Improving Outcomes in Patients with Refractory Idiopathic and Neurogenic Detrusor Overactivity: Management Strategies

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Abstract
Neurogenic detrusor overactivity (NDO) is a lower urinary tract dysfunction commonly seen in rehabilitation settings. The emotional, medical, and financial consequences of NDO can be substantial and management typically requires a multidisciplinary team approach. Physiatrists need to be able to identify patients who require referral to specialists for diagnostic testing or higher-tiered treatment and need to engender open lines of communication between their patients and all treating clinicians. This requires an understanding of the evaluation, diagnosis, and treatment of neurogenic lower urinary tract dysfunctions.

Keywords
Urinary bladder; neurogenic; urinary incontinence; lower urinary tract symptoms; spinal cord diseases; botulinum toxins, type A

Abbreviations
FDA, US Food and Drug Administration
HRQOL, health-related quality of life
MS, multiple sclerosis
NDO, neurogenic detrusor overactivity
NGB, neurogenic bladder
NLUTD, neurogenic lower urinary tract dysfunction
OAB, overactive bladder
PTNS, percutaneous (or posterior) tibial nerve stimulation
SCI, spinal cord injury
SNM, sacral neuromodulation
UI, urinary incontinence
UTI, urinary tract infection
INTRODUCTION

Neurogenic detrusor overactivity (NDO) and refractory idiopathic overactive bladder (OAB) are lower urinary tract dysfunctions (LUTDs) commonly seen in rehabilitation settings. Common populations affected by these disorders include patients with multiple sclerosis (MS), spinal cord injury (SCI), Parkinson’s disease, stroke, dementia, and diabetes. Both NDO and OAB involve a disturbance in storage and emptying of the bladder. NDO is a urodynamic condition, defined as uninhibited, involuntary bladder contraction during the filling phase of a urodynamic study.\(^1\) Neurogenic bladder (NGB) involves abnormal bladder function and/or sphincter dysfunction secondary to central nervous system injury or neurologic disease.\(^2,3\) According to the Standardization Subcommittee of the International Continence Society, OAB is defined as a symptom syndrome suggestive of lower urinary tract dysfunction, characterized by urinary urgency, with or without urge urinary incontinence, and usually with urinary frequency and nocturia.\(^1,3,4\)

The medical, psychosocial, and economic consequences of NDO and OAB are significant, including increased morbidity and mortality. NDO can be detrimental to the upper urinary tract, causing hydronephrosis or renal failure,\(^5,6\) as well as to the lower tract, resulting in urinary tract infections (UTIs)\(^7,8\) or kidney and/or bladder stones.\(^8\) Historically, renal failure was the leading cause of death in patients with spinal cord injury. However, earlier diagnosis and advances in treatment of NLUTD have reduced the incidence of renal failure in patients with SCI with respiratory infections now being the leading cause of death.\(^9\) NLUTD is rarely a significant cause of mortality in patients with MS or Parkinson’s disease, but remains a risk among patients with meningomyelocele who do not undergo urologic treatment.\(^9\) Chronic incontinence can lead to dermatologic problems and skin breakdown.\(^10,11\) In addition, studies have shown that post-stroke UI is negatively associated with 2-year survival rates, worsened disability as measured by the Barthel index, and increased rates of institutionalization.\(^12\) In fact, urinary incontinence is a powerful predictor for whether stroke patients can be discharged to home from an inpatient setting.\(^13\) UI has also been associated with an increased risk of falls and fractures in the elderly\(^14\) and in persons in nursing homes,\(^15\) leading to higher rates of institutionalization among frail older persons.\(^16\)

The impact of NDO or OAB on health-related quality of life (HRQOL) is significant,\(^17-20\) and NDO with UI causes a significantly greater effect on HRQOL than NDO without incontinence.\(^19\) UI and OAB are associated with depression,\(^21\) loss of self-respect or dignity, decreased productivity in
the workplace, interference with sleep\textsuperscript{23} and sexual activity\textsuperscript{24} and a restriction of social activities due to fear of UI or because of the need for frequent voids.\textsuperscript{22} In addition, incontinence pads are particularly expensive, and their use has been estimated to account for nearly two-thirds of the annual per-patient costs of OAB management.\textsuperscript{25} In fact, in 2009, the cost to treat OAB was estimated at nearly $25 billion,\textsuperscript{26} and the overall cost of nonneurogenic OAB with urge incontinence was $65.9 billion in 2007 and is estimated to reach $76.2 billion by 2015.\textsuperscript{27} Other cost factors include diagnostic testing, medications, healthcare providers, and equipment, as well as costs associated with lost productivity and health-related consequences.\textsuperscript{28-30}

