Botulinum toxin for treatment of lower urinary tract conditions: Indications and clinical evaluation

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INTRODUCTION

Botulinum toxin (BoNT) is used to treat a wide array of clinical conditions, including neuromuscular disorders (strabismus, blepharospasm, dystonia, spasticity) and pain syndromes (migraine headaches, temporomandibular joint pain). After initial use for patients with neurogenic urologic disorders, botulinum toxin use expanded to include patients without neurologic disorders who had symptoms of refractory urinary incontinence, urgency, and/or frequency.

This topic will review the use of botulinum toxin in adults with non-neurogenic and neurogenic overactive bladder syndrome, as well as off-label use in other lower urinary tract symptom and pain disorders. For the purposes of this topic, the use of "female" and "male" refers to the patient's natal anatomy. The specific language and care needs of transgender and nonbinary patients should also be considered. Related content on the procedure for botulinum toxin injection and complications, as well as pharmacology and formulations, is presented elsewhere:

- (See "Botulinum toxin for treatment of overactive bladder: Injection and complications".)
- (See "Overview of botulinum toxin for cosmetic indications", section on 'Mechanism of action'.)
- (See "Overview of botulinum toxin for cosmetic indications", section on 'Formulations'.)

In this topic, when discussing study results, we will use the terms "woman/en" or "patient(s)" as they are used in the studies presented. However, we encourage the reader to consider the specific counseling and treatment needs of transgender and gender-expansive individuals.

BACKGROUND FOR BOTULINUM TOXIN USE

Mechanism of action — Briefly, botulinum toxin prevents muscular contraction by inhibiting acetylcholine release at the neuromuscular junction. Botulinum toxin has been studied for treating bladder dysfunction because acetylcholine is the predominant neurotransmitter involved in parasympathetic nerve control of the detrusor (bladder) smooth muscle. In the lower urinary tract, botulinum toxin may work through this classical mechanism of interfering with efferent (motor) nerve stimulation of muscle. However, there are also limited data suggesting other mechanisms of action, which remain poorly understood [1]. Data suggest that botulinum toxin may also decrease afferent (sensory) nerve signaling during bladder filling [2] or affect other ATP-mediated extracellular signaling mechanisms involved in bladder sensation and function [1-4].

A detailed discussion of the mechanism of action is presented elsewhere. (See "Overview of botulinum toxin for cosmetic indications", section on 'Mechanism of action'.)

Formulations — Botulinum toxin is a neurotoxin that is produced by *Clostridium botulinum*. In clinical applications, there are two available serotypes: botulinum toxin type A (BoNT-A) and botulinum toxin type B (BoNT-B). BoNT-A has been most widely studied and is most commonly used when treating lower urinary tract dysfunction. Commercial formulations of BoNT-A include onabotulinumtoxinA (onabotA; Botox) and abobotulinumtoxinA (abobotA; Dysport); other formulations are available. Only onabotA and abobotA have been studied for lower urinary tract dysfunction. Clinicians who use other products should note that dosing among different formulations is not consistent. The different serotypes and formulations are discussed in detail separately. (See "Overview of botulinum toxin for cosmetic indications", section on 'Formulations'.)

OnabotA therapy is endorsed by multiple national medical societies for treatment of neurogenic and non-neurogenic overactive bladder (OAB) [5-9]. However, botulinum toxin therapy is also used for off-label indications in the treatment of urologic bladder pain syndromes and occasionally in the treatment of voiding dysfunction when injected into the sphincter and pelvic floor musculature (females) or the prostate (males).

Rationale in lower urinary tract disorders — Beginning in 1990, botulinum toxin was evaluated for the treatment of neurogenic urologic disorders [10-12]. Initial treatment groups included patients with detrusor sphincter dyssynergia and spinal cord injury with resultant detrusor overactivity (DO) and urinary urgency incontinence (UUI) [12-14]. In 2011,

the US Food and Drug Administration (FDA) approved botulinum toxin use in patients with DO associated with a neurologic condition (eg, spinal cord injury or multiple sclerosis) [15]. UUI and DO also occur in patients without neurologic conditions. Based on subsequent trial data, the FDA expanded its botulinum toxin approval to include patients with non-neurogenic OAB in 2013 [16]. Thus, botulinum toxin is considered for patients with OAB who are either intolerant or refractory to conservative treatment options such as medications and behavioral management. (See 'Refractory non-neurogenic overactive bladder syndrome' below and "Female urinary incontinence: Treatment", section on 'Urgency incontinence/overactive bladder (OAB)'.)

TERMINOLOGY

Refinements in terminology continue to evolve with additional research. The following terms are used throughout the sections below [17,18]:

- **Urinary urgency –** Urinary urgency is the awareness of a sudden, strong desire to pass urine that is difficult to ignore. This symptom is often accompanied by urinary frequency. When occurring in the absence of urinary incontinence, infection, and other pathology, this condition is referred to as "OAB-dry."
- **Urinary incontinence (UI) –** UI is the involuntary loss of urine.
- **Urinary urgency incontinence (UUI) –** UUI is the involuntary loss of urine associated with a sensation of urgency, also known as "OAB-wet."
- **Overactive bladder syndrome (OAB) –** OAB is a symptom complex defined as "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology." The presence of relevant neurologic disease allows subcategorization of OAB.
  - **Non-neurogenic or idiopathic OAB –** OAB in the absence of obvious pathology, including neurologic disorder.
  - **Neurogenic OAB –** Neurogenic OAB is diagnosed in the setting of a clinically relevant neurologic disorder with at least partially preserved sensation [19].
- **Detrusor overactivity (DO) –** The occurrence of involuntary detrusor muscle contractions during the filling cystometry portion of urodynamic testing. Contractions may be spontaneous or provoked. Symptoms, including UI and UUI, may or may not be present.

- **Idiopathic DO** – DO in the absence of obvious pathology, including a neurologic disorder.
- **Neurogenic DO** – DO in the setting of a relevant neurologic disorder [19].

REFRACTORY NON-NEUROGENIC OVERACTIVE BLADDER SYNDROME

The evaluation and initial management options for individuals with overactive bladder syndrome (OAB; wet or dry) and urinary urgency incontinence (UUI) are presented in detail in the following topics:

- (See "Female urinary incontinence: Evaluation".)
- (See "Female urinary incontinence: Treatment".)
- (See "Urgency urinary incontinence/overactive bladder (OAB) in females: Treatment".)
- (See "Urinary incontinence in men".)
- (See "Lower urinary tract symptoms in males".)

Comparison of therapies for refractory OAB

Botulinum toxin versus behavioral or medical therapy — For patients with idiopathic, non-neurogenic OAB, first-line therapies include behavioral management strategies, and second-line therapies are anticholinergic or beta-3 agonist medications. Patients who have medication intolerances or persistent OAB symptoms despite a trial of medication for a duration of at least four weeks are considered to have refractory OAB. For refractory patients, third-line therapies such as botulinum toxin, sacral nerve stimulation, and percutaneous tibial nerve stimulation (PTNS) are offered. (See "Female urinary incontinence: Treatment", section on 'Urgency incontinence/overactive bladder (OAB)'.)

