CME FEATURE

Part II: Current Treatment Options for Neurogenic Bladder Dysfunction

Clinicians need to keep abreast of the most current treatment options for NGB, which can result in improved patient outcomes and quality of life

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STATEMENT OF NEED: Urologists and other healthcare professionals caring for patients with neurogenic bladder (NGB) dysfunction need to be knowledgeable about the various treatment options for NGB, including options for patients who fail behavioral or oral therapy, to provide optimal therapy. Since successful treatment encompasses patient satisfaction as well as meaningful improvement in symptoms, clinicians need to be aware of the impact of patient considerations and satisfaction in the management of NGB dysfunction.

TARGET AUDIENCE: This activity has been designed to meet the educational needs of urologists and other clinicians involved in the treatment of patients with bladder dysfunction.

EDUCATIONAL OBJECTIVES: After completing the activity, the participant should be better able to:

- Evaluate management options for neurogenic bladder dysfunction, including evidence-based treatments and novel therapeutic approaches
- Explain the impact of patient considerations and satisfaction in the management of neurogenic bladder dysfunction

ACCREDITATION STATEMENT: This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Medical Education Resources (MER) and Haymarket Medical Education. MER is accredited by the ACCME to provide continuing medical education for physicians.

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BY MICHAEL B. CHANCELLOR, MD

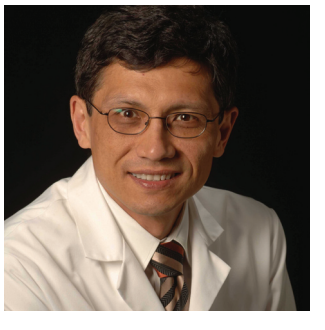
Neurogenic lower urinary tract dysfunction—or neurogenic bladder (NGB) dysfunction—may be caused by various diseases and events affecting the nervous system controlling the lower urinary tract. The resulting dysfunction depends on location and extent of the neurologic lesion; thus, the population with NGB dysfunction is quite diverse **(Table 1)**.[1] Two common neurologic causes of neurogenic detrusor overactivity (NDO), which may cause symptoms similar to overactive bladder, are multiple sclerosis (MS) and spinal cord injury (SCI).[2] Limitations imposed by the underlying disease and the broad range of symptoms encompassed by NGB dysfunction can have a significant effect on patient quality of life, necessitating both a multidisciplinary and an individualized approach to management and treatment.[3]

Treatment goals

One proposed treatment paradigm for patients with NGB dysfunction is to optimize oral therapy, provide local bladder treatment, and offer bladder augmentation and urinary diversion. Considerations in managing patients with NGB include the high rates of discontinuation of antimuscarinics,[4] pharmacologic safety,[5,6] and surgical and emerging therapies that can maximize adherence and minimize risk of systemic effects.[7]

The overarching goal for the patient with NGB dysfunction—including both NDO and detrusor sphincter dyssynergia, which can cause high intravesical pressure, leading to upper urinary tract damage—is to preserve renal function, decrease potential urologic complications, and improve quality of life by relieving symptoms. Patients with SCI or MS often have NDO, which also frequently causes urinary incontinence.[8] The more independent a patient can become by reducing symptoms of urgency, frequency, and incontinence, the less likely he or she will need to rely on assistance or be institutionalized.

Individualized treatment plans should take into account a patient's history and physical examination, urodynamic findings, renal function, and personal goals and limitations, including mobility, degree of disability, hand function,



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cognition, willingness and/or ability to perform clean intermittent catheterization (CIC), and the need for and ability of caregivers.[9] Selection of therapy should focus on minimizing risks to patients while maximizing social, emotional, and vocational acceptability, including psychological, social, occupational, physical, and intimacy domains. There are no definitive consensus guidelines, however, for how to manage NDO symptoms in patients with MS and SCI.

