalities suggesting that duration of elevated bladder pressures is a factor [15]. The proposed treatment, whether medical or surgical, must be acceptable to the patient to ensure compliance. Lastly, quality of life is also an important aspect in the care of these patients and should be continuously assessed.

Assessment of Neurogenic Bladder

Patient assessment should begin with an evaluation of the patient's symptoms. Lower urinary tract symptoms can be categorized into three groups: storage, voiding, and post-micturition [16]. Storage symptoms include frequency, nocturia, urgency, and urinary incontinence. Voiding symptoms include hesitancy, intermittency, and straining. Post-micturition symptoms are the sensation of incomplete emptying and post-micturition dribbling. The symptoms can provide insight into the underlying pathophysiology of the NLUTD. A detailed physical examination, including not only of the genitourinary system but also neurologic findings, is important because this will affect treatment selection. For example, it is prudent to understand the feasibility of performing self-intermittent catheterization prior to initiating treatment that may result in urinary retention. Urinalysis, serum creatinine, and upper tract imaging should also be performed at initial presentation.

Table 1 Functional classification of neurogenic lower urinary tract dysfunction

	Storage dysfunction	Emptying dysfunction
Bladder	Neurogenic detrusor overactivity	Detrusor areflexia
Outlet	Sphincter underactivity	Detrusor sphincter dyssynergia

Videourodynamic evaluation is performed to document the specific dysfunctions of the lower urinary tract. The functional classification system for voiding dysfunction developed by Wein [17] is a practical method to understand the underlying pathophysiology based on urodynamic findings and is shown in Table 1. These abnormalities of the bladder and outlet can occur in isolation, yet in cases of NLUTD, they often occur in combination. This classification system can then direct appropriate treatment options, either medical or surgical, aimed at correcting the functional abnormality.

Patients with neurogenic bladder often also have concomitant neurogenic bowel dysfunction due to a common underlying neurologic process. Also, the side effects of medications used in the treatment of NLUTD can exacerbate constipation. Treatment of neurogenic bowel should not be overlooked as constipation can worsen detrusor overactivity and bladder emptying, while fecal incontinence may increase the risk of urinary tract infections and predispose to skin breakdown. Medical therapy of neurogenic bowel dysfunction is beyond the scope of this chapter, but in general, aggressive treatment of constipation and involvement of gastroenterology specialists early are beneficial [18].

Pharmacologic Management of Neurogenic Lower Urinary Tract Dysfunction

The remainder of this chapter will discuss the pharmacologic management of neurogenic bladder based on the functional classification system shown in Table 1. Patients should additionally be counseled on non-pharmacologic interventions including behavioral management, such as fluid regulation and timed voiding or catheterization, and pelvic floor physical therapy when appropriate.

Detrusor Areflexia

Detrusor areflexia occurs during the period of spinal shock immediately following spinal cord injury (SCI) and in cases of lower motor neuron lesions, such as cauda equina syndrome. Patients with detrusor areflexia may be in urinary retention, or some may be able to void with straining. Initially detrusor areflexia can be managed with indwelling catheterization, but it is important to establish a reliable and acceptable long-term method of bladder emptying. The earliest record for management of bladder emptying was by transurethral bronze tubes, reeds, and palm leaves and

dates to 1500 BC [19]. The use of clean, intermittent, self-catheterization was formally reintroduced in the 1970s by Lapides [20]. Clean intermittent catheterization has been shown to preserve bladder compliance in SCI patients [13]. In some instances, intermittent catheterization is not a feasible option, and long-term indwelling catheterization is required, and in these cases, suprapubic tube placement is often preferred over urethral catheterization.

As an alternative to catheterization, women with detrusor areflexia can consider using the inFlow™ device, which is a magnetized valve-pump device inserted into the urethra. During voiding, an activator is held over the pubic bone and turned "on" to open the valve and allow urine flow. Once finished, the "on" button is released and the valve closes. In a multicenter trial, of the women who completed the study, there were significant improvements in the quality of life. Eighty-one subjects withdrew during the active treatment phase with the most commonly reported reasons being discomfort and leakage. Women who completed the study were more likely to have a lower baseline quality of life, more limited ability to ambulate, and poorer manual dexterity [21]. The inFlow™ device is a nonsurgical alternative option to catheterization and may have a bigger role in those patients with poorer quality of life or more difficulty performing self-catheterization.