**ETIOLOGY AND SYMPTOMS**

The function of the lower urinary tract is primarily to store and void urine. The lower urinary tract is regulated by a neural control system located in the brain and spinal cord that coordinates the activity of the bladder and bladder outlet/urinary sphincter (Figure 1).\textsuperscript{9} Consequently, NLUTD results from any disturbance in the nervous systems that control the lower urinary tract. Disruption of the connection between the pontine micturition center and the sacral cord (i.e., suprasacral lesion/injury) results in poor coordination between the detrusor muscles and the external urethral sphincter muscles, leading to detrusor-sphincter dyssynergia. Poor sphincter competence or sphincter incompetence can lead to stress urinary incontinence. Detrusor overactivity is associated with suprasacral neurologic lesions and is characterized by involuntary detrusor contractions during the filling phase that may be spontaneous or provoked, and can result in increased urinary frequency, urgency, and urge incontinence (or UI).
The 2 most common causes of NDO are MS and SCI; other common causes include Parkinson’s disease and stroke. As seen in Table 1, a wide range of neurologic conditions have been associated with NDO. Supraspinal neurologic diseases, such as Parkinson’s disease and cerebral palsy, occur above the pontine micturition center and generally cause NDO with synergistic voiding (e.g., no detrusor-sphincter dyssynergia). Suprasacral injuries involving the spinal cord result in NDO with detrusor-sphincter dyssynergia, as well as an increased risk for other urologic complications such as hydronephrosis, vesicourethral reflux, or urolithiasis. Sacral spinal cord lesions, associated with spina bifida or myelodysplasia, and peripheral neurologic disease are associated with acontractile detrusor—with reduced perianal sensation and sphincter tone. However, the high rate of “exceptions” to these categorizations necessitates proper and comprehensive neuourologic evaluations.
Table 1. Neurologic Conditions Associated With NDO

<table>
<thead>
<tr>
<th>Brain</th>
<th>Spinal Cord</th>
<th>Peripheral Nervous System and Neuromuscular Junction</th>
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<td>Cerebellar ataxia</td>
<td>Acquired immune deficiency syndrome</td>
<td>Pernicious anemia</td>
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<td>Diabetic neuropathy</td>
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<td>Cerebral palsy</td>
<td>Ankylosing spondylitis and disk disease</td>
<td>Poliomyelitis</td>
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<td>Myasthenia gravis</td>
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<td>Dementia</td>
<td>Guillain-Barré syndrome</td>
<td>Spinal cord injury</td>
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<td>Pelvic plexus injury</td>
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<td>Multiple system atrophy</td>
<td>Herpes zoster</td>
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<td>Neoplasms</td>
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<td>Parkinson’s disease</td>
<td>Multiple sclerosis</td>
<td>Transverse myelitis</td>
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<td>Stroke</td>
<td>Myelomeningocele</td>
<td>Tropical spastic paraparesis</td>
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Patients with NDO often present with UI, although the symptoms vary.33 An estimated 23.6% of patients with stroke, one-third of patients with Parkinson’s disease, half of patients with MS, and 52.3% of patients with SCI have UI.34 The incidence of bladder dysfunction, including but not solely due to NDO, is also high—affecting 68% of those with SCI, 37% to 72% of patients with MS, and 35% to 70% of patients with Parkinson’s disease.35 The interplay between the urodynamic condition and symptom awareness/presentation can be complex and hard to predict. Patients with MS often manifest with frequency, urgency, and urge incontinence. They typically have intact sensation—as such, they are aware of the ‘urge’ feelings. However, they may also have problems with holding/storing urine or incomplete emptying. Patients who have had a stroke may also have frequency, urgency, and urge incontinence; their sensation is also usually intact, although sometimes they may not feel uninhibited bladder contractions and may have UI without their knowledge. The bladder consequences of SCI depend on the degree of the spinal injury. Patients with complete SCI usually will have UI without any bladder sensation; however, they may be aware of bladder activity because of autonomic dysreflexia. In contrast, patients with incomplete SCI may have some sensation. Finally, management of patients with Parkinson’s disease can be particularly challenging as they can have UI, urgency, and
incomplete emptying combined with the inability to move rapidly enough to get to the toilet.

There are also non-urologic causes for UI. For example, some patients may not be able to communicate their need to urinate—whether owing to aphasia, dysfluency, dysphonia, or even language barriers. They may have impaired or decreased mobility, poor dexterity, or confusion and delirium. Older patients can have non-neurologic as well as neurologic urinary issues (e.g., normal-pressure hydrocephalus). Women might have concomitant stress urinary incontinence, prolapse, and/or OAB; men may also have prostate problems such as benign prostatic hyperplasia.

**EVALUATING REFRACTORY IDIOPATHIC OAB AND NDO PATIENTS**

Urinary symptoms in neurologic patients may stem from non-neurologic etiologies, such as bladder abnormalities—bladder cancer, bladder stones, or interstitial cystitis; prostate or urethral abnormalities, prostate cancer, or urethral stone (in men); pelvic prolapse (in women); or stress urinary incontinence. Symptoms can also stem from urogenital infections, such as bacterial cystitis, prostatitis, or urethritis.