Treatment options

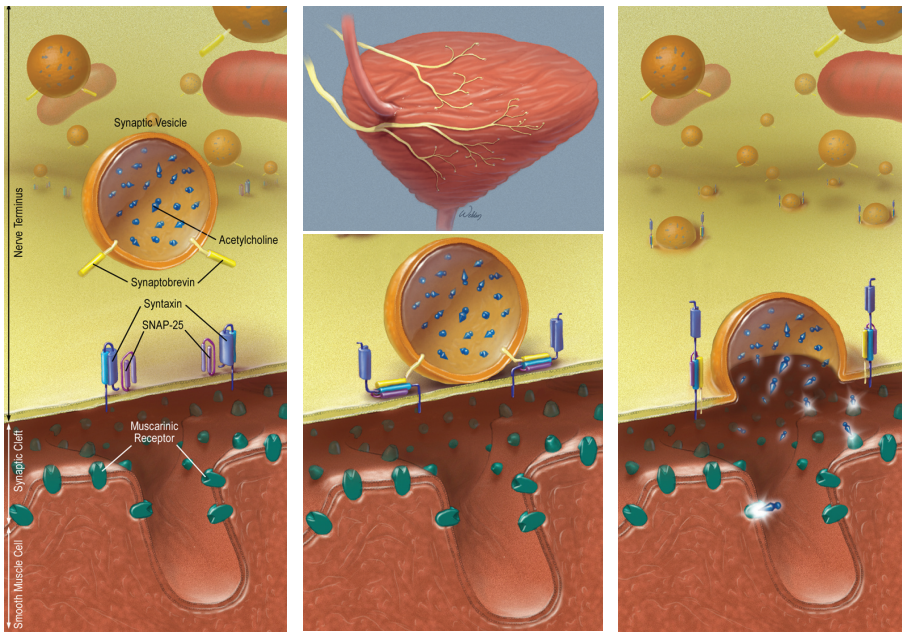
Treatment for dysfunction usually includes a combination of both pharmacologic agents and nonpharmacologic approaches,[10] including noninvasive, minimally invasive, and surgical options.

Noninvasive treatments

Noninvasive treatment options for NGB dysfunction include intermittent catheterization, Crede and Valsalva, indwelling catheterization, lifestyle changes/behavioral modification, and oral pharmacotherapy.

Table 1: Common Neurologic Conditions Associated with NGB

Conditions affecting the brain
• Cerebellar ataxia
• Cerebral palsy
• Dementia
• Multiple system atrophy
• Neoplasms
• Parkinson's disease
• Stroke
Conditions affecting the spinal cord
• Acquired immune deficiency syndrome
• Ankylosing spondylosis and disk disease
• Guillain-Barré syndrome
• Herpes
• Lyme disease
• Multiple sclerosis
• Myelomeningocele
• Pernicious anemia
• Poliomyelitis
• Spinal cord injury
• Tabes dorsalis
• Tethered cord syndrome and short filum terminale
• Transverse myelitis
• Tropical spastic paraparesis
Conditions affecting the peripheral nervous system and neuromuscular junction
• Diabetic neuropathy
• Myasthenia gravis
• Pelvic plexus injury



Schematic diagram demonstrating normal fusion and release of acetylcholine from nerve terminals via interaction of SNARE proteins.

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Lifestyle changes/behavioral modification. These approaches may be helpful for patients with lower urinary tract rehabilitation.[11] These include moderate fluid intake, reducing or eliminating caffeine, dietary changes, pelvic floor muscle exercises, biofeedback, timed voiding, toileting assistance, and bladder education/retraining.[12]

Clean intermittent catheterization (CIC). CIC is one of the most commonly used methods for patients with NGB that fails to empty. Adequate hand function or a caregiver willing to perform CIC is necessary for this method to be successful. Abnormal urethral anatomy, strictures, bladder capacity <200 mL, adverse reaction to catheters, or autonomic dysreflexia with high bladder volumes may interfere with the ability to conduct CIC. Urinary tract infections, one potential side effect of CIC, may be avoided by using hydrophilic-coated catheters; for example, in patients with SCI.[13] Strictures, hematuria, and bladder stones are other side effects that can occur.[14]

Table 2: Oral Pharmacologic Agents for the Treatment of NGB

Drug Class
Estrogen derivatives
• Conjugated estrogen
Anticholinergic
• Propantheline bromide
• Dicyclomine hydrochloride
• Hyoscyamine sulfate
Antispasmodic
• Solifenacin succinate
• Darifenacin
• Oxybutynin chloride
• Tolterodine L-tartrate
• Trospium chloride
• Fesoterodine
Tricyclic antidepressants*
• Imipramine hydrochloride
• Amitriptyline hydrochloride

*Off-label use

Rackley R. Neurogenic bladder. http://emedicine.medscape.com/article/453539-overview. Accessed April 12, 2012.