Bethanechol

Recall that bladder contraction is mediated by parasympathetic pathways via action on muscarinic cholinergic receptors. Bethanechol (Urecholine®) is an oral cholinergic agonist that is resistant to degradation by acetylcholinesterase and acts on the parasympathetic postganglionic neurons. It has been proposed to improve voiding in patients with nonobstructive urinary retention; however, the clinical outcomes in randomized placebo-controlled trials have not shown efficacy [22].

In a study of patients with detrusor areflexia, 9 of 11 patients that responded to electromotive administration of bethanechol subsequently had return of spontaneous voiding with oral bethanechol, suggesting that it may be only patients with some degree of detrusor contractility that derive any benefit from oral bethanechol [23]. Prostaglandin E2 and bethanechol in combination demonstrated limited effectiveness in a group of patients with detrusor underactivity [24].

In summary, there are no pharmacologic agents effective in the treatment of detrusor areflexia, although several have been studied. Given the pharmacologic properties of bethanechol, it seemed promising to treat detrusor underactivity, but clinical studies have been unable to definitively demonstrate effectiveness.

Neurogenic Detrusor Overactivity

Neurogenic detrusor overactivity (NDO) can cause sustained elevated bladder pressures due to a hyperreflexic, overactive detrusor muscle. Subjectively, patients may experience urinary frequency, urgency, and incontinence. In

general, initial management includes antimuscarinic medications in combination with intermittent catheterization. Antimuscarinics have been shown to be effective in improving maximum cystometric bladder capacity (MCC) and compliance and reducing detrusor pressure compared to placebo in neurogenic populations [25, 26].

Antimuscarinic Drugs

Antimuscarinic agents that have been studied in the adult neurogenic population for treatment of NDO include oxybutynin, darifenacin, solifenacin, tolterodine, trospium, and propiverine. Clinically, antimuscarinics appear to act primarily on M3 receptors to reduce bladder contractions in the filling phase. With standard dosages, there appears to be minimal effect on bladder contraction during voiding, although urinary retention is a risk factor with higher doses [27]. The most common side effects of antimuscarinics include dry mouth, dry eyes, and constipation. Of concern are also the CNS side effects associated with antimuscarinics including cognitive impairment and poor memory. Contraindications to their use include acute angle glaucoma and gastric retention.

Oxybutynin

Oxybutynin is available in immediate (Ditropan®) and extended-release (Ditropan XL®) formulations. Oral immediate-release oxybutynin 15 mg versus placebo showed significant differences in MCC (125 vs. −10 mL, $p < 0.0001$), maximum detrusor pressure (−35 vs. −4 cmH_2O, $p < 0.0001$), and post-void residual (15 vs. 3 mL, $p = 0.012$); however clinical parameters were not measured in this study [26]. A prospective study of extended-release oxybutynin in SCI patients with NDO started treatment at a dosage of 10 mg daily and increased to 30 mg daily. At 12 weeks, voiding diaries showed decreased urinary frequency and incontinence episodes, and urodynamic evaluation demonstrated increased MCC from baseline. There were no adverse events reported indicating that extended-release oxybutynin dosages up to 30 mg daily are safe and well tolerated.

Transdermal oxybutynin (Oxytrol®) is another available route of administration with the benefit of lower incidence of anticholinergic side effects by avoiding first-pass metabolism [28]. In a study of patients with NDO and incontinence between intermittent catheterizations, there were improvements in the number of incontinence episodes and catheterized volumes. Additionally, there was significant increase in MCC and a decrease in detrusor pressure at capacity. The most common adverse event was application site reaction, occurring in 12.5% of the patients [29].

Intravesical administration of oxybutynin has also been studied. Crushed oxybutynin pills are diluted in water or saline and instilled into the bladder via catheterization and allowed to dwell. Compared to oral oxybutynin, intravesical administration has a higher bioavailability by avoiding first-pass hepatic metabolism resulting in

higher efficacy and lower rate of side effects [30]. In a randomized controlled trial comparing intravesical administration of 10 mL 0.1% oxybutynin three times daily (TID) to oral 5 mg TID, there was a significant increase in MCC in the intravesical group compared to the oral group (116 vs. 18 mL, $p = 0.0086$). However, there were no significant differences in maximum detrusor pressure, volume at which vesicoureteral reflex occurred, or bladder compliance. Clinically, there were no differences in the number of incontinence episodes or frequency of catheterization [31]. Oxybutynin is also thought to have potential local anesthetic effects, which may be of some additional benefit in this use [32].

Tolterodine

Tolterodine (Detrol®, Detrol LA®) acts on both M2 and M3 receptors. The immediate-release tablet is generally administered as 2 mg twice daily and the extended-release capsule is 4 mg once daily.