When compared with oral medications, botulinum toxin has similar reductions in incontinence episodes but also has a more favorable impact on quality-of-life measures and is more likely to result in complete continence (27 percent for onabotulinumtoxinA (onabotA) versus 13 percent for oral medications) [20]. A network meta-analysis of 56 randomized trials corroborated these findings and suggested that onabotA 100 units provided greater symptom relief than OAB medications [21]. However, behavioral management strategies and oral medications are tried first, as they are noninvasive and do not have the procedural risks associated with botulinum toxin injection. (See 'Injection procedure and adverse events' below.)

Botulinum toxin compared with other third-line OAB treatments — Third-line therapies for OAB include botulinum toxin injections and neuromodulation, which uses electrical stimulation to improve bladder symptoms. Common neuromodulation techniques include PTNS and sacral nerve modulation (SNM) [22,23].

For patients and clinicians considering third-line therapies, conversations should focus on efficacy, potential adverse events, logistical factors, and time commitments that may affect compliance with a treatment course. In some cases, financial factors may play a role, particularly if certain therapies are not covered by a patient's insurance. (See 'Neurogenic overactive bladder and detrusor overactivity' below.)

- **Botulinum toxin versus PTNS –** For patients who desire the intervention that appears to be more efficacious and durable, we suggest a trial of botulinum toxin. However, for patients who prefer a less invasive approach and/or to avoid the adverse effects associated with botulinum toxin, PTNS is a reasonable approach for those who can commit to the full course of treatment (typically 12 weeks of weekly visits) and maintenance therapy.

  Although supporting data are limited, one small trial reported botulinum toxin achieved more durable improvement in OAB symptoms at nine months of follow-up compared with treatment with PTNS [24]. Other studies have reported PTNS appears to reduce symptoms equal to, or slightly better than, medication therapy [22,25]. Limitations of botulinum toxin include the need for injection via cystoscope and potential adverse effects, including urinary retention. Limitations of PTNS include the time commitment (weekly treatment for 12 weeks plus additional maintenance), lack of efficacy in patients with nerve conduction disorders or peripheral neuropathy, and variable cost coverage [26]. Initial trial data of an implanted PTNS device are promising, but trials are ongoing [27,28].

- **Botulinum toxin versus SNM –** In the appropriate patient, we discuss both therapies, as the efficacy of botulinum toxin compared with SNM has been a topic of debate. The selection is often determined by a comparison of potential risks and adverse events, other medical considerations, recovery (SNM involves an implantable device), and cost [29]. In a multicenter trial, 364 women with refractory UUI were randomly assigned to injections of onabotA (200 units) or SNM [30]. After six months, those in the onabotA group had a statistically greater improvement in UUI episodes per day, but the magnitude of difference between the two groups was of uncertain clinical significance (-3.9 versus -3.3 UUI episodes per day, mean difference 0.63, 95% CI 0.13-1.14). After two years of follow-up, both therapies had similar reduction in UUI symptoms (-3.88 versus -3.50 UUI episodes per day for onabotA and SNM, respectively) and similar rates of complete symptom resolution (5 percent for each group) [31]. Although patients

receiving onabotA had more urinary tract infections (UTI), they also reported greater treatment endorsement, satisfaction, and preference compared with those undergoing SNM [31].

Both therapies are routinely offered to most patients, and shared decision making is used to guide the selection. However, in the setting of certain coexisting medical conditions, one treatment may be favored over the other:

- In patients with combined urinary and fecal incontinence, SNM is our preferred option as it has demonstrated efficacy for both conditions.
- For patients with ongoing recurrent UTIs, and if UTIs are difficult to manage, we prefer SNM over botulinum toxin since UTI is one of the major adverse events to consider after botulinum toxin. (See 'Injection procedure and adverse events' below.)
- For patients who have ongoing imaging needs that include body magnetic resonance imaging (MRI), botulinum toxin has historically been preferred because of concerns for MRI incompatibility with implantable devices. However, multiple MRI-compatible SNM devices are now available. Thus, the need for future MRIs is no longer a relative contraindication for SNM.
- For patients with another implanted nerve stimulator (eg, for chronic back pain), botulinum toxin may be preferred to avoid electrical interference with stimulation in two locations proximate to each other. However, multiple stimulators may still be used if they are distant in location (eg, SNM with cardiac pacemakers or deep brain stimulators).

Botulinum toxin for refractory OAB

Counseling — For patients with non-neurogenic (idiopathic) OAB, botulinum toxin injections are considered third-line therapy in the general OAB treatment algorithm [5-7,32-35]. Botulinum toxin type A (BoNT-A) is the main formulation for injection. Prior to treatment, counseling should include discussion of efficacy, duration of effect, and risk of adverse events, such as UTI and the need for temporary postprocedure intermittent catheterization. Although preprocedure teaching of intermittent self-catheterization has been advocated, the actual rate of postprocedure catheterization use is 4 percent after 100 units [20] and 8 percent after 200 units [30]. Therefore, some practices reserve preprocedure self-catheterization teaching for patients who have a higher risk of retention or those who are likely to have difficulty with catheterization. Counseling should also include that the onset of effect is generally one to two weeks and usually lasts for 4 to 10 months, after which repeat injections are necessary to maintain the therapeutic effect. For initial injection, 100 units of onabotA is the typical starting dose (compared with 200 units when treating patients with neurogenic OAB).

Clinical evaluation — Prior to botulinum toxin injection, all patients with OAB should undergo the following evaluation:

- A careful history, physical examination, and urinalysis [32].
- Assessment of voiding function, including postvoid residual volume [32].
- Bladder diary or symptom questionnaires may be helpful to better differentiate bladder symptoms or if confirmation of OAB diagnosis is still needed [32].
- Based on symptoms and/or urinalysis results, urine culture may be indicated. If present in non-neurogenic patients, asymptomatic bacteruria and UTI should be treated with antibiotics prior to BoNT-A injection as injection breaks the mucosal barrier [32,36,37].

For an uncomplicated patient with non-neurogenic OAB, we do not require cystoscopy or urodynamics prior to treatment with botulinum toxin injection [32]. Limited data suggest that outcomes are similar for patients treated with botulinum toxin with or without pretreatment urodynamic testing [38]. For a patient with complicating factors, such as prior genitourinary surgery, obstructive voiding symptoms, or elevated postvoid residual volume, urodynamic testing may be helpful in determining if botulinum toxin therapy is appropriate [32]. Cystoscopy would be indicated for evaluation of hematuria or other abnormal findings on initial clinical evaluation.