Crede and Valsalva. Third-party bladder expression (Crede) and voiding by abdominal straining (Valsalva) may be appropriate for patients with low outlet resistance. Risks include high intravesical pressures, which can lead to worsening vesicoureteral reflux or hydronephrosis; incomplete bladder emptying, leading to chronic urinary tract infections; pelvic organ prolapse; hernia; and hemorrhoids.

Indwelling and suprapubic catheterization. Considered temporary methods, these may be preferred when other approaches have failed. Complications can include bladder stones, infections, and malignancies.

Oral pharmacotherapy. Anticholinergics/antimuscarinics, the most commonly used class of agents for NGB, bind to muscarinic receptors in the detrusor muscle, reducing bladder storage pressure and increasing capacity **(Table 2)**.[15-17] They are generally used in conjunction with CIC to treat NGB dysfunction.

Perceived lack of efficacy, costs of medication, polypharmacy, dosing frequency, poor counseling, and adverse effects—including dry mouth (a well-known effect), facial flushing, dizziness, constipation, and neurologic deficits—can all lead to patients discontinuing treatment with anticholinergics.[4] Studies have shown that among 6 therapeutic classes—angiotensin receptor blockers, bisphosphonates, oral antidiabetics, overactive bladder agents, prostaglandin analogs, and statins—medication for overactive bladder had the lowest adherence rate.[18] One study found that at 1 year after initiating therapy for overactive bladder, <30% of patients are still taking antimuscarinics;[19] another showed that of patients initiated on either oxybutynin and tolterodine, <14% continued for 1 year, with a median of 31 days until discontinuation.[20]

Individual responses to anticholinergics vary; therefore, patients may find another medication or a combination of agents can increase efficacy or reduce adverse effects.[21] Other oral agents that have been used in patients with NGB include phosphodiesterase type 5 inhibitors, gonadotropin-releasing hormone antagonists, neurokinin receptor-1 antagonists, beta-3 adrenoceptor agonists,[22] and desmopressin.[23]

Minimally invasive treatments

Patients with NGB who have refractory detrusor overactivity may benefit from minimally invasive treatment. Refractory detrusor overactivity is marked by persistent urgency, frequency, and incontinence, and remains bothersome despite oral pharmacologic therapy.

Sacral neuromodulation. Although this approach is approved by the U.S. Food and Drug Administration (FDA) for the treatment of urinary retention and the symptoms of overactive bladder, its safety and efficacy have not been established for patients with neurologic disease origins. An alternative treatment option in patients with voiding dysfunction and chronic pelvic pain, it is generally performed in stages to identify responders; those who respond proceed to full implantation of pulse generator and leads.

Intravesical drug delivery. Neurogenic overactivity can be decreased for several months by intravesical instillation of agents that desensitize afferent C-fibers in the bladder. Sensation is restored when the sensory nerves regenerate. Higher levels of anticholinergics such as oxybutynin can be increased and adverse effects decreased by avoiding hepatic first-pass metabolism.[24] Vanilloid compounds, capsaicin, and resinifera-

Case Study: Managing Urinary Incontinence in Multiple Sclerosis

K.A. is a 52-year-old woman with multiple sclerosis (MS) that was diagnosed at the age of 37 years. She has had to take a medical leave of absence from her job as an elementary schoolteacher because of fatigue, lack of adequate bladder control, and urinary incontinence (UI) that impaired her ability to teach. She can walk 50 feet without a cane but must watch her balance, and going up and down stairs is difficult for her. K.A. is currently on beta interferon for her MS and has not had a flare-up for more than 2 years. Her overall health is otherwise stable, with only borderline hypertension and normal lipid profiles.

