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Disease-Specific Outcomes of Botulinum Toxin Injections for Neurogenic Detrusor Overactivity

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Abstract

Intradetrusor injection of botulinum toxin A (BTX-A) is an effective option in the management of patients with neurogenic detrusor overactivity (NDO) who do not respond to or tolerate oral pharmacologic agents. There is level I evidence that intradetrusor injection of onabotulinumtoxinA for the treatment of refractory NDO in patients with multiple sclerosis and spinal cord injury is associated with a significantly greater achievement of patients' goals and improved performance in urodynamic studies than results with placebo. Only pilot studies or small case series support the use of BTX-A for NDO in patients with Parkinson's disease (PD) and cerebrovascular accident (CVA). BTX-A seems to be effective in children with myelomeningocele (MMC) but this statement is not supported by high level of evidence.

Keywords

Botulinum toxin; Overactive bladder; Neurogenic; Detrusor overactivity; Urinary incontinence; Parkinson's Disease; Myelomeningocele; Multiple sclerosis

Introduction

Neurogenic detrusor overactivity (NDO) is a bladder dysfunction caused by a neurological disease such as multiple sclerosis (MS), spinal cord injury (SCI), Parkinson's disease (PD), cerebrovascular accident (CVA), or myelomeningocele (MMC). NDO might be associated with urinary frequency, nocturia, urgency, and urinary incontinence (UI). A systematic review of 189 articles by Ruffion et al. showed that the prevalence of UI was 50.9%, 52.3%, 33.1% and 23.6% in patients with MS, SCI, PD, and CVA respectively.[1] NDO leads to a negative impact on a patient's quality of life (QOL)[2] and may contribute to deterioration of the upper urinary tract.[3] Accordingly, urodynamic study (UDS) findings including impaired detrusor compliance with a high detrusor leak point pressure, detrusor sphincter dyssynergia (DSD), and vesicoureteral reflux (VUR) require special attention in neurogenic bladder patients.[3]

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Even though anticholinergic or beta agonist drugs have limited effectiveness and moderate adverse side effect profiles, they are the first-line pharmacotherapy for patients with NDO.[4] However, long-term treatment with these medications may be suboptimal, and many patients discontinue their medications because of lack of efficacy, and/or significant bothersome side effects, especially patients with neurogenic bladders in whom higher doses of medications are needed. In addition, recent studies highlight the possibility of cortical atrophy, cognitive decline, and an increased risk of dementia with chronic use of strong anticholinergics such as oxybutynin.[5,6] These data are of significant concern for urologists who would otherwise prescribe high doses of anticholinergics for management of NDO in patients with preexisting neurologic compromise and cognitive decline, such as patients with MS, PD, MMC, or CVA. Until recently, augmentation cystoplasty was the next step in the management of refractory neurogenic bladder (NGB). However, augmentation cystoplasty is a major reconstructive surgery with significant immediate and long-term morbidity.[7,8]

Botulinum toxin A (BTX-A) blocks the release of acetylcholine at the neuromuscular junction and leads to a temporary chemodenervation of the bladder. Motor effects of BTX-A on the bladder have been studied extensively,[9] which has led to its approval by the US Food and Drug Administration (FDA) in August of 2011 for the treatment of refractory NDO in patients with MS and SCI.

In this topic review, we appraised the disease-specific outcome of BTX-A injection in patients with NDO. NGB encompasses a broad spectrum of patients because of the heterogeneity of neurologic diseases. Our review focuses on the more common patient populations, including patients with MS, SCI, CVA, PD, and MMC. We performed a search in PubMed for all abstracts that contained the terms “bladder” and “botulinum”. In order not to restrict our PubMed search to MEDLINE we did not use MeSH terms. Other searches of PubMed were also carried out to obtain additional related information. A total of 301 abstracts were identified and reviewed. The articles most relevant to the purpose of this manuscript were then selected.

Efficacy of intradetrusor injection of botulinum toxin A

Two forms of BTX-A, onabotulinumtoxinA (OnabotA, Botox®) and abobotulinumtoxinA (AbobotA, Dysport®), have been evaluated for the treatment of refractory NDO[10] with comparable outcomes. In this review, the abbreviation BTX-A will be used when we refer to botulinum toxin A in general (both available forms).