In contrast to uncomplicated OAB, which is a clinical syndrome primarily diagnosed through urologic history, urogenital physical examination, and urinalysis, diagnosis of NDO is generally more involved. However, some patients with OAB may require a more extensive evaluation such as that recommended for NDO. The evaluation for patients with suspected NDO involves an expanded physical examination (pelvic, rectal, and neurologic), urinalysis and urine culture, and blood chemistry, as well as a more comprehensive history that should encompass medical, social, and general history; history of diabetes, stroke, accidents or surgeries, especially those involving the spine or central nervous system; QOL; social history, including smoking and drug or alcohol use as well as hereditary or familial risk factors. Physical examination needs to note sensations from S2-S5 on both sides—presence of sensation, type of sensation, reflexes; anal sphincter tone; and prostate exam (men) or evaluation of pelvic organ prolapse (women). The urologic history should include information about initiation of micturition—normal, precipitate, reflex, strain, Credé; whether the patient is catheterized; bladder sensations; relief after voiding, and incontinence patterns. A bowel and sexual history may also be important.

Neurologic history should address acquired or congenital neurologic conditions (e.g., parkinsonism, MS, stroke), mental status, and onset and evolution of any neurologic symptoms; spasticity, mobility, hand function, and presence of autonomic dysreflexia. Helpful studies
include a bladder and/or renal ultrasound if indicated, and urodynamics including postvoid residual volume. The key for evaluating the patient with presumed NDO is multichannel urodynamic testing. Additional assessments that may be used to supplement the findings include questionnaires, diaries, and pad tests.

The clinical presentation, symptoms, and course of NDO all depend on the location and extent of the underlying neurologic condition. Not all patients will require a urodynamic workup—some patients, including those with MS, may be treated empirically; a full discussion of this is beyond the scope of this paper. Many MS patients, especially female patients, can be empirically treated without a concern of upper tract damage. However, if there is any concern or suboptimal response to therapy, then further evaluation with UDS would be indicated. However, symptoms and the physical exam do not always correlate with the injury type, extent, or level or with the prognosis or danger to kidney function. Patients with SCI or adult spina bifida require an urodynamic evaluation to ensure safe bladder storage pressure prior to determining treatment.

**PHARMACOLOGIC AND NONPHARMACOLOGIC TREATMENT OPTIONS FOR NDO**

Currently, the only guidelines that specifically and solely address neurogenic lower urinary tract dysfunction are by the European Association of Urology in 2011. In order of importance, the EAU guidelines report the goals of treatment for NDO are to (1) protect the upper urinary tract by reducing the risk of NLUTD, (2) improve the level of urinary continence; (3) preserve and restore lower urinary tract function; and (4) improve patient QOL by relieving symptoms. Table 2 lists the range of available guidelines related to diagnosis and management of bladder problems in adults. It should be noted that not all treatments recommended for OAB are equally effective or beneficial for patients with NDO.
There are numerous objective and subjective approaches that can be used for assessing patient baseline parameters and defining treatment success. Bladder diaries are useful tools to evaluate baseline lower urinary tract dysfunction, follow changes with treatment, and help monitor patient satisfaction; however, patients do not always maintain diaries optimally. Other potential outcomes that should be factored include number of UTIs and AD. For OAB patients, success is determined by patient satisfaction, which can objectively be evaluated by a variety of validated questionnaires. For NDO patients, success is often a combination of clinical and urodynamic outcomes. Weighing pads before and after exercise is a more objective approach for determining whether a patient is incontinent and, if so, how much a patient is leaking. Similarly, medications like pyridium can determine if there is UI. Evaluating the number of UTIs, episodes of autonomic dysreflexia in patients with SCI, can also be used to define success. Qualitative outcomes such as community participation, self-esteem, sleep quality and quantity, mood, and other measures of QOL are also important. Urodynamics allow for an objective measurement of improvement and are an extremely important measure for patients that have elevated bladder pressures that place their upper tracts at risk prior to initiation of therapy.

**First-line Treatments**

According to the EAU guidelines for NLUTD, first-line options include a range of noninvasive conservative treatments, such as behavioral modification techniques, lifestyle modifications, prompted voiding and timed voiding/bladder training. Pelvic floor muscle exercises aimed at improving continence may be helpful in select patients, and biofeedback may be useful in supporting voiding pattern modification. These recommendations are similar to those of the
American Urological Association/Society for Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (AUA/SUFU) Guidelines for OAB, in which the first line of treatment involves lifestyle changes and behavioral modifications, with or without antimuscarinics. Consistent with both the EAU and AUA/SUFU guidelines, first, second and third line treatments are tiered in order of invasiveness, and, as per the guidelines, are recommended to be used in a stepwise approach.

Lifestyle changes and behavioral modifications can include modifying fluid and caffeine intake, timed voiding, pelvic floor muscle training, biofeedback, and/or toileting assistance. Nicotine irritates the detrusor muscle and causes bladder contractions and urgency, and repeated coughing can cause urinary leakage; consequently, clinicians recommend that patients with OAB or NDO quit smoking. Straining associated with constipation can also put pressure on the bowel; as such, interventions to minimize constipation are warranted.