Approximately 3 years ago, K.A. presented with urge UI and was prescribed extended-release oral oxybutynin 15 mg/day. At her initial follow-up, she noted a moderate degree of dry mouth but no other complications. She decided to continue with this medication, as she believed it increased her health-related quality of life by decreasing episodes of UI.

One year ago, K.A. admitted she was increasingly constipated and often felt dizzy if she stood up too quickly. Her clinician determined she was having involuntary detrusor contractions starting at 79 mL and had a maximal detrusor pressure of approximately 40 cm H_20. She did not have stress incontinence or pelvic prolapse on examination. Several options were suggested, including switching to a different anticholinergic agent, clean intermittent catheterization, and a suprapubic catheter, since increasing her current oxybutynin dose was not a viable alternative.

She agreed to switch to a different anticholinergic and was placed on tolterodine tartrate extended-release tablets 4 mg/day. At her 2-week follow-up, postvoid residual (PVR) was 75 mL, symptoms had improved, and incontinence was 75% better.

However, at her 10-month follow-up, K.A. asks her clinician to discuss any other options, as treatment with this anticholinergic has resulted in blurred vision and drowsiness, interfering with her ability to walk up and down stairs without fear of falling, and her UI seems to be worse. At this visit, her PVR is 35 mL, her incontinence has returned to baseline, and her urgency symptoms have returned.

Three suggested treatment modalities are neuromodulation, bladder injection of botulinum toxin, or augmentation. The efficacy and safety of each of the options are explained. K.A. opts for treatment with intradetrusor injection of onabotulinumtoxinA 200 U because she does not want to undergo a surgical procedure. She understands that the treatment with onabotulinumtoxinA will last approximately 10 months.

toxin have been shown to be effective in refractory urge incontinence in adults with SCI and MS. Further studies are needed to determine long-term efficacy and safety.[25] Advances in development of intravesical drug delivery, including the use of liposomal nanoparticles, will help improve management of symptoms of the lower urinary tract.[26]

Botulinum neurotoxin (BoNT) injection. Cystoscopic injections of BoNT modulate acetylcholine and other biochemical messengers at presynaptic nerve terminals and noncholinergic mechanisms in the detrusor smooth muscle,[27] preventing detrusor contraction and leading to transient smooth muscle paralysis and symptom alleviation. A broader mechanism of action has been proposed that suggests BoNT blocks release of acetylcholine, ATP, and substance P, leading to central desensitization and effectiveness in detrusor overactivity.[28]

In August 2011, the FDA approved the use of onabotulinumtoxinA (Botox) injection to treat urinary incontinence in patients with NDO who have failed or cannot tolerate the adverse effects of anticholinergic therapy.[29] Although three other BoNT serotype preparations are available—abobotulinumtoxinA (Dysport), incobotulinumtoxinA (Xeomin), and rimabotulinumtoxinB (Myobloc)—they are not approved to treat NDO and cannot be used interchangeably.[30]

An initial 24-week study found that onabotulinumtoxinA 200 U and 300 U clinically significantly decreased signs and symptoms of urinary incontinence caused by NDO in 59 patients due to SCI or MS vs. placebo.[31]

The FDA approval was based on results of two subsequent phase 3 randomized clinical studies involving 691 patients.[32,33] The studies assigned patients with NDO resulting from SCI or MS not adequately managed with anticholinergics to onabotulinumtoxinA 200 U, 300 U, or placebo. Primary end point was changed from baseline in weekly urinary incontinence episodes at week 6. Patients in the onabotulinumtoxinA 200 U and 300 U arms had significant decreases in weekly frequency of incontinence episodes vs. placebo and had similar improvements in incontinence episodes, urodynamic parameters, and health-related quality-of-life scores **(Figure 1)**.[32-34]