Efficacy — The majority of efficacy studies have been performed in females with UUI (ie, OAB-wet). Data specific to male patients or patients with urinary urgency without leakage (ie, OAB-dry) are limited.

- **Urinary urgency incontinence (OAB-wet) –** In studies that pooled data from males and females with UUI (or OAB-wet), patients receiving onabotA reported significantly fewer daily UUI episodes compared with placebo (approximately three fewer UUI per day after BoNT-A and one fewer UUI per day after placebo) [39-41]. In long-term follow-up, the duration of effect after each injection was 8 to 10 months, and for patients who continued with onabotA therapy, efficacy persisted over six retreatments [42,43].

  There are few studies specifically looking at males. Although there is biologic plausibility for onabotA injections to reduce UUI in males with OAB, particularly following prostate surgery, two small observational studies reported lack of meaningful impact for most males, with one study reporting onabotA treatment continuation rates of only 25 percent [44,45].

- **Urinary urgency and/or frequency (OAB-dry) –** Botulinum toxin injections to treat refractory urinary urgency and frequency without leakage in both males and females are reasonable, although supporting data are limited. Studies of patients with OAB do

not typically separate out the OAB-dry population. Thus, most of the clinical evidence is derived from those with OAB-wet and extrapolated to OAB-dry. Two placebo-controlled trials of 100 unit injections of onabotA in patients with OAB-wet reported decreases in urinary urgency (approximately four per day) and daily voids (approximately three per day) when compared with baseline [39,40]. Efficacy is extrapolated from these studies as well as other trials of females with UUI [20,30].

In males, BoNT-A treatment may be an option for patients with refractory OAB symptoms, but small studies have reported limited to no improvements and low treatment continuation rates [45,46]. Prior to botulinum toxin injection, urinary retention and urethral stricture should be excluded.

Dose — The recommended starting dose for non-neurogenic OAB is 100 units. A dose-ranging clinical trial investigated the efficacy of 50, 100, 150, 200, and 300 units of onabotA and found durable efficacy for doses greater than 100 units and diminishing improvements in symptoms in doses greater than 150 units [47]. Higher doses may improve the efficacy and duration of effects but may also result in higher rates of adverse events, such as urinary retention [47,48].

Repeat injections — Patients with non-neurogenic OAB treated successfully with botulinum toxin can expect the effects to last approximately 4 to 10 months. Long-term data from botulinum toxin clinical trials demonstrated a median duration of 7.6 months [42]. Therefore, repeat injections are generally offered when clinical OAB symptoms recur but no sooner than three months. Overall, efficacy after the first treatment is maintained across subsequent injections, as is the rate of adverse events [42].

For patients who do not experience a successful initial treatment, we offer a repeat trial of injection at an increased dose after a thorough discussion of the increased risk of adverse events. Dose escalation from the starting dose of 100 units can be initiated either in 50 or 100 unit increments. The maximum total cumulative dose of onabotA should not exceed 360 units over a three month period from all sources, including injections in other sites of the body.

PELVIC PAIN SYNDROMES

- **Bladder pain syndrome/interstitial cystitis (BPS/IC) –** In patients with BPS/IC, we would offer botulinum toxin bladder injections if standard treatment options have not alleviated their symptoms [49]. Two meta-analyses demonstrated significant differences favoring botulinum toxin type A (BoNT-A) over placebo for pooled standardized mean differences in patient-reported outcome measures, urodynamic parameters, and bladder diary measures, including specific measures assessing pain

[50,51]. However, one systematic review that included studies with different comparators reported mixed efficacy results for BoNT-A injections in this population [52]. Most studies have investigated transurethral or cystoscopic bladder injection of BoNT-A; however, a few pilot studies have investigated alternative delivery methods, including liposomal and gel-based symptoms for bladder instillation [53-55].

While use of botulinum injections for BPS/IC is an off-label use of the medication, many BPS/IC patients also have significant urinary frequency, urgency, and incontinence for which botulinum injection is indicated and approved. As BPS/IC are diagnoses of exclusion, underlying disorders and appropriate standard therapies should be tried first.

- (See "Interstitial cystitis/bladder pain syndrome: Clinical features and diagnosis".)
- (See "Interstitial cystitis/bladder pain syndrome: Management".)

- **Chronic prostatitis (CP)/chronic pelvic pain syndrome (CPPS)** – The role of botulinum injections for males with CP/CPPS is unclear as study results are mixed [56-59]. Study limitations have included lack of standardized treatment and small sample sizes. At least one guideline supports limited off-label use of BoNT-A for these patients based on possible modest treatment effect as demonstrated by weak data [60]. (See "Chronic prostatitis and chronic pelvic pain syndrome".)

- **Female chronic pelvic pain** – Botulinum injections into pelvic floor muscles have also been explored for patients with chronic pelvic pain. Initial studies support a role for botulinum injections in this population, although data are limited [61]. This use represents an off-label application of botulinum therapy. (See "Chronic pelvic pain in adult females: Treatment", section on 'Less studied targeted treatments'.)

  Established treatments for chronic pelvic pain in females, which include physical therapy, medication, and behavioral therapies, should be tried first.

  - (See "Chronic pelvic pain in nonpregnant adult females: Causes".)
  - (See "Chronic pelvic pain in adult females: Evaluation".)
  - (See "Chronic pelvic pain in adult females: Treatment".)

VOIDING DYSFUNCTION

In patients who experience difficulties with bladder emptying, botulinum toxin plays a minor role, particularly for patients without known neurologic conditions. Patients with neurologic

causes of their voiding dysfunction are discussed below. (See 'Specific neurogenic populations' below.)

Benign prostatic enlargement or hyperplasia — Bladder outlet obstruction, such as from benign prostatic enlargement (BPE) or hyperplasia (BPH), is a common cause of voiding dysfunction in males without neurologic conditions. However, several medical societies have recommended against offering intraprostatic botulinum toxin type A (BoNT-A) injection treatment to patients with male lower urinary tract symptoms, as the body of evidence supporting BoNT-A injections into the prostate is weak [62-67]. Evaluation and treatment of males with BPE and BPH are reviewed elsewhere.

- (See "Clinical manifestations and diagnostic evaluation of benign prostatic hyperplasia".)
- (See "Medical treatment of benign prostatic hyperplasia".)
- (See "Surgical treatment of benign prostatic hyperplasia (BPH)".)

Female non-neurogenic voiding dysfunction — In females without neurologic disorders, there are instances when inadequate relaxation of the pelvic floor during voiding can cause ineffective bladder emptying [68]. This may be seen in high-tone pelvic floor dysfunction or Fowler's syndrome (a condition associated with inappropriate neuromuscular activity near the urethral sphincter). A small observational study of 10 patients with Fowler's syndrome treated with urethral BoNT-A injections reported promising results, but data from larger trials will be needed before this approach can be considered for standard of care [69]. (See "Chronic urinary retention in females", section on 'Fowler's syndrome'.)