The first phase II randomized, double-blind, placebo-controlled clinical trial using BTX-A to treat NDO was reported by Schurch et al. in 2005, They randomized a total of 59 patients (53 with SCI and 6 with MS) to receive a single dose of onabotulinumtoxinA (200U or 300U) or placebo and concluded that intradetrusor injection of onabotulinumtoxinA was associated with a clinically significant improvement in UI caused by NDO.[11] Another randomized, double-blind, placebo-controlled trial was reported by Herschorn et al. in 2011, Patients had experienced a reduction in their UI by 50% at week 6 after onabotulinumtoxinA injection.[12] In a systematic review by Duthie et al. in 2011, of a heterogeneous population of NDO and idiopathic overactive bladder (OAB) patients, BTX-A results were superior to

those with a placebo in all 19 included studies. OnabotulinumtoxinA and abobotulinumtoxinA were used in 17 and 2 studies respectively. Patients receiving repeated doses did not become refractory to BTX-A.[13] Other systematic reviews by Zhoe et al. (2015), Cui et al. (2015), and Lopez et al. (2016) also concluded that intravesical injections of BTX-A significantly improve NDO symptoms.[14-16] Zhoe et al. identified four randomized double-blind, placebo-controlled trials combining a total of 807 patients, and reported that onabotulinumtoxinA effectively improved clinical outcomes and UDS findings in patients with NDO.[14] Moreover, BTX-A injection seems to be cost-effective in the management of UI related to NDO compared with costs of supportive care which consists of incontinence pads and possible use of anticholinergics and clean intermittent catheterization (CIC).[17]

Pivotal Clinical Trials

The data offering strongest support for the use of onabotulinumtoxinA in NDO comes from two double-blind, placebo-controlled, phase-three studies that were carried out after several phase-two studies.[18] These two pivotal clinical trials constitute the two trials of the DIGNITY clinical research program (Double-Blind Investigation of Purified Neurotoxin Complex in Neurogenic Detrusor Overactivity). DIGNITY compared response to onabotulinumtoxinA with response to placebo in patients with NDO due to SCI or MS. [19] MS or SCI patients with NDO who had ≥ 14 incidents of UI per week were randomized to receive 200U or 300U of onabotulinumtoxinA or placebo, and the outcomes were assessed at week 6 post injection.[20] In 2011, Cruz et al.[21] published the results of the first trial of DIGNITY which was conducted in 63 centers in Europe, North America, South America, South Africa, and the Asia Pacific. They enrolled and randomized a total of 275 patients (Table 1).[22] In 2012, Ginsberg et al. reported the results of the second trial of DIGNITY from 85 centers and 416 patients randomized to intradetrusor injections of placebo or onabotulinumtoxinA 200U or onabotulinumtoxinA 300U (Table 1).[23] In addition, a follow-up study that pooled the data from these two trials of 691 patients is summarized in Table 1.[24] To evaluate the long-term efficacy of onabotulinumtoxinA injection for NDO in MS and SCI patients, Kennelly et al. performed a prospective, multicenter extension trial on the patients in the initial DIGNITY study. [18] The number of UI incidents/week at week 6 was significantly decreased following repeated onabotulinumtoxinA injections. The reductions from baseline were −22.7, −23.3, −23.1, −25.3, and −31.9 in the 200U dose group and −23.8, −25.0, −23.6, −24.1, and −29.5 in the 300U dose group in treatment rounds 1 to 5, respectively.[25] Final analysis of patients who completed 4 years of treatment showed that the decrease in UI episodes, which was 4.3 UI episodes per day at the baseline, consistently ranged from –3.4 to –3.9 episodes per day.[26]

Recommended dose and injection template—Phase III trials reported by Cruz, Ginsberg, Kennelly and their colleagues found no statistically significant differences in efficacy between 200U and 300U of onabotulinumtoxinA. [18] Other trials have shown 200U to be more effective than 50U and 100U in NDO.[18,27] FDA approved intradetrusor injection of 200U of onabotulinumtoxinA (OnabotA, BOTOX®) for NDO in 2011. There is no standard method of injection onabotulinumtoxinA, however, the abovementioned phase III studies used a trigone-sparing template. Two randomized clinical trials administered BTX-A

to include versus exclude the trigone in SCI patients and both favored trigone-including template with improvements in efficacy, as measured by detrusor pressure, higher volume to void and episodes of incontinence without any difference in complications.[28,29] At our institution and in the clinic setting, we would use a rigid or flexible cystoscope with a intradetrusor/suburethral combination technique to deliver 200U of onabotulinumtoxinA in 20 cc at 20-30 sites including the trigone, base, lateral, and dome of the bladder.

Shortcomings of botulinum toxin-A

Adverse Event (AEs) and Precautions

The adverse events associated with intradetrusor injection of BTX-A are not negligible. The most common adverse events reported are urinary tract infections (UTI) and increased post-void residual, especially in patients with multiple sclerosis or diabetes mellitus with the incidence of UTI reported to be 51.8%-56%.[24] In addition, BTX-A should be avoided in settings where concomitant neuromuscular disorder may exacerbate clinical effects of treatment such as myasthenia gravis or Lambert-Eaton syndrome. Caution must be taken when BTX-A is used in specific patient population with neurogenic bladder such as patients under age 18 years of age and in geriatric patients. BTX-A is specified as pregnancy category C, where there are no adequate and well-controlled studies in humans and it should only be used if the potential benefits justify the potential risk to the fetus.