OnabotulinumtoxinA is injected intramuscularly at multiple sites throughout the bladder,[35] in an outpatient procedure. The recommended dose of onabotulinumtoxinA is 200 U per treatment and should not be exceeded. Patients may be considered for reinjection when the clinical effect of the previous injection diminishes (median 42-48 weeks in clinical studies) but no sooner than 12 weeks from the prior bladder injection.[36]

The most common adverse events associated with intravesical BoNT injection are incomplete bladder emptying and urinary tract infections.[27] Contraindications to onabotulinumtoxinA are active infection and known hypersensitivity to agents; relative contraindications include preexisting neuromuscular disorders and concomitant use of agents interfering with neuromuscular transmission; pregnancy (Class C) and nursing mothers; and bladder outlet obstruction. Incidence of autonomic dysreflexia may occur in patients treated for detrusor overactivity associated with a neurologic condition that requires prompt medical therapy.[36]

Surgical treatments

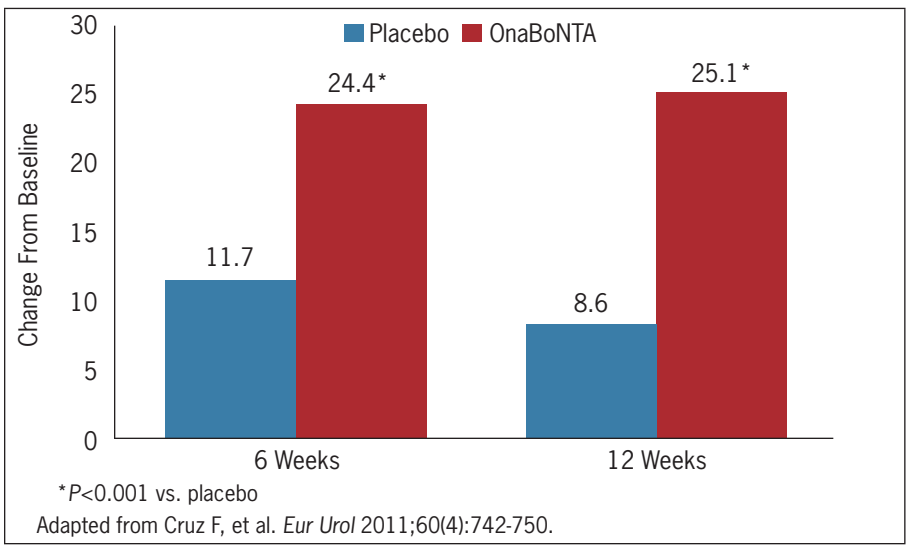
Surgical options include transurethral sphincterotomy, endourethral stents, urethral and bladder neck procedures, bladder augmentation, and urinary diversion **(Table 3)**.

Long-term follow-up of patients with NDO must be conducted, as changes in detrusor compliance and urodynamic patterns may occur over time.[37]

Barriers to care

Barriers to care include patient embarrassment about their condition, lack of awareness that serious complications can result from mismanagement of inconti-

Figure 1. Change from Baseline in Incontinence Quality-of-Life Total Score with OnabotulinumtoxinA 200 U or Placebo



*P<0.001 vs. placebo

Adapted from Cruz F, et al. *Eur Urol* 2011;60(4):742-750.

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nence, the perception that bladder issues are not life-threatening, fear of needing invasive surgical intervention, a lack of awareness that effective treatment options are available, and a lack of access to treatment options covered under insurance-plan benefits. Patients and clinicians need to be aware of the potentially detrimental effects of poorly managed or unmanaged NDO on disease outcomes.

Patient satisfaction with treatment

Patient perceptions, expectations, and satisfaction with treatment can affect adherence,[38] as can costs[7,10] and reimbursement issues. To ensure treatment adherence and a successful outcome, patients and clinicians need to be informed of available options and any training as well as the day-to-day requirements and long-term expectations for treatment. Ideally, bladder management strategy should be adapted to the underlying disease.

Patient satisfaction with treatment in the NGB population has been inadequately studied, using tools developed for idiopathic overactive bladder.[39,40] The Actionable MS Urinary Function Screening Tool is a new measurement instrument developed to assess the impact of NGB dysfunction on quality of life in patients with MS.[41] Until study results are available, clinicians cannot accurately assess patient satisfaction with treatment.