Bladder rehabilitation techniques, generally based on electric or magnetic stimulation, aim to help patients with NLUTD regain voluntary control over their lower urinary tract. Some of the techniques—electrostimulation, intravesical electrostimulation, and peripheral temporary electrostimulation—may be beneficial to a small group of patients, such as those with MS or an incomplete SCI; however, there is a lack of well-designed studies to evaluate the benefits and appropriate candidates for these techniques.

Some patients may prefer a nonpharmacologic, behavioral approach. In general, some patients do respond well to these first-line approaches; however, lifestyle modifications are often labor intensive and time consuming, requiring active patient participation and persistence, and the results are very gradual. Behavioral training is most valuable in patients who have some degree of bladder control and intact bladder sensation, including those with neurologic lesions involving the brain such as cerebrovascular disease, Parkinson’s disease, multiple system atrophy, dementia, and cerebral palsy, as well as those with MS, incomplete SCI, transverse myelitis, and diabetes mellitus.

**Second-line Options**
Pharmacologic approaches comprise second-line therapy for both NDO and OAB and includes antimuscarinics and the beta3-agonist mirabegron. As yet, there is no single optimal medical therapy for NLUTD, and many patients require combination pharmacotherapy.
selection depends on patient history of prior antimuscarinic use, prior adverse events and their impact on the patient, patient preferences, whether there are any comorbid conditions, and the use of other medications. In general, there are 3 classes of agents used to treat OAB: antimuscarinics, the beta3-agonist mirabegron, and tricyclic antidepressants.

Antimuscarinic agents are first-line choice for treating NLUTD because of their established action to stabilize and relax the detrusor muscle, leading to improved bladder compliance and reduced lower urinary tract symptoms. Among the commonly used antimuscarinics are oxybutynin chloride, tolterodine tartrate, solifenacin, darifenacin, trospium chloride, and fesoterodine. These agents normalize intravesical pressure and increase cystometric bladder capacity. They significantly reduce maximum detrusor pressure; however, reduction in detrusor overactivity persists only while the patient remains on the treatment. In addition, antimuscarinics are associated with several commonly noted adverse effects, particularly dry mouth and constipation, which can interfere with patient adherence to treatment. While there are differences in tolerability and safety between the agents, there is no compelling evidence for differential efficacy across the medications. Patients with NDO may benefit from higher doses of medications than do patients with OAB—e.g., 30 mg oxybutynin, 8 mg tolterodine extended release, or 90 mg trospium—which can lead to increased incidence of adverse effects. American Urological Association guidelines for OAB recommend the use of once-daily, extended-release dosing regimens whenever possible, to limit the bothersome side effects associated with the peaks and troughs of multidosing, immediate-release, regimens. This approach, as well as alternative routes of administration—transdermally or intravesically—may help reduce side effects in patients with NDO.

There has been growing awareness that antimuscarinic treatments may have adverse central nervous system effects, including headaches and cognitive impairment. Studies have shown that there are differences among the various antimuscarinic agents, predominantly in their ability to penetrate the blood-brain barrier. Specifically, oxybutynin and other lipophilic tertiary amines are more likely to cross the blood-brain barrier than are hydrophilic quaternary amines, such as trospium chloride, which has few reports of adverse central nervous system effects. In fact, the potential for anticholinergic central nervous system events has been included in product labeling for oral oxybutynin since 2008. Clinicians need to be cognizant of the potential for cognitive impairment with nonselective antimuscarinic agents, particularly among older patients or those with diseases or injuries affecting the brain, and select treatment
Antimuscarinics should not be used in patients with narrow-angle glaucoma unless otherwise approved by the treating ophthalmologist, should be used with extreme caution in patients with impaired gastric emptying or a history of urinary retention except for the patient with NDO where the goal in medical therapy is placing the patient into urinary retention and bladder management with CIC; and used with caution in patients using other medications with anticholinergic properties or in frail OAB/NDO patients. Although long-term persistence with pharmacotherapy is required for consistent results, adherence after 3 months is relatively poor due to bothersome side effects such as dry mouth and constipation. Clinicians need to manage constipation and dry mouth before abandoning effective antimuscarinic therapy. Although antimuscarinic agents do not have an FDA-indication for the management of NDO they are well-accepted as first line pharmacotherapy. Studies have demonstrated efficacy of at least 4 of them—oxybutynin, trospium chloride, tolterodine, and darifenacin—in this patient population.

The detrusor muscle contains beta-adrenoceptors. Human bladder and urothelium contain beta1-, beta2-, and beta3-adrenoceptors; 97% of beta adrenoceptors in the human bladder are beta3. Beta2-adrenoceptors are important in muscle relaxation through activation of adenylate cyclase; evidence indicates that beta3-adrenoceptors mediate relaxation of human detrusor muscle. Consequently, selective beta3-adrenoceptor agonists have been investigated and developed as treatment for OAB syndrome. Evidence suggests the effect of beta-adrenoceptor stimulation is similar in both normal and neurogenic bladders. Mirabegron is the first and only beta3-agonist with FDA approval for OAB. It has minimal intrinsic activity on beta1 or beta2 adrenoceptors, and thus minimizes or eliminates the undesirable adverse effects associated with them, such as increased heart rate and muscle tremors. The incidence of dry mouth associated with mirabegron is similar to that with placebo and reportedly threefold lower than that with tolterodine. The most common side effect is dose-related elevation in blood pressure, which occurs in 7.5% to 11.3% of patients. Mirabegron is taken once daily and can be used as a primary treatment or add-on therapy with an antimuscarinic in OAB.