NEUROGENIC OVERACTIVE BLADDER AND DETRUSOR OVERACTIVITY

Patients with neurologic disorders are at higher risk for voiding dysfunction, elevated bladder pressures, and resulting renal sequelae. Therefore, the evaluation and management of neurogenic patients differ from that in idiopathic, non-neurogenic patients, even when the same treatments are used. History and physical examination, with detailed assessment of the underlying neurologic disease, are key aspects to the initial evaluation of the neurogenic lower urinary tract dysfunction (NLUTD) patient. Urodynamics are also an important component to the management of most NLUTD patients as patient-reported symptoms may not accurately characterize the bladder dysfunction present. Furthermore, depending on the nature of the neurologic disease and its effects on the urinary tract, patients with neurologic conditions may have a constellation of complicating urologic factors, such as elevated bladder pressures, bladder compliance abnormalities, vesicoureteral reflux, and voiding dysfunction [70], that may need to be addressed to achieve their management goals.

Primary management goals are preservation or protection of upper urinary tract and renal function, achieving or maintaining urinary continence, restoration of the lower urinary tract function, and improvement in quality of life [70].

Botulinum toxin plays a key clinical role in patients with neurogenic overactive bladder (OAB) and detrusor overactivity (DO).

Pretreatment evaluation — Prior to botulinum toxin therapy, we advise patients with suspected neurogenic DO or OAB to undergo urodynamic testing to confirm the diagnosis and determine whether any other complicating urologic factors exist. If complicating factors are identified, additional evaluation with cystoscopy, upper tract imaging, and renal function tests may be warranted.

In a patient with neurogenic OAB but without complicating factors, the initial management may proceed in a similar fashion to non-neurogenic OAB, with first-line behavioral and lifestyle changes and second-line oral medical therapy. In patients who do not achieve their goals or are intolerant of oral medical therapy, we would recommend botulinum toxin therapy as the next line of therapy.

Botulinum toxin efficacy — For patients with neurogenic OAB, botulinum toxin type A (BoNT-A) treatment has demonstrated efficacy compared with placebo and remains the therapy of choice for patients with poor response to oral medications [41,71-75]. In one trial of patients with neurogenic DO, over 80 percent of patients (162/195) reported ≥50 percent reduction in urinary incontinence (UI) episodes from baseline with the first injection (onabotulinumtoxinA [onabotA] 200 units) [76]. Conflicting data have been reported regarding the effect of percutaneous tibial nerve stimulation and sacral nerve modulation (SNM) on neurogenic OAB symptoms, particularly those associated with multiple sclerosis [77-80]. Thus, some commercial insurers will not reimburse for these therapies in this patient group, although coverage, particularly for SNM, varies greatly by region [81,82]. A clinical trial to assess the effect of early SNM in patients with spinal cord injury and neurogenic bladder is ongoing [83].

- **Primary injection** – The majority of studies investigating botulinum toxin for patients with neurogenic bladder used onabotA. In a meta-analysis including over 1900 patients that compared onabotA with placebo in patients with neurogenic DO, patients receiving either 200 or 300 unit injections of onabotA had a mean decrease of 10 to 11 episodes of urinary urgency incontinence per week versus placebo, decreased maximum detrusor pressure, and increased maximum cystometric capacity [71]. Outcomes were similar between 200 and 300 unit doses. Thus, for onabotA, the standard dose is 200 units. There is some evidence specific for abobotulinumtoxinA (abobotA) in this population, and there are two ongoing clinical trials of abobotA in patients with spinal cord injury or multiple sclerosis [15,84].

- **Repeat injection** – For patients with neurogenic OAB whose symptoms improve with botulinum toxin injection, response durations of 8 to 15 months have been reported [85]. Subsequent injections typically have a similar efficacy and safety profile and, thus, are the approach of choice. In a meta-analysis of 18 studies including over 1500 patients, maximum cystometric capacity, maximum detrusor pressure, reflex volume, and bladder compliance were similar between first and last injections [85]. A three-year extension of a phase III trial reported that patients with ≥50 percent reduction in UI after first injection experienced a similar magnitude of improvement with subsequent injections (up to six injections) [76].

- **Treatment failure and drug change** – For patients who do not improve after the first injection, they will often experience improvement with repeat injection. In a three-year extension of a phase III trial, those with <50 percent reduction in UI episodes after initial injection reported increased treatment response with repeat injections [76]. Thus, even in patients with less than 50 percent improvement after the first injection, subsequent injections can further reduce symptoms.

  Some clinicians have tried switching between onabotA and abobotA in patients with neurogenic OAB who did not improve with initial injection of one formula. In two small studies that evaluated such patients, approximately 50 percent of the patients who initially had a poor response to one formula had improved response with subsequent treatment with the other formula [86,87]. However, abobotA is not available in the United States.

Specific neurogenic populations

- **Spina bifida** – While we would expect BoNT-A to decrease UI episodes and improve urodynamic outcomes in patients with spina bifida, supporting data are limited. In a series of 125 adults with spina bifida, 62 percent had successful symptomatic and urodynamic outcomes after treatment with BoNT-A [88]. Female sex and increased age were associated with higher chances of successful treatment while patients with poor bladder compliance were less likely to respond [88]. However, long-term treatment success, as measured by continuation of treatment, appears to be lower. A retrospective study of 140 patients reported a 10-year discontinuation rate of approximately 50 percent, with primary or secondary treatment failure being the most common reasons [89]. (See "Myelomeningocele (spina bifida): Management and outcome".)

- **Parkinson's disease** – Data on the use of BoNT-A in patients with Parkinson's disease are limited but suggest improvement [90,91]. One observational study of 16 patients reported full resolution of leakage in 6 individuals after BoNT-A injection [92]. One concern in this population is that patients with tremor may not be able to perform

intermittent self-catheterization, if needed, for posttreatment urinary retention. Therefore, assistance from care providers or temporarily indwelling catheter may be needed. (See "Placement and management of urinary bladder catheters in adults".)

- **Cerebral vascular accident (CVA) or stroke** – There are few data on BoNT-A treatment specific to patients with CVA. Two case series reported poorer functional outcomes after BoNT-A in those with CVA compared with other neurogenic populations, with only 8 percent achieving full continence [93]. (See "Complications of stroke: An overview", section on 'Urinary incontinence'.)

- **Prior augmentation cystoplasty** – In a patient with neurogenic OAB who also has a history of prior augmentation cystoplasty, there is some evidence that BoNT-A treatment can still reduce UI episodes, but data are extremely limited [94]. (See "Myelomeningocele (spina bifida): Urinary tract complications", section on 'Bladder augmentation'.)