Table 3: Types of Surgical Treatments for the Patient with NGB

Surgery	Patient Selection	Advantages/Disadvantages
Transurethral sphincterotomy	• Detrusor external sphincter dyssynergia	• May need to be repeated • Minimal comorbidities
Endourethral stents	• Patients with detrusor sphincter dyssynergia who desire reflex voiding and have difficulty catheterizing, or with repeated autonomic dysreflexia	• Beneficial in long-term management in patients with SCI • Potentially reversible procedure • Reduced hospital stay • Second stent can be deployed after first stent is epithelialized
Urethral and bladder neck procedures	• Bladder neck incision indicated in secondary changes of the bladder neck caused by scarring and fibrosis • Autologous fascial slings effective in increasing the Valsalva or stress leak point pressures without increasing leak point pressures	• Upper tracts not endangered
Bladder augmentation	• Generally reserved for patients refractory to more conservative therapy	• Complications include bacteriuria, metabolic disorders, absorption disorders, stones, risk of malignancy, and long recovery period • Excellent continence rates with high patient satisfaction
Other options	• Detrusor myectomy (auto-augmentation) in selected patients is an extraperitoneal procedure wherein the detrusor muscle over the dome of the bladder is removed and the compliance and capacity of the bladder can be increased much like a diverticulum	• Simple procedure, relatively low adverse-effect profile
Urinary diversion	• Patients with indwelling urinary catheters when the urethra is destroyed and capacity is lost • Patients with urethrocutaneous fistulas, perineal pressure ulcers, hydronephrosis and vesicoureteral reflux, or a thickened noncompliant detrusor muscle • Incontinent diversion with a urine collecting device • Can be combined with a bladder neck reconstruction to limit incontinence from the urethra	• Potential complications include intestinal or urinary leak, stomal stricture or hernia, urinary tract infection, and stone disease • Umbilical access can increase risks for strictures • Incontinent urinary diversions can be converted to continent ones • Improved quality of life, self-image, and sexual satisfaction in women

Conclusion

Successful treatment of the patient with NGB dysfunction encompasses satisfaction with therapy as well as meaningful improvement in symptoms. Optimal management can result in improved patient outcomes, and a consistent effect on bladder control can result in sustained improvement in quality of life. ■

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CME Post-test

Expiration Date: July 2013

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1. Which of the following is generally used in conjunction with clean intermittent catheterization to treat neurogenic bladder dysfunction?
   a. Bladder augmentation
   b. Intravesical instillation
   c. Antimuscarinic agents
   d. Sacral neuromodulation

2. The most commonly used class of agents for neurogenic bladder dysfunction is:
   a. Tricyclic antidepressant
   b. Anticholinergics
   c. Capsaicin
   d. Botulinum toxin

3. Patients may discontinue oral pharmacotherapy primarily due to what well-known adverse effect?
   a. Facial flushing
   b. Dizziness
   c. Hypotension
   d. Dry mouth

4. Which of the following statements is true regarding various botulinum toxin serotypes?
   a. They are interchangeable
   b. The dosing units are not equivalent
   c. All have the same generic name
   d. They are all approved to treat neurogenic detrusor overactivity

5. One of the most common adverse events of intravesical injection of BoNT is:
   a. Urinary tract infection
   b. Stones
   c. Autonomic dysreflexia
   d. Urinary leak

6. Which of the following statements about endourethral stents is false?
   a. Patients with spinal cord injury can have long-term benefit
   b. Hospital stay can be reduced
   c. Procedure is generally irreversible
   d. Patients who have difficulty catheterizing can benefit

7. Which of the following is among the most commonly used methods for patients with normal hand function and neurogenic bladder that fails to empty?
   a. Crede
   b. Valsalva
   c. Indwelling catheter
   d. Clean intermittent catheterization

8. A surgical treatment with excellent continence rates and high patient satisfaction is:
   a. Bladder augmentation
   b. Transurethral sphincterotomy
   c. Detrusor myectomy
   d. Urinary diversion