Adherence to Therapy

In the extension trial of two phase III trials of DIGNITY study, in which 388 patients were offered repeat injections for up to 5 cycles, only 241 and 113 received the 4^{th} and 5^{th} cycles, respectively.[25] Authors report that discontinuation as a result of AEs and lack of efficacy was noted in only 12 (3.1%) and 8 (2.1%) of the 388 patients, respectively.[26]

Disease specific findings

Multiple Sclerosis (MS)

MS is a chronic multifocal demyelinating disease that can affect any part of CNS. Up to 90% of patients with MS develop lower urinary tract dysfunction within the first 18 years of the disease.[30] Neurogenic lower urinary tract dysfunction symptoms experienced by patients with MS can include abnormalities in the storage phase, voiding phase, or both.[30] Because of the diffuse, multifocal involvement of CNS in patients with MS, symptom severity and impact on quality of life may vary from patient to patient. Urinary frequency, urgency, and urgency incontinence are the most common symptoms, occurring in 37% to 99% of MS patients[31] in whom they negatively impact health-related quality of life.[32]

Analysis of pooled DIGNITY study, which included 381 patients with MS, demonstrated that onabotulinumtoxinA injections improved clinical outcomes and UDS findings in these patients (Table 2).[33] Patients were considered overall responders if one of their goals was reached. These goals were to “be dry”, “reduce incontinence”, “reduce other urinary symptoms”, ”reduce activity limitations”, “improve bladder control”,” improve QOL, sleep, and emotions”, “reduce number of oral medication therapies”, and “other”. Patients with MS

or SCI reported significantly greater overall goal accomplishment with onabotulinumtoxinA injection than with placebo ($P < 0.001$).[34] Table 2 summarizes the urodynamic outcomes following onabotulinumtoxinA injections in MS patients. [33]

Despite overall improvements in UI, QOL, and cystometric bladder capacity in these patients, some effects were modest in MS patients. In pooled DIGNITY data analysis, being dry, the highest reported goal at baseline, was reached in only 42.9% of MS patients at week 6 after treatment while dryness occurred in 21.7% of MS patients who received only a placebo.[34] In addition, in contrast to SCI patients of whom only 13.5% were voiding voluntarily at baseline, the majority of MS patients were voiding spontaneously and were not using CIC at the baseline (69.6%). In this group at week 2, the overall percentage of patients who required initiation of CIC because of urinary retention was 30.8%-44.0%. Therefore, it is recommended that all MS patients who are planning to undergo BTX-A should be taught, or agree to learn to do, CIC because as many as up to 88% of patients may need to perform CIC.[35] Initiating CIC is a burden in general, and it is even more so to patients in whom lower extremity spasms, compromised hand dexterity, or visual disturbances may be present. The cost and side effects (hematuria, pain, trauma, strictures, and UTI) associated with CIC also need to be considered..[36] Clinicians should also be aware that UTIs worsen urinary symptoms in MS patients and significantly impact their QOL[37] and may trigger pathways that result in exacerbation of MS and its neurological progression.[38,39] Furthermore, in the longest follow-up study of the use of onabotulinumtoxinA (15 years), the overall discontinuation rate amongst all neurogenic patients (SCI, MS, MMC) was 40%, and only 14% of MS patients continued with the treatment.[40]

In summary, there is level I evidence that intradetrusor injection of onabotulinumtoxinA for the treatment of refractory NDO in patients with MS is associated with significant achievement of patients' goals and improvement in UDS performance. However, the authors believe that despite these overall improvements in urinary symptoms, UDS parameters, and QOL following onabotulinumtoxinA injection, its efficacy in MS patients who do not perform CIC is modest compared to the burden of initiating CIC. The cost, adverse events associated with onabotulinumtoxinA, and the significantly low adherence to therapy in MS patients who do not perform CIC need to be considered during shared decision making regarding NDO management in this specific patient group.

Spinal Cord Injury (SCI)

More than 50% of patients with SCI suffer from UI.[1] Some of these patients do not respond to or tolerate oral medications to control their NDO. In this group, Intravesical injection of BTX-A has been shown to decrease UI, improve UDS parameters, and increase QOL. [41] A systematic review by Mehta et al. in 2013 of fourteen studies representing data from 734 patients with SCI demonstrated that the average proportion of patients that experienced incidents of UI was reduced from a mean of 23% to 1.31% per day after BTX-A treatment. [42] The DIGNITY study, which included 310 patients with SCI, showed that OnabotulinumtoxinA injections effectively improve clinical outcomes and UDS parameters(Table 2). [33] Another clinically important consideration of BTX-A use in patients

with SCI is its potential effect on autonomic dysreflexia (AD). Bladder-related events, including NDO, are an important cause of AD in SCI patients. Animal and human studies have shown that intradetrusor injections of BTX-A decrease the severity and frequency of bladder-related incidents of AD in this setting.[43,44] In summary, there is level I evidence that intradetrusor injection of onabotulinumtoxinA for the treatment of refractory NDO in patients with SCI is associated with significantly improved UDS performance and achievement of patients' goals.

Parkinson's Disease (PD)

Fifty per cent of patients with PD suffer from UI. Some of these patients do not tolerate or do not respond to oral medications to control their NDO. In addition, the anti-cholinergic action of the medications may complicate their PD medications to ameliorate the cholinergic system neurologic deficits present with the disease. Intradetrusor injection of BTX-A has been used by a few groups in patients with PD and NDO with good outcomes (Table 3).[45] However, currently the literature does not provide a high level of evidence for BTX-A efficacy or indicate dosage and risk factors for retention or difficulty voiding in PD patients.[46] International Continence Society (ICS) guidelines for the management of bladder dysfunction in PD published in 2016 mention that BTX-A can be used for intractable UI in PD.[46]

Cerebrovascular Accident (CVA)

Of patients with history of CVA, 23.6% suffer from NDO.[1] Intravesical injection of onabotulinumtoxinA has been reported in just a few groups of such patients (Table 3).[47,48] This data indicates that onabotulinumtoxinA might be effective in these patients but the results might not be as favorable as in other settings. In addition, the possibility of urinary retention and urinary tract infection must receive serious consideration in this chronically ill and fragile group of patients.

Myelomeningocele (MMC)

For many years bladder management in patients with myelomeningocele (MMC) has been dependent on CIC and high doses of oral anticholinergics. However, some patients do not respond to anticholinergics or their neurogenic constipation can be worsened by their side effects. Intradetrusor injection of BTX-A has been used in various groups to delay or avoid the need for augmentation cystoplasty.[49] The most commonly used dose of onabotulinumtoxinA in these patients is 10-12 U/kg with a maximal dose of 300U.[50] A systematic review was performed by Hascoet et al. in 2016 which included 12 studies and 293 patients who were all younger than 18 years of age [51] (Table 4). In this review, there was no randomized trial comparing BTX-A versus placebo and most studies had no control group. This review concluded that most studies demonstrated an improvement in both clinical symptoms and UDS parameters. Complete resolution of incontinence occurred in 32–100% of patients. Two studies suggested that BTX-A has lower efficacy in patients with low bladder compliance. Intradetrusor injections of BTX-A could be effective in children with MMC but this possibility is not supported by a high level of evidence.[51] Currently, **there are no published data available in BTX-A use in adult MMC patients.** However,

recently, we investigated the outcomes of intravesical injection of onbotulinumtoxinA in adults with spinal dysraphism.

Billing codes were used to identify patients who underwent onabotulinumtoxinA injection between 2012-2016 at our institution and within our transitional urology clinic. A total of 18 (8 males and 10 females) patients with mean age of 20.8 with history of spinal dysraphism were identified where all patients reported refractory urinary incontinence from native urethra or continent catheterizable channel. 14 patients had myelomeningocele, 2 sacral agenesis, 1 tethered cord, and 1 occult spina bifida. All patients completed urodynamic study (UDS) prior to onabotulinumtoxinA injection. Urinary incontinence improved by onabotulinumtoxinA injection in 81.25% of patients and 63.66% of them became dry (p= 0.0 23). Degree of hydronephrosis improved in 3 of 4 (75%) patients who had follow-up imaging. Repeat UDS after injection was done in 11 patients who did not clinically improve or who had loss of bladder compliance on their baseline UDS (29.34 ml/cmH2O vs. 67.24 ml/cmH2O). Mean maximum cystometric capacity (MCC) before and after injection was 310.18 mL and 380.27mL (p=.045). However, mean bladder compliance before and after treatment was 29.26 ml/cmH2O and 28.76 ml/cmH2O respectively (p=0.48). Therefore, we believe that intravesical onabotulinumtoxinA injection may improve refractory urinary incontinence in selected group of adults with spinal dysraphism. However, despite improvement in maximum cystometric capacity, bladder compliance does not seem to improve following therapy in patients who had loss of compliance at baseline. We propose that possibly earlier intervention might be more beneficial in this specific patient population, when significant bladder remodeling has not occurred. Future prospective and multicenter trials are