In a dose-ranging study comparing tolterodine (0.5, 1, 2, or 4 mg twice daily) to placebo, there was a dose-dependent improvement in urodynamic variables. Two patients taking the 4 mg twice daily dosing experienced urinary retention, causing the authors to conclude that 1–2 mg twice daily is the optimal dose for NDO [33]. In a small, randomized, double-blind study, tolterodine 2 mg twice daily reduced incontinence episodes and increased catheterized volumes compared to placebo, but there was no difference in MCC [34].

In a single-arm study evaluating the efficacy of extended-release tolterodine 4 mg/day for NDO showed that after 12 weeks of treatment, there were significant improvements in urinary frequency, urgency, and incontinence episodes. Also, patients had increased MCC and bladder compliance [35]. The rate of reported dry mouth was 8%.

A Cochrane review [36] compared oxybutynin to tolterodine, both immediate and extended-release formulations, with the conclusions that there was no difference in clinical outcomes between the drugs, but tolterodine had less dry mouth, reflecting the lower affinity of tolterodine for M3 receptors in the parotid gland, compared to oxybutynin [37]. Also, in general, extended-release formulations had fewer side effects than the immediate release.

Darifenacin

Darifenacin (Enablex®) is a selective M3 receptor antagonist. It is available in an extended-release formulation at 7.5 mg daily. In a randomized placebo-controlled, crossover study, of patients with NSO, darifenacin was found to significantly suppress unstable bladder contractions [38]. In another study of 38 patients with multiple sclerosis and NDO, 12 weeks of treatment with 15 mg of darifenacin resulted in increased MCC and improved bladder compliance as well as an 82% continence rate [39].

Despite darifenacin being a selective M3 receptor, it is not specific to the bladder. Salivary glands, gastrointestinal tract, and other tissues also contain M3 receptors, so side effects of dry mouth and constipation remain.

Solifenacin

Solifenacin (Vesicare®) is a selective M3 receptor antagonist. The initial dose is 5 mg once daily which can be increased to 10 mg daily if tolerated. In a prospective, randomized, placebo-controlled double-blind trial comparing solifenacin 10 mg to placebo in 51 patients with NDO either due to SCI or multiple sclerosis, the treatment group had a greater increase in MCC (360 vs. 232 mL, $p < 0.001$) and bladder volume at first detrusor contraction (216 vs. 131 mL, $p < 0.001$) and leak (230 vs. 141 mL, $p < 0.05$). Maximum detrusor pressure was also lower in the solifenacin group (50 vs. 82 cmH_2O, $p < 0.01$). There was no difference in the number of incontinence episodes in a 24-h period, but there were significant improvements in treatment satisfaction scores and patient perception of bladder condition. The most common reported side effects were dry mouth (8%) and blurred vision (8%) [40].

Trospium

Trospium (Sanctura®, Sanctura XR®, Trosec®) is a quaternary amine with both immediate-release (20 mg twice daily) and extended-release (60 mg daily) formulations. The benefit of the quaternary amine structure is that it should not be able to cross the blood-brain barrier and should have decreased risk of causing cognitive impairment compared to the other antimuscarinic drugs.

A randomized, placebo-controlled trial comparing trospium 20 mg daily for 3 weeks to placebo showed pre- and posttreatment improvements in MCC (mean difference of 138 mL) and bladder compliance (mean difference of 12 mL/cmH_2O) and a decrease in maximum detrusor pressure (mean change of −38 cmH_2O) in the treatment group [41]. The described side effects were low with only one patient reporting constipation.

In a comparison of trospium 20 mg twice daily to oxybutynin 5 mg TID, there was improvement within each arm in MCC, compliance, and maximum voiding pressure. There were no differences between the two groups, suggesting equivalent efficacy between the two medications. However, there was fewer reports of dry mouth in the trospium group (4% vs. 23%) [42].

Menarini and colleagues [43] conducted a prospective double-blind study comparing standard dose (45 mg/day) to adjustable dose (90–135 mg/day depending on urodynamic response) trospium. Results showed that doses up to 135 mg/day appeared to be well tolerated without any differences in adverse effects between the two groups. However, there were also no significant clinical differences between the standard and higher dosing, suggesting that 45 mg/day provides an effective therapeutic response in patients with NDO.