Neurogenic voiding dysfunction — Detrusor-sphincter dyssynergia (DSD) is a urodynamic finding in patients with some neurologic disorders. In DSD, a detrusor contraction occurs concurrently with an involuntary contraction of the urethral and/or periurethral striated muscle [19]. Urine flow can be hesitant, decreased, or prevented altogether. This loss of voiding coordination typically results from lesions at the suprasacral spinal cord or pontine micturition centers, often resulting in a significantly elevated postvoid residual as well as a "high pressure" bladder. (See "Chronic urinary retention in females", section on 'Detrusor sphincter dyssynergia'.)

For a patient presenting with DSD, we generally do not treat with external urethral sphincter injections of botulinum toxin, even though this has been described in the literature. This injection location is different from the intradetrusor injections noted above in other bladder conditions, and the application, including dose, is not standardized. A meta-analysis of four small studies with limited data reported sphincter BoNT-A injections resulted in some limited improvements in urodynamic findings, including increased voided volumes and decreased postvoid residuals [95]. However, the quality of the evidence was low. Other interventions, such as sphincterotomy, may provide more robust and lasting treatment effects.

INJECTION PROCEDURE AND ADVERSE EVENTS

The standard method for delivery of botulinum toxin type A (BoNT-A) to the bladder is through direct injection into the urothelium or bladder wall with cystoscopic equipment. The only formulation approved for lower urinary tract indications is onabotulinumtoxinA (onabotA). In non-neurogenic patients, the starting dose is 100 units; in neurogenic overactive bladder (OAB) patients, the starting dose is 200 units [16]. Details on injection

techniques and dose adjustments are discussed separately. (See "Botulinum toxin for treatment of overactive bladder: Injection and complications", section on 'Procedure for administration'.)

Of note, the US Food and Drug Administration-approved drug label states that injection in the setting of active urinary tract infection (UTI) is contraindicated [16]. Therefore, if UTI is present, we treat prior to injection. We also recommend periprocedural antibiotic prophylaxis as stipulated in the American Urological Association guidelines for cystourethroscopy with manipulation [96]. (See "Botulinum toxin for treatment of overactive bladder: Injection and complications", section on 'Urinary tract infection detection, treatment, and prevention'.)

The two main adverse events after BoNT-A injection are UTI and incomplete bladder emptying or urinary retention, which may require a period of bladder catheterization. Randomized trials of non-neurogenic OAB report a retention rate between 4 and 8 percent, depending on the dose used [20,30]. Transient weakness and hypersensitivity are less common but must also be considered in patients receiving BoNT-A therapy. Adverse events associated with injection are presented in detail separately. (See "Botulinum toxin for treatment of overactive bladder: Injection and complications", section on 'Adverse effects and precautions'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Urinary incontinence in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles

on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Treatments for urgency incontinence in females (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Description of botulinum toxin –** Botulinum toxin (BoNT) is a neurotoxin that is produced by *Clostridium botulinum*. It inhibits muscular contraction by decreasing acetylcholine release at the neuromuscular junction. In clinical applications, there are two available serotypes: botulinum toxin type A (BoNT-A) and botulinum toxin type B (BoNT-B). (See 'Background for botulinum toxin use' above.)

- **Overactive bladder treatment –** For patients with either non-neurogenic or neurogenic overactive bladder (OAB), initial therapies include behavioral management strategies (first-line) and anticholinergic or beta-3 agonist medications (second-line). Patients who have had an inadequate response to or cannot tolerate these interventions are candidates for third-line treatments, including botulinum toxin injection.

  - (See 'Refractory non-neurogenic overactive bladder syndrome' above.)

  - (See 'Botulinum toxin versus behavioral or medical therapy' above.)

- **Third-line therapies for refractory OAB–** Third-line therapies for refractory OAB include botulinum toxin injections and neuromodulation, which uses electrical stimulation to improve bladder symptoms. Neuromodulation techniques include percutaneous tibial nerve stimulation (PTNS) and sacral nerve modulation (SNM) with an implantable device. (See 'Botulinum toxin compared with other third-line OAB treatments' above.)

  - **Favoring noninvasive treatment –** For patients with refractory symptoms who desire a less invasive technique and/or to avoid the adverse effects associated with botulinum toxin or SNM, we suggest a trial of PTNS rather than botulinum toxin or SNM (**Grade 2C**). Patients desiring PTNS are counseled that they need to commit to the full course of treatment (typically 12 weeks of weekly visits) and maintenance therapy.

  - **Favoring procedure-based treatment –** For patients with refractory symptoms who are accepting of an invasive procedure, we suggest both botulinum toxin and SNM (**Grade 2C**). As the long-term efficacy appears to be similar, treatment choice is determined by a comparison of potential risks and adverse events, other medical

considerations, recovery (SNM involves an implantable device), and cost. Both therapies are routinely offered to most patients, and shared decision making is used to guide the selection. However, in the setting of certain coexisting medical conditions, one treatment may be favored over the other. (See 'Botulinum toxin compared with other third-line OAB treatments' above.)

- **Botulinum toxin for other urinary symptoms –** Botulinum toxin for treatment of voiding dysfunction and pelvic pain syndromes is less well studied and considered an off-label use of the medication. (See 'Pelvic pain syndromes' above and 'Voiding dysfunction' above.)

- **Neurogenic OAB –** For patients with neurogenic OAB, botulinum toxin treatment has demonstrated efficacy compared with placebo and remains the third-line therapy of choice for patients with poor response to oral medications. Pretreatment evaluation typically includes urodynamic testing to confirm the diagnosis and to identify complicating factors that may have an impact on efficacy or adverse events. (See 'Neurogenic overactive bladder and detrusor overactivity' above.)

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REFERENCES

1. Malde S, Fry C, Schurch B, et al. What is the exact working mechanism of botulinum toxin A and sacral nerve stimulation in the treatment of overactive bladder/detrusor overactivity? ICI-RS 2017. Neurourol Urodyn 2018; 37:S108.
2. Collins VM, Daly DM, Liaskos M, et al. OnabotulinumtoxinA significantly attenuates bladder afferent nerve firing and inhibits ATP release from the urothelium. BJU Int 2013; 112:1018.
3. Apostolidis A, Dasgupta P, Fowler CJ. Proposed mechanism for the efficacy of injected botulinum toxin in the treatment of human detrusor overactivity. Eur Urol 2006; 49:644.
4. Hanna-Mitchell AT, Wolf-Johnston AS, Barrick SR, et al. Effect of botulinum toxin A on urothelial-release of ATP and expression of SNARE targets within the urothelium. Neurourol Urodyn 2015; 34:79.
5. Apostolidis A, Averbeck MA, Sahai A, et al. Can we create a valid treatment algorithm for patients with drug resistant overactive bladder (OAB) syndrome or detrusor overactivity

(DO)? Results from a think tank (ICI-RS 2015). Neurourol Urodyn 2017; 36:882.