Tricyclic antidepressants, including imipramine, doxepin, desipramine, and nortriptyline, are frequently used for pain and sleep in the rehabilitation setting. Although they have an
anticholinergic and direct muscle relaxant effect on the urinary bladder, they are not FDA-approved for OAB or NDO. In fact, physiatrists and other clinicians need to be aware of their effects on the bladder and the potential for adverse effects.\(^{46}\)

**Third-line Options**

Patients who have failed to respond to behavioral interventions or pharmacotherapy may be considered for any of the third-line options, including percutaneous (or posterior) tibial nerve stimulation (PTNS), sacral neuromodulation (SNM), or injections with botulinum toxin A. Intravesical pharmacotherapy, including intravesical administration of anticholinergics, may be beneficial in minimizing detrusor overactivity in some patients. Catheterization may be appropriate for a select group of patients with NDO in whom detrusor overactivity can be pharmacologically controlled.\(^{9}\)

**Percutaneous (or posterior) Tibial Nerve Stimulation (PTNS).** PTNS involves stimulation of the posterior tibial nerve. It is the least invasive form of neuromodulation, involving retrograde stimulation of the sacral nerve plexus. This therapy is FDA-approved for OAB; however, there is also a fair amount of data on use of PTNS in patients with MS, leading to statistically significant improvements in urodynamic and clinical parameters after 12 weeks.\(^{76}\) Further, chronic PTNS appears effective in MS patients.\(^{77}\) Other, albeit limited studies in patients with NDO appear promising.\(^{33}\) An important component of successful PTNS treatment is compliance with the protocol: patients are initially treated in the office once weekly for 12 weeks; patients who demonstrate a response are then treated on a once-monthly basis. Currently, PTNS is only FDA-approved for OAB and urge incontinence and may be beneficial for refractory patients with moderately severe baseline UI and urinary frequency.

**Sacral Neuromodulation.** As with PTNS, SNM is approved for the treatment of the symptoms of OAB, including urge incontinence and significant symptoms of urgency-frequency alone or in combination, among patients who have failed or cannot tolerate more conservative treatments. It is also indicated for fecal incontinence and nonobstructive urinary retention in patients who have failed or cannot tolerate more conservative treatments, and it is used off-label for patients with NGB/NDO.\(^{46,78}\)

SNM involves stimulation of the 3rd sacral foramen—the nerve most responsible for bladder function (Figure 2). The treatment is performed in stages. The initial test phase identifies
patients who respond to temporary percutaneous nerve evaluation. Patients who respond—defined as those who demonstrate at least a 50% improvement in target symptoms—can then proceed to full implantation of the pulse generator and leads. The implanted device includes a battery that must be changed every 5 years; the safety of full-body MRI has not been established for patients with this device and is not recommended by the manufacturer.

**Figure 2: Sacral Neuromodulation**

![Figure 2: Sacral Neuromodulation](image-referenced)

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Although SNM is a well-established and widely accepted treatment for refractory non-neurogenic LUTD, its use in patients with NLUTD is unclear, and data on its efficacy in neurogenic patients are lacking. A prospective multicenter study is currently underway in Switzerland to evaluate the efficacy and value of SNM in patients with NLUTD.

Among patients with NDO, SNM has been most often studied in the MS population but is generally limited to those patients who do not have progressive disease—specifically, only patients with relapsing-remitting MS who have not had a relapse in at least the prior 2 years. A recent study examining efficacy of SNM in NDO noted the results depend upon the underlying
Specifically, 54% of patients with MS, 46% of those with an incomplete SCI, and only 25% of those with Parkinson’s disease had a positive test stimulation result. After a mean follow-up of 4.3 years for those receiving the treatment, 75.7% of implanted patients considered the treatment successful. A retrospective case study of 23 patients in China with NGB and bowel dysfunction secondary to spinal cord disease found 13 patients responded to the initial testing phase with SNM, but only 6 responded to permanent SNM. However, combining chronic SNM with other treatments improved symptomatic relief.

Studies on patients with intractable (non-neurogenic) urge incontinence, urgency-frequency, and retention have demonstrated safety and sustained efficacy of the device in those patients who have responded to the initial test phase. Patients with the device who reported a significant decrease in 24-hour pad weight reported substantially greater satisfaction than did patients who did not report improvement in this incontinence parameter. Lack of efficacy and device pain are 2 factors that contribute to device dissatisfaction.

**Botulinum Neurotoxin Injections.** OnabotulinumtoxinA is the only third-line option that is FDA-approved for NDO, as well as for urge incontinence and OAB. It is an effective alternative for NDO patients who fail pharmacotherapy, and is safe and effective in catheterized refractory NDO patients. The EAU guidelines note that “botulinum toxin injection in the detrusor is the most effective minimally invasive treatment to reduce neurogenic detrusor overactivity”.