Propiverine

Propiverine (Detrunorm®, Mictoryl®) is a nonselective antimuscarinic that also has some calcium antagonistic actions, although the clinical importance of this is unclear [27]. It is not available in the United States but is available in Canada and Europe in immediate- and extended-release formulations. Adult initial dosing is 30 mg daily with a maximum of 45 mg daily. Propiverine demonstrated superiority to placebo in a neurogenic population of 113 patients where the treatment group had significant increases in MCC (104 vs. −6 mL), maximum detrusor pressure (27 vs. 0.2 cmH_2O), volume at first detrusor contraction, and duration of contractions (−20 vs. −1.6 s) compared to placebo, but there was no difference in bladder compliance between the treatment and placebo groups. Subjectively, 63% of patients in the propiverine group reported subjective improvement compared to 23% in the placebo group. The treatment group reported the expected anticholinergic side effects with dry mouth being the most common in 37% [44].

An investigation of 66 patients with NDO comparing propiverine extended release 45 mg daily to 15 mg immediate-release TID found no differences in urodynamic parameters. There was a 25% improvement in the reduction of incontinence rates in the extended-release group. The total number of adverse events was slightly lower in the extended-release group (42% vs. 36%) with dry mouth being the most common in both treatment arms [45].

In a randomized comparison of oxybutynin 5 mg TID to propiverine 15 mg TID in patients with NDO, both agents improved urodynamic parameters, and there were no differences between the treatment groups [46].

In brief, antimuscarinic drugs have demonstrated improvements in MCC and bladder compliance, as well as decreased maximum detrusor pressure, with oxybutynin being the most extensively studied. The decrease in maximum detrusor pressure to values under 40cmH_2O is crucial to prevent upper tract deterioration [12] Although more limited data, there is still support for using darifenacin, solifenacin, trospium, tolterodine, and propiverine. Most of the studies are short duration (<12 weeks), so the long-term efficacy and tolerability of antimuscarinics are largely unknown in this population.

Mirabegron

Mirabegron (Myrbetriq®) is a selective β-3 agonist. Initial starting dose is 25 mg daily and can be increased to 50 mg daily. A retrospective study of 15 patients with NDO demonstrated improvements in urinary frequency and number of incontinence episodes. There were also improvements in urodynamic parameters, including increased MCC and compliance [47].

Since mirabegron has a different mechanism of action from antimuscarinics, combining the treatments may provide additional benefit. In an animal model of rats with SCI, the combination of oxybutynin and mirabegron reduced detrusor contractions and increased bladder compliance to a greater extent than either medication alone [48].

Mirabegron avoids the anticholinergic effects of constipation and dry mouth but can have cardiovascular side effects including mild elevations in blood pressure and small, dose-dependent increases in heart rate [49, 50]. Caution should be used in patients with uncontrolled hypertension and tachycardia.

Imipramine

Imipramine is a tricyclic antidepressant (TCA) that has systemic antimuscarinic effects and inhibits reuptake of noradrenaline and serotonin and may potentially work by both decreasing bladder contractility and increasing outlet resistance. In a study from 1972 of 9 patients, receiving imipramine 1.0–2.5 mg/kg/day, 6 had improved urinary incontinence. No adverse events were reported in this study, but the cardiovascular toxicity of TCAs has been well described, so it should be used with caution [51]. No other studies have been done assessing efficacy of imipramine on NDO.

Combined Medications

Patients not responsive to high-dose single antimuscarinic drug therapy may respond to combined high-dose antimuscarinic therapy with comparable side effects to standard dosing [52]. Multidrug therapy with two or three drugs may provide additional benefit as one study suggests, particularly in those patients who failed a single antimuscarinic drug [53].

Other Medications

Cyclooxygenase inhibitors have shown a benefit in treatment of NDO in animal models through suppression of unmyelinated C fibers [54]. However the potential side effects on the gastrointestinal, renal, and cardiovascular systems have prevented widespread clinical application for this indication. Tramadol is a μ-receptor agonist that has shown inhibition of detrusor contractions in animal studies but has not been specifically studied in patients with NDO [55].

Botulinum Toxin A

Botulinum toxin A (BTX-A) (Botox®) is a potent neurotoxin produced by *Clostridium botulinum*. It works by blocking the release of ACh from both preganglionic and postganglionic parasympathetic nerves at the neuromuscular junction leading to flaccid paralysis of the detrusor muscle. The injection of BTX-A into the detrusor for management of NDO was first described by Schurch and colleagues in 2000 [56]. Six weeks following injection, 89% (17/19) of patients had continence

restored. Also, both MCC (216–416 mL) and reflux volume (296–481 mL) significantly increased. Since then, many studies have done showing long-term efficacy and safety. Over a 4-year study, patients with NDO received BTX-A 200 or 300 units as needed for symptom control and on average had a 9-month duration of effect. Improvements in incontinence episodes and quality of life were consistent over the duration of the study, suggesting that subsequent injections do not have decreased efficacy. Urinary tract infection was the most common complication at a rate of 13.2% [57].