6. Chung E, Lee D, Gani J, et al. Position statement: a clinical approach to the management of adult non-neurogenic overactive bladder. Med J Aust 2018; 208:41.
7. Giannantoni A, Carbone A, Carone R, et al. Real-life clinical practice of onabotulinum toxin A intravesical injections for overactive bladder wet: an Italian consensus statement. World J Urol 2017; 35:299.
8. American Urological Association. Guideline on Diagnosis and Treatment of Non-Neurogenic Overactive Bladder (OAB) in Adults (2019). https://www.auanet.org/guidelines/overactive-bladder-(oab)-guideline (Accessed on May 06, 2019).
9. The National Institute for Health and Care Excellence. Urinary incontinence and pelvic organ prolapse in women overview. https://pathways.nice.org.uk/pathways/urinary-incontinence-and-pelvic-organ-prolapse-in-women (Accessed on May 06, 2019).
10. Dykstra DD, Sidi AA. Treatment of detrusor-sphincter dyssynergia with botulinum A toxin: a double-blind study. Arch Phys Med Rehabil 1990; 71:24.
11. Dykstra DD, Sidi AA, Scott AB, et al. Effects of botulinum A toxin on detrusor-sphincter dyssynergia in spinal cord injury patients. J Urol 1988; 139:919.
12. Schurch B, Stöhrer M, Kramer G, et al. Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. J Urol 2000; 164:692.
13. Karsenty G, Denys P, Amarenco G, et al. Botulinum toxin A (Botox) intradetrusor injections in adults with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic literature review. Eur Urol 2008; 53:275.
14. Rohrsted M, Nordsten CB, Bagi P. Onabotulinum toxin a (botox®) in the treatment of neurogenic bladder overactivity. Nephrourol Mon 2012; 4:437.
15. Dysport® Treatment of Urinary Incontinence in Adults Subjects With Neurogenic Detrusor Overactivity (NDO) Due to Spinal Cord Injury or Multiple Sclerosis - Study 1 (CONTENT 1). https://clinicaltrials.gov/ct2/show/NCT02660138 (Accessed on May 06, 2019).
16. BOTOX (onabotulinumtoxinA) for injection, for intramuscular, intradetrusor, or intradermal use. US Food and Drug Administration (FDA) approved product information. Revised January 2013. (Available online at https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/103000s5251lbl.pdf.).
17. Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Int Urogynecol J 2010; 21:5.
18. Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn 2010; 29:4.

19. Gajewski JB, Schurch B, Hamid R, et al. An International Continence Society (ICS) report on the terminology for adult neurogenic lower urinary tract dysfunction (ANLUTD). Neurourol Urodyn 2018; 37:1152.
20. Visco AG, Brubaker L, Richter HE, et al. Anticholinergic therapy vs. onabotulinumtoxina for urgency urinary incontinence. N Engl J Med 2012; 367:1803.
21. Drake MJ, Nitti VW, Ginsberg DA, et al. Comparative assessment of the efficacy of onabotulinumtoxinA and oral therapies (anticholinergics and mirabegron) for overactive bladder: a systematic review and network meta-analysis. BJU Int 2017; 120:611.
22. Staskin DR, Peters KM, MacDiarmid S, et al. Percutaneous tibial nerve stimulation: a clinically and cost effective addition to the overactive bladder algorithm of care. Curr Urol Rep 2012; 13:327.
23. Tutolo M, Ammirati E, Heesakkers J, et al. Efficacy and Safety of Sacral and Percutaneous Tibial Neuromodulation in Non-neurogenic Lower Urinary Tract Dysfunction and Chronic Pelvic Pain: A Systematic Review of the Literature. Eur Urol 2018; 73:406.
24. Sherif H, Khalil M, Omar R. Management of refractory idiopathic overactive bladder: intradetrusor injection of botulinum toxin type A versus posterior tibial nerve stimulation. Can J Urol 2017; 24:8838.
25. Stewart F, Gameiro OL, El Dib R, et al. Electrical stimulation with non-implanted electrodes for overactive bladder in adults. Cochrane Database Syst Rev 2016; 4:CD010098.
26. The National Institute for Health and Care Excellence. Invasive procedures for overactive bladder in women, Percutaneous posterior tibial nerve stimulation. https://pathways.nice.org.uk/pathways/urinary-incontinence-and-pelvic-organ-prolapse-in-women#path=view%3A/pathways/urinary-incontinence-and-pelvic-organ-prolapse-in-women/invasive-procedures-for-overactive-bladder-in-women.xml&content=view-node%3Anodes-percutaneous-posterior-tibial-nerve-stimulation (Accessed on May 06, 2019).
27. van Breda HMK, Martens FMJ, Tromp J, Heesakkers JPFA. A New Implanted Posterior Tibial Nerve Stimulator for the Treatment of Overactive Bladder Syndrome: 3-Month Results of a Novel Therapy at a Single Center. J Urol 2017; 198:205.
28. Wireless, Implantable Tibial Nerve Stimulator System (eCoin™) for the Treatment of Refractory Lower Urinary Tract Symptoms in Patients With MS. https://clinicaltrials.gov/ct2/show/NCT03753698 (Accessed on May 06, 2019).
29. Balk EM, Rofeberg VN, Adam GP, et al. Pharmacologic and Nonpharmacologic Treatments for Urinary Incontinence in Women: A Systematic Review and Network Meta-analysis of Clinical Outcomes. Ann Intern Med 2019; 170:465.
30. Amundsen CL, Richter HE, Menefee SA, et al. OnabotulinumtoxinA vs Sacral Neuromodulation on Refractory Urgency Urinary Incontinence in Women: A

Randomized Clinical Trial. JAMA 2016; 316:1366.

31. Amundsen CL, Komesu YM, Chermansky C, et al. Two-Year Outcomes of Sacral Neuromodulation Versus OnabotulinumtoxinA for Refractory Urgency Urinary Incontinence: A Randomized Trial. Eur Urol 2018; 74:66.
32. Gormley EA, Lightner DJ, Faraday M, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment. J Urol 2015; 193:1572.
33. Lucas MG, Bosch RJ, Burkhard FC, et al. EAU guidelines on assessment and nonsurgical management of urinary incontinence. Eur Urol 2012; 62:1130.
34. Committee Opinion No. 604: OnabotulinumtoxinA and the bladder. Obstet Gynecol 2014; 123:1408.
35. Urinary incontinence and pelvic organ prolapse in women: management. National Institute for Health Care and Excellence. April 2019. www.nice.org.uk/guidance/ng123 (Accessed on June 06, 2019).
36. Botox- onabotulinumtoxina injection. US Food and Drug Administration (FDA) approved product information. Revised 9/2018. US National Library of Medicine. www.dailymed.nlm.nih.gov (Accessed on June 06, 2019).
37. Nicolle LE, Gupta K, Bradley SF, et al. Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America. Clin Infect Dis 2019; 68:e83.
38. Rachaneni S, Latthe P. Effectiveness of BTX-A and neuromodulation in treating OAB with or without detrusor overactivity: a systematic review. Int Urogynecol J 2017; 28:805.
39. Chapple C, Sievert KD, MacDiarmid S, et al. OnabotulinumtoxinA 100 U significantly improves all idiopathic overactive bladder symptoms and quality of life in patients with overactive bladder and urinary incontinence: a randomised, double-blind, placebo-controlled trial. Eur Urol 2013; 64:249.
40. Nitti VW, Dmochowski R, Herschorn S, et al. OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo controlled trial. J Urol 2013; 189:2186.
41. Duthie JB, Vincent M, Herbison GP, et al. Botulinum toxin injections for adults with overactive bladder syndrome. Cochrane Database Syst Rev 2011; :CD005493.
42. Nitti VW, Ginsberg D, Sievert KD, et al. Durable Efficacy and Safety of Long-Term OnabotulinumtoxinA Treatment in Patients with Overactive Bladder Syndrome: Final Results of a 3.5-Year Study. J Urol 2016; 196:791.
43. Chohan N, Hilton P, Brown K, Dixon L. Efficacy and duration of response to botulinum neurotoxin A (onabotulinumA) as a treatment for detrusor overactivity in women. Int Urogynecol J 2015; 26:1605.