Injections with onabotulinumtoxinA have been shown to significantly improve QOL. The most common adverse effects associated with onabotulinumtoxinA treatment include UTIs, urinary retention (a temporary risk), hematuria, fatigue, and insomnia. There is a black box warning in the United States, stating that the effects may spread from the area of injection to produce symptoms consistent with botulinum neurotoxin effects, from an hour to a week after the injections. In addition, clinicians need to be aware if the patient is undergoing onabotulinumtoxinA treatments for other conditions such as spasticity, as there is a total dose limit of 360 units over a 3-month period of time and a similar interval between injections.

Injections can be performed in the office, using either a rigid or flexible cystoscope. Typically, a patient receives 20-30 injections of 0.5-1 mL (approximately 6-10 U) onabotulinumtoxinA in the bladder, located 1 cm apart and 2 mm into the detrusor (Figure 3). Go to [www.paradigmmc.com/342injvid](http://www.paradigmmc.com/342injvid) to view a short video of one of the authors performing the procedure.
The FDA approved doses are 200 U for NDO and 100 U for OAB. However for NDO/NGB patients that continue to void volitionally—often MS and Parkinson’s disease—the 100 U dose is usually considered to reduce the risk of post-injection retention requiring CIC. Most injection templates do not include injections into the trigone. Patients should be observed for at least 30 minutes after the injections. Treatment effects persist for 6 to 10 months and are dose-dependent. Patients may benefit from a local anesthetic prior to the injections.

There are 4 botulinum neurotoxin products available in the United States—but they are not interchangeable; only onabotulinumtoxinA has FDA-approval for NDO as well as OAB and urge incontinence. The other marketed formulations of botulinum neurotoxin are abobotulinumtoxinA, incobotulinumtoxinA, and rimabotulinumtoxinB.

Data from 2 double-blind, placebo-controlled trials demonstrated the safety and efficacy of onabotulinumtoxinA injections for NDO and led to its FDA approval. The first trial involved 154 patients with MS and 121 with SCI. The second trial involved 227 patients with MS and 189 with SCI, all of whom had at least 14 UI episodes per week and had already failed oral therapy. The patients were randomized to receive 30 intradetrusor injections of onabotulinumtoxinA 200 units (n=227), onabotulinumtoxinA 300 units (n=223), or placebo.
In each trial, both doses of onabotulinumtoxinA led to significant decreases in UI episodes per week versus placebo for patients with either MS or SCI (Figure 4). In the first trial, the reduction in UI episodes per week was 21.8 and 19.4 among patients receiving onabotulinumtoxinA injections, 200 units and 300 units, respectively, compared with a reduction of 13.2 episodes per week among patients receiving placebo.90 Similarly, the number of UI episodes per week decreased by 21 and 23 among patients in the second trial receiving onabotulinumtoxinA 200 units and 300 units, respectively, compared with a reduction of 9 UI episodes per week among those receiving placebo.91 Significant differences were also observed in the secondary endpoints in both studies (Figure 5).92 At week 6, treatment with onabotulinumtoxinA led to significant improvements in maximum cystometric capacity, maximum detrusor pressure during the first involuntary detrusor contraction, and I-QOL compared with placebo, as well as significantly longer median time to patient request for retreatment: 36-42 weeks versus 13 weeks, respectively. Further, both trials noted a significantly greater proportion of patients achieving dry status in the active treatment arms versus placebo. There were substantial and significant decreases in bladder pressures associated with the 2 treatment arms compared with placebo.92,96 However, the studies demonstrated no clinically relevant benefit in efficacy or duration for the 300-unit dose over the 200-unit dose, and there was a greater risk of urinary retention reported with the higher dose, resulting in approval for the 200-unit dose.90-92,96

Figure 4. Mean Change From Baseline in Weekly UI Episodes in MS and SCI

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Figure 5. OnabotulinumtoxinA Phase 3 Trials in NDO: Urodynamics

The most frequently reported adverse events noted within the first 12 weeks after intradetrusor injection were UTI, seen in 24% of patients treated with onabotulinumtoxinA 200 units and 17% receiving placebo, and new onset urinary retention requiring catheterization, seen in 17% and 3%, respectively. As such, it is important to discuss the possibility of self-catheterization with potential patients before beginning these treatments and make sure they are willing and able to initiate catheterization post-treatment, if required, for urinary retention.92

AbobotulinumtoxinA has also been evaluated and shown to be effective, although it does not have FDA approval for NDO. A trial involving 22 patients with NDO—13 men and 9 women—evaluated successive doses of abobotulinumtoxinA injected repeatedly into the bladder. Twelve patients received 500 units, and 10 received 1000 units. There was a constant effect following the 4 sets of injections, with similar duration and efficacy for both doses.97

Data from BOTOX [Prescribing Information]. Irvine, CA: Allergan, Inc; 2013.92
Surgical Options: Rare Cases