In summary, antimuscarinic medications are currently considered first-line medical treatment in the management of NDO [58]. In head-to-head trials, the antimuscarinic medications appear to have equal effect, such that one cannot be recommended over another in the management of NDO. Depending on receptor selectivity, the side effects vary slightly among the medications, with tolterodine and trospium having fewer side effects than oxybutynin. Additionally, the side effect profile favors extended-release formulations over immediate release when possible. It is also necessary to note the administration of antimuscarinics to elderly adults should be done with caution due to risk of development of CNS effects.

More recent data supports the use of mirabegron as effective in improving clinical and urodynamic parameters in the NDO population. Combination of drugs for treatment of NDO may provide additional benefit over monotherapy. BTX-A should be considered in patients whose bladder capacity or compliance declines despite optimal medical therapy or patients who are intolerant to the side effects of the medications.

Detrusor Sphincter Dyssynergia (DSD)

Suprasacral lesions can result in detrusor sphincter dyssynergia (DSD) [59]. DSD is diagnosed on urodynamic study and is characterized by increased electromyography activity and a closed sphincter, with secondary ballooning of the posterior urethra, on voiding cystourethrogram during detrusor contraction [60]. Measurement of urethral pressures has also been described in the diagnosis of DSD [61]. Diagnosis and management of DSD are critical to prevent renal dysfunction from impaired bladder compliance. As mentioned, patients with DSD often also have NDO, and in combination, this can lead to a poorly compliant bladder. Additionally, patients with DSD may be at risk for autonomic dysreflexia.

Baclofen

When baclofen, an antispasmodic drug, is delivered intrathecally, it may inhibit neurons of the CNS, in particular, of Onuf's nucleus. In three patients with spastic paraplegia who received continuous intrathecal baclofen, there was resolution of DSD in one patient although all reported significant improvements in urinary

symptoms [62]. Other skeletal muscle relaxants, including dantrolene and valium, have also been trialed without any significant success [63].

Alpha Blockers

It was considered that alpha blockers may have a role in the treatment of DSD to induce sphincter relaxation; however, a study of terazosin 5 mg daily did not demonstrate improvements in voiding pressures [64].

Botulinum Toxin A

As mentioned, botulinum toxin A (BTX-A) inhibits the release of ACh from presynaptic neurons at the neuromuscular junction. Its use for the management of DSD was first evaluated by Dykstra and colleagues. They injected the sphincter with a low dose of BTX-A in 11 men once per week for 3 weeks with resultant decreased urethral pressures and post-void residuals, with an average duration of efficacy of 50 days [65]. In a more recent study, significant reductions in urethral pressures and post-void residuals were seem following intrasphincteric injection of 100 units [66].

BTX-A can be injected into the sphincter either transurethrally or transperineally. There is no standard protocol, but the sphincter is usually injected in a few places along the dorsal aspect (between 9 and 3 o'clock) with a total dose of 100 units [61].

A Cochrane review including four trials showed that injection of BTX-A in the sphincter can improve urodynamic parameters, specifically higher voided volumes and lower detrusor pressures [67]. Intrasphincteric injection of BTX-A could be considered an alternative to sphincterotomy given the lower morbidity, although repeated injections are needed when the effects of the BTX-A dissipate.

Potential side effects of intrasphincteric BTX-A injection is spread to adjacent muscles, as seen in the study by Dykstra et al. who noted limb paresthesia that resolved over 2–3 weeks [68]. However, later series did not note any complications [69].

Sphincter Underactivity

Sphincter underactivity causes low outlet resistance and symptoms of stress urinary incontinence. Drugs targeting bladder outlet resistance have not been specifically studied in the neurogenic population. Nonetheless, several classes of medications have been studied for SUI including alpha adrenergic receptor agonists, beta adrenergic receptor agonists, and tricyclic antidepressants; only serotonin-norepinephrine reuptake inhibitors have shown some benefit.