44. Habashy D, Losco G, Tse V, et al. Botulinum toxin (OnabotulinumtoxinA) in the male non-neurogenic overactive bladder: clinical and quality of life outcomes. BJU Int 2015; 116 Suppl 3:61.
45. Rahnama'i MS, Marcelissen TAT, Brierley B, et al. Long-term compliance and results of intravesical botulinum toxin A injections in male patients. Neurourol Urodyn 2017; 36:1855.
46. Chughtai B, Dunphy C, Lee R, et al. Randomized, double-blind, placebo controlled pilot study of intradetrusor injections of onabotulinumtoxinA for the treatment of refractory overactive bladder persisting following surgical management of benign prostatic hyperplasia. Can J Urol 2014; 21:7217.
47. Dmochowski R, Chapple C, Nitti VW, et al. Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial. J Urol 2010; 184:2416.
48. Brubaker L, Richter HE, Visco A, et al. Refractory idiopathic urge urinary incontinence and botulinum A injection. J Urol 2008; 180:217.
49. Malde S, Palmisani S, Al-Kaisy A, Sahai A. Guideline of guidelines: bladder pain syndrome. BJU Int 2018; 122:729.
50. Shim SR, Cho YJ, Shin IS, Kim JH. Efficacy and safety of botulinum toxin injection for interstitial cystitis/bladder pain syndrome: a systematic review and meta-analysis. Int Urol Nephrol 2016; 48:1215.
51. Wang J, Wang Q, Wu Q, et al. Intravesical Botulinum Toxin A Injections for Bladder Pain Syndrome/Interstitial Cystitis: A Systematic Review and Meta-Analysis of Controlled Studies. Med Sci Monit 2016; 22:3257.
52. Ochoa Vargas DC, García Perdómo HA. Efficacy of Botulinum toxin A for the treatment of Bladder pain syndrome: A systematic review. Actas Urol Esp (Engl Ed) 2018; 42:152.
53. El Shatoury MG, DeYoung L, Turley E, et al. Early experimental results of using a novel delivery carrier, hyaluronan-phosphatidylethanolamine (HA-PE), which may allow simple bladder instillation of botulinum toxin A as effectively as direct detrusor muscle injection. J Pediatr Urol 2018; 14:172.e1.
54. Kuo HC, Liu HT, Chuang YC, et al. Pilot study of liposome-encapsulated onabotulinumtoxina for patients with overactive bladder: a single-center study. Eur Urol 2014; 65:1117.
55. Rappaport YH, Zisman A, Jeshurun-Gutshtat M, et al. Safety and Feasibility of Intravesical Instillation of Botulinum Toxin-A in Hydrogel-based Slow-release Delivery System in Patients With Interstitial Cystitis-Bladder Pain Syndrome: A Pilot Study. Urology 2018; 114:60.

56. Abdel-Meguid TA, Mosli HA, Farsi H, et al. Treatment of refractory category III nonbacterial chronic prostatitis/chronic pelvic pain syndrome with intraprostatic injection of onabotulinumtoxinA: a prospective controlled study. Can J Urol 2018; 25:9273.

57. El-Enen MA, Abou-Farha M, El-Abd A, et al. Intraprostatic injection of botulinum toxin-A in patients with refractory chronic pelvic pain syndrome: The transurethral vs. transrectal approach. Arab J Urol 2015; 13:94.

58. Falahatkar S, Shahab E, Gholamjani Moghaddam K, Kazemnezhad E. Transurethral intraprostatic injection of botulinum neurotoxin type A for the treatment of chronic prostatitis/chronic pelvic pain syndrome: results of a prospective pilot double-blind and randomized placebo-controlled study. BJU Int 2015; 116:641.

59. Gottsch HP, Yang CC, Berger RE. A pilot study of botulinum toxin A for male chronic pelvic pain syndrome. Scand J Urol Nephrol 2011; 45:72.

60. European Association of Urology. EAU Guidelines on Chronic Pelvic Pain. https://uroweb.org/wp-content/uploads/26-Chronic-Pelvic-Pain_LR.pdf (Accessed on May 06, 2019).

61. Abbott JA, Jarvis SK, Lyons SD, et al. Botulinum toxin type A for chronic pain and pelvic floor spasm in women: a randomized controlled trial. Obstet Gynecol 2006; 108:915.

62. McVary KT, Roehrborn CG, Chartier-Kastler E, et al. A multicenter, randomized, double-blind, placebo controlled study of onabotulinumtoxinA 200 U to treat lower urinary tract symptoms in men with benign prostatic hyperplasia. J Urol 2014; 192:150.

63. Shim SR, Cho YJ, Shin IS, Kim JH. Efficacy and safety of botulinum toxin injection for benign prostatic hyperplasia: a systematic review and meta-analysis. Int Urol Nephrol 2016; 48:19.

64. Totaro A, Pinto F, Pugliese D, et al. Intraprostatic botulinum toxin type "A" injection in patients with benign prostatic hyperplasia and unsatisfactory response to medical therapy: A randomized, double-blind, controlled trial using urodynamic evaluation. Neurourol Urodyn 2018; 37:1031.

65. Chen JL, Chen CY, Kuo HC. Botulinum toxin A injection to the bladder neck and urethra for medically refractory lower urinary tract symptoms in men without prostatic obstruction. J Formos Med Assoc 2009; 108:950.

66. Biardeau X, Haddad R, Chesnel C, et al. [Use of botulinum toxin A in pelvic floor dysfunctions in the elderly: A review]. Prog Urol 2019; 29:216.