Surgical options are reserved as a last resort for patients who have not responded to any other approaches. When appropriate, patients may undergo bladder augmentation or urinary diversion; myomectomy and sacral rhizotomy are very rarely performed.9,33

MULTIDISCIPLINARY CARE, PHYSICIAN-PATIENT COMMUNICATION

Optimal management of patients with NDO requires a multidisciplinary team approach.98-100 Typically, the primary care physician and the physiatrist are aware of all active medical conditions and must be updated on medication or treatment decisions. In addition to the physiatrist, many patients in rehabilitation settings see a neurologist, nurse/nurse practitioner, and urologist for the evaluation and management of the bladder problems. Additionally, many patients need guidance and support from a wide range of other healthcare workers—including a nutritionist to monitor not only nutrition but also hydration; a counselor or social worker to provide emotional guidance, and a case manager to coordinate the patient’s other needs—from transportation, acquiring durable medical equipment or materials, and/or negotiating insurance, among others. The patient’s caregivers can, and in many cases should be an integral part of the team.

A recent study investigated the follow-up care of patients with NDO at 1 year.2 The study involved 46,271 patients overall; 9315 had SCI and 4168 had MS. Overall, 39% of the patients had been seen by a urologist at 1 year, including 36% of SCI patients and 26% of MS patients. More than half of the MS patients (53%) had been seen by a neurologist, compared with 18.5% of patients with SCI. However, fewer than 1 in 5 patients with SCI (18%) and only 7.5% of patients with MS had received physiatric care.2 Because of the potential impact of NDO on QOL and other health-related parameters, it is imperative that physiatrists follow up and monitor their patients throughout treatment for NDO, including establishing open lines of communication with the other treating clinicians.

Facilitating a patient-provider relationship based on trust, open dialogue and good communication has been shown to be beneficial for a patient’s HRQOL.101 This is true for all members of the multidisciplinary team. The importance of establishing appropriate treatment expectations cannot be underestimated. In a survey of 5400 patients, nearly half (45.4%) had discontinued treatment for bladder dysfunction because of unmet treatment expectations—not necessarily treatment failure—despite objective treatment success.102 Patients must
understand their various treatment options, including possible side effects; they need to understand the treatment goal may not be a “cure.”

In summary, both NDO and OAB are common among patients in rehabilitation settings, and both can have significant negative impact on medical stability and QOL. These patients need to be differentially identified and evaluated by the appropriate clinician(s) and treated accordingly (see Case Studies 1 and 2, below). In certain cases, patients can be treated empirically based on clinical presentation, but in the majority of cases of NDO, urodynamic studies are required. The pathophysiology may not be obvious. Initial treatment approaches focus on noninvasive lifestyle and behavioral modifications; however, many patients with NDO fail to adequately respond to these interventions, requiring second-tier options. Pharmacotherapies, particularly with specific antimuscarinics, have shown some efficacy for NDO. There are several third-tier options to treat patients who have failed oral pharmacologic therapy, including SNM, PTNS, and botulinumtoxin injections. Only the latter is specifically approved for management of NDO.
Case Study 1
A 44-year-old woman, gravida 3 para 2, with MS diagnosed at age 33 years, who uses a cane when walking, although she has been relying on a wheelchair with increased frequency. Fatigue and spasticity are contributing to her decreased mobility. She is on baclofen to treat her muscle spasticity, which can cause loss of bladder control in about 1% of patients.103

Complaint and Evaluation: Her presenting complaints are urinary frequency/urgency and worsening UI. She is currently taking solifenacin 5 mg without optimal response. Her exam is unremarkable, Urinalysis: white blood count, 6-10; postvoid residual volume: 95 mL.

Initial treatment: The treating clinician considers numerous treatment options: increasing the dose of solifenacin from 5 to 10 mg; adding or switching to mirabegron; referring her for pelvic floor muscle training; SNM; performing urodynamics; and botulinum neurotoxin injections. She is not likely to be a good candidate for pelvic floor muscle training and is not willing to try more involved treatments, so the clinician adds mirabegron to the solifenacin.

Follow-up: The patient reports minimal benefit to the addition of mirabegron to solifenacin. The clinician now performs urodynamics, which demonstrate detrusor overactivity with significant leakage. The clinician discusses the benefits and risks associated with indwelling (Foley) catheters and suprapubic (SP) tubes, and notes that these options may be ideal for a group of patients, but can carry risks of UTI, hematuria, stones, cancer, and urethral erosion. The patient considers and decides against an indwelling catheter and off-label PTNS; the clinician determines she is a good candidate for onabotulinumtoxinA injections. Because she is voiding volitionally, a total of 100 units of onabotulinumtoxinA are used. She reports a substantial response to the treatment on follow-up.
Case Study 2

A 68-year-old male with an SCI from a motor vehicle accident 8 years earlier. He has hypertension and diabetes. He’s a C6, American Spinal Injury Association Impairment Scale D. He lives with his wife who assists with his care, and he has an aide come in for 1 hour a day. When last checked 12 months earlier, his postvoid residual volume was low. He is on oxybutynin 5 mg TID.

Complaint and Evaluation: He voids volitionally but has new onset UI and recurrent UTIs over the past 6 months. On digital rectal examination, he has a 45-g prostate that is moderately enlarged. Urinalysis is within normal limits and his postvoid residual volume is 250 mL.

Initial Treatment: The treating urologist considers tamsulosin, mirabegron, antimuscarinics, botulinum neurotoxin injections, and SNM. However, because this is an older patient, the clinician must consider the possibility of an obstruction. The patient is treated empirically with tamsulosin, and his postvoid residual volume decreases to 150 mL, but he remains symptomatic. Urodynamics are consistent with detrusor overactivity and bladder outlet obstruction with a low peak flow of 6 mL/s and an elevated detrusor pressure at peak flow of 73 cm H₂O. His treatment options are limited because of the obstruction—he is not willing to consider an indwelling catheter; and the obstruction minimizes therapies aimed solely at OAB/detrusor overactivity.

Follow-up: The clinician explains to the patient that his treatment must be multistep: First they must address the obstruction. If, after that, his detrusor overactivity does not normalize, additional examination would be warranted. The clinician explains that approximately 60% of men with lower urinary tract symptoms who have detrusor overactivity and bladder outlet obstruction on urodynamics will see improvement of the lower urinary tract dysfunction once the obstruction is removed. Other options would then include an antimuscarinic or mirabegron; if he fails those, he would then be a candidate for a third-tier option, including PTNS, SNM, and onabotulinumtoxinA.
<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name(s)</th>
<th>Dose</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin</td>
<td>Enablex</td>
<td>Starting dose is 7.5 mg once daily. May be increased to 15 mg once daily based on response.</td>
<td>Oral tablet</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Norpramin</td>
<td>For depression: usual adult dose is 200 mg daily</td>
<td>Oral tablets</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Sinequan</td>
<td>For depression: starting dose of 75 mg once daily. May be increased or decreased up to 300 mg daily</td>
<td>Oral capsule</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>Toviaz</td>
<td>2 mg twice daily. May be lowered to 1 mg twice daily</td>
<td>Oral tablet</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Tofranil</td>
<td>For depression, initially, 75 mg/day increased to 150 mg/day</td>
<td>Oral tablets</td>
</tr>
<tr>
<td>Mirabegron</td>
<td>Myrbetrix</td>
<td>Starting dose of 25 mg once daily. Dose may be increased to 50 mg once daily based on individual patient efficacy and tolerability</td>
<td>Oral tablet</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Pamelor, generic</td>
<td>For depression: normal adult dose is 25 mg 3 or 4 times daily</td>
<td>Oral capsules, oral solution</td>
</tr>
<tr>
<td>OnabotulinumtoxinA</td>
<td>Botox</td>
<td>For OAB: total dose of 100 units as 0.5 mL injections across 20 sites into the detrusor For NDO: total dose of 200 units as 1 mL injections across 30 sites into the detrusor</td>
<td>Single-use vial for injection</td>
</tr>
<tr>
<td>Oxybutynin chloride</td>
<td>Ditropan XL</td>
<td>Starting dose is 5 or 10 mg once daily. May be adjusted in 5-mg increments up to a maximum of 30 mg/d.</td>
<td>Oral tablet</td>
</tr>
<tr>
<td>Oxybutynin chloride</td>
<td>Gelnique</td>
<td>Contents of one sachet should be applied once daily to dry, intact skin on the abdomen, upper arms/shoulders, or thighs</td>
<td>Gel</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>VESIcare</td>
<td>5 mg once daily. If well tolerated, dose may be increased to 10 mg once daily</td>
<td>Oral tablets</td>
</tr>
<tr>
<td>Tolterodine tartrate</td>
<td>Detroil</td>
<td>2 mg twice daily. May be lowered to 1 mg twice daily.</td>
<td>Oral tablet</td>
</tr>
<tr>
<td>Tolterodine tartrate</td>
<td>Detroil LA</td>
<td>4 mg once daily may be lowered to 2 mg daily</td>
<td>Oral capsules</td>
</tr>
<tr>
<td>Trospium chloride</td>
<td>Sanctura</td>
<td>20 mg twice daily</td>
<td>Oral tablet</td>
</tr>
<tr>
<td>Trospium chloride</td>
<td>Sanctura XR</td>
<td>60 mg once daily</td>
<td>Oral tablet</td>
</tr>
</tbody>
</table>


23. Shaw C. A systematic review of the literature on the prevalence of sexual impairment in women with urinary incontinence and the prevalence of urinary


92. BOTOX (onabotulinumtoxinA) [Prescribing Information]. Irvine CA: Allergan, Inc.; 2013.

93. DYSPORT (abotulinumtoxinA) [Prescribing Information]. Wrexham, UK: Ipsen Biopharm Ltd; 2009.


103. Gablofen (baclofen injection) [Prescribing Information]. Hazelwood, MO; Mallinckrodt Brand Pharmaceuticals, Inc. 2013.