Duloxetine (Cymbalta®) inhibits the presynaptic reuptake of serotonin and norepinephrine at the level of the sacral spinal cord. Duloxetine is approved for use in Europe for women with SUI. A systematic review of nine randomized controlled trials comparing duloxetine to placebo showed improvements in incontinence episode frequency and quality of life, but there was no clear difference in objective data causing the authors to conclude that long-term clinical efficacy of duloxetine on SUI is unclear [70]. Overall, the evidence is weak in the female SUI population and not studied in the neurogenic population. Surgical therapy remains the mainstay in the definitive management of an incompetent sphincter in the NDO population.

Adjunct Medical Treatment

Nocturnal Polyuria

Desmopressin (Minirin®, Nocdurna®, Noctiva™) is a synthetic analogue of vasopressin, which binds V2 receptors in the renal collecting ducts, resulting in increased water reabsorption, urine concentration, and decreased urine volume [71]. It is currently approved for use in patients with nocturnal polyuria. A meta-analysis on the efficacy of desmopressin in patients with multiple sclerosis showed a significantly lower voiding frequency in the first 6–8 h following administration and reduced nocturnal urine volume [72]. Desmopressin is contraindicated in patients with hyponatremia or renal dysfunction. Given the risk of hyponatremia, baseline and periodic serum chemistry after initiation of treatment are recommended.

Patients with neurologic disease affecting the autonomic system may have loss of diurnal variation in blood pressure due to loss of vascular tone. Fluid redistribution while supine at night can result in a relative hypertension and increased renal blood flow which can lead to increase in urine production or nocturnal polyuria [73]. Additionally altered levels of antidiuretic hormone, with higher concentrations during the day, influence renal filtration of sodium and water, increasing urine production at night relative to daytime, which is the opposite of normal physiology [74].

Autonomic Dysreflexia

Spinal cord injury patients with lesions above the level of T6 are at risk for autonomic dysreflexia, which is the result of unopposed sympathetic discharge that can occur with noxious stimuli, such as bladder distention. The symptoms of autonomic dysreflexia include headache, sweating, flushing above the level of the lesion, hypertension, and reflex bradycardia, although there is a variable spectrum of presentation. If not properly recognized and treated, this can become life-threatening. If the cause of the autonomic dysreflexia is bladder distention, the first step in management is bladder drainage. Several pharmacologic agents can

be used for the treatment of autonomic dysreflexia; current recommendation is placement of 2% nitroglycerin paste above the level of the lesion for rapid blood pressure reduction [75].

Terazosin has also been studied in a small group of adult SCI patients for its effect on decreasing the severity and frequency of autonomic dysreflexia. At all follow-up time points (1 week, 1 month, and 3 months), there were significant decreases in the frequency of AD episodes. At 3 months, during an AD episodes, there were improvements in the severity of systolic blood pressure elevation, heart rate, degree of sweating, and duration compared to baseline severity [76].

Management of DSD may also influence frequency and severity of autonomic dysreflexia. Following intrasphincteric injection of BTX-A for DSD, Dykstra et al. also noted improvements in autonomic dysreflexia [65].

Follow-Up of Patients with Neurogenic Bladder

NLUTD is an evolving condition, and lifelong follow-up is necessary in this patient population to prevent the occurrence of complications, particularly renal failure. Periodic assessments must be performed, including upper tract imaging and repeat urodynamic evaluation at least every 1–2 years and sooner if clinical condition warrants [58]. If a patient's bladder function worsens despite optimal medical treatment, surgical intervention should be considered.

Future of Medical Therapy

As understanding of the pathophysiologic mechanisms underlying NLUTD continues to increase, there is potential for new pharmacologic therapies to be developed. The role of ICCs is unfolding, and there is potential for targets of c-kit, a proto-oncogene expressed by ICCs, to aid in the treatment of detrusor overactivity [8]. Additionally, as the field of regenerative medicine continues to expand, the role for tissue engineering may move to clinical applications in patients with NLUTD. Currently, researchers are able to induce urothelial cells from stem cells, but continued work is needed to create a sustainable bladder reservoir capable of filling and emptying [77].

Conclusions

Early diagnosis and treatment are imperative to preventing long-term complications from NLUTD. A multidisciplinary and individualized approach is often necessary in this complex patient population. The success of antimuscarinic therapy for NDO

is well documented and when used in combination with other drugs may maximize efficacy. BTX-A injection into the bladder and sphincter has shown great efficacy in the management of NDO and DSD, respectively. In the future, the use of stem cells in bladder tissue engineering may play a bigger role in the management of NLUTD. Close and lifelong follow-up of all patients with NLUTD is essential to prevent secondary complications.

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