67. European Association of Urology. EAU Guidelines on Management of Non-Neurogenic M ale Lower Urinary Tract Symtpoms (LUTS), incl. Benign Prostatic Obstruction (BPO). http s://uroweb.org/wp-content/uploads/EAU-Guidelines-on-the-Management-of-Non-neuro genic-Male-LUTS-2018-large-text.pdf (Accessed on May 06, 2019).

68. Kuo TL, Ng LG, Chapple CR. Pelvic floor spasm as a cause of voiding dysfunction. Curr Opin Urol 2015; 25:311.
69. Panicker JN, Seth JH, Khan S, et al. Open-label study evaluating outpatient urethral sphincter injections of onabotulinumtoxinA to treat women with urinary retention due to a primary disorder of sphincter relaxation (Fowler's syndrome). BJU Int 2016; 117:809.
70. Groen J, Pannek J, Castro Diaz D, et al. Summary of European Association of Urology (EAU) Guidelines on Neuro-Urology. Eur Urol 2016; 69:324.
71. Cheng T, Shuang WB, Jia DD, et al. Efficacy and Safety of OnabotulinumtoxinA in Patients with Neurogenic Detrusor Overactivity: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. PLoS One 2016; 11:e0159307.
72. Linsenmeyer TA. Use of botulinum toxin in individuals with neurogenic detrusor overactivity: state of the art review. J Spinal Cord Med 2013; 36:402.
73. Cruz F, Herschorn S, Aliotta P, et al. Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. Eur Urol 2011; 60:742.
74. Ginsberg D, Gousse A, Keppenne V, et al. Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity. J Urol 2012; 187:2131.
75. Rovner E, Dmochowski R, Chapple C, et al. OnabotulinumtoxinA improves urodynamic outcomes in patients with neurogenic detrusor overactivity. Neurourol Urodyn 2013; 32:1109.
76. Denys P, Dmochowski R, Aliotta P, et al. Positive outcomes with first onabotulinumtoxinA treatment persist in the long term with repeat treatments in patients with neurogenic detrusor overactivity. BJU Int 2017; 119:926.
77. Gobbi C, Digesu GA, Khullar V, et al. Percutaneous posterior tibial nerve stimulation as an effective treatment of refractory lower urinary tract symptoms in patients with multiple sclerosis: preliminary data from a multicentre, prospective, open label trial. Mult Scler 2011; 17:1514.
78. Kabay S, Kabay SC, Yucel M, et al. The clinical and urodynamic results of a 3-month percutaneous posterior tibial nerve stimulation treatment in patients with multiple sclerosis-related neurogenic bladder dysfunction. Neurourol Urodyn 2009; 28:964.
79. Gaziev G, Topazio L, Iacovelli V, et al. Percutaneous Tibial Nerve Stimulation (PTNS) efficacy in the treatment of lower urinary tract dysfunctions: a systematic review. BMC Urol 2013; 13:61.
80. Kessler TM, La Framboise D, Trelle S, et al. Sacral neuromodulation for neurogenic lower urinary tract dysfunction: systematic review and meta-analysis. Eur Urol 2010; 58:865.

81. BlueCross BlueShield of North Carolina. Corporate Medical Policy, Percutaneous Tibial Nerve Stimulation for Voiding Dysfunction. https://www.bluecrossnc.com/sites/default/files/document/attachment/services/public/pdfs/medicalpolicy/percutaneous_tibial_nerve_stimulation_for_voiding_dysfunction.pdf (Accessed on May 06, 2019).
82. Zhang P, Wang JY, Zhang Y, et al. Results of Sacral Neuromodulation Therapy for Urinary Voiding Dysfunction: Five-Year Experience of a Retrospective, Multicenter Study in China. Neuromodulation 2019; 22:730.
83. Redshaw JD, Lenherr SM, Elliott SP, et al. Protocol for a randomized clinical trial investigating early sacral nerve stimulation as an adjunct to standard neurogenic bladder management following acute spinal cord injury. BMC Urol 2018; 18:72.
84. Dysport Treatment of Urinary Incontinence in Adults Subjects with Neurogenic Detruso Overactivity (NDO) Due to Spinal Cord Injury of Multiple Sclerosis- Study 2. U.S. National Library of Medicine. January 2019. clinicaltrials.gov/ct2/show/NCT02660359?term=NCT02660359&rank=1 (Accessed on June 06, 2019).
85. Ni J, Wang X, Cao N, et al. Is repeat Botulinum Toxin A injection valuable for neurogenic detrusor overactivity-A systematic review and meta-analysis. Neurourol Urodyn 2018; 37:542.
86. Bottet F, Peyronnet B, Boissier R, et al. Switch to Abobotulinum toxin A may be useful in the treatment of neurogenic detrusor overactivity when intradetrusor injections of Onabotulinum toxin A failed. Neurourol Urodyn 2018; 37:291.
87. Peyronnet B, Roumiguié M, Castel-Lacanal E, et al. Preliminary results of botulinum toxin A switch after first detrusor injection failure as a treatment of neurogenic detrusor overactivity. Neurourol Urodyn 2016; 35:267.
88. Peyronnet B, Even A, Capon G, et al. Intradetrusor Injections of Botulinum Toxin A in Adults with Spinal Dysraphism. J Urol 2018; 200:875.
89. Baron M, Peyronnet B, Aublé A, et al. Long-Term Discontinuation of Botulinum Toxin A Intradetrusor Injections for Neurogenic Detrusor Overactivity: A Multicenter Study. J Urol 2019; 201:769.
90. Kaviani A, Khavari R. Disease-Specific Outcomes of Botulinum Toxin Injections for Neurogenic Detrusor Overactivity. Urol Clin North Am 2017; 44:463.
91. Peyronnet B, Gamé X, Vurture G, et al. Botulinum Toxin Use in Neurourology. Rev Urol 2018; 20:84.
92. Kulaksizoglu H, Parman Y. Use of botulinim toxin-A for the treatment of overactive bladder symptoms in patients with Parkinsons's disease. Parkinsonism Relat Disord 2010; 16:531.
93. Jiang YH, Liao CH, Tang DL, Kuo HC. Efficacy and safety of intravesical onabotulinumtoxinA injection on elderly patients with chronic central nervous system

lesions and overactive bladder. PLoS One 2014; 9:e105989.

94. Michel F, Ciceron C, Bernuz B, et al. Botulinum Toxin Type A Injection After Failure of Augmentation Enterocystoplasty Performed for Neurogenic Detrusor Overactivity: Preliminary Results of a Salvage Strategy. The ENTEROTOX Study. Urology 2019; 129:43.
95. Utomo E, Groen J, Blok BF. Surgical management of functional bladder outlet obstruction in adults with neurogenic bladder dysfunction. Cochrane Database Syst Rev 2014; :CD004927.
96. American Urological Association. Best practice statement on urologic surgery antimicrobial prophylaxis. https://www.auanet.org/guidelines/antimicrobial-prophylaxis-best-practice-statement (Accessed on August 21, 2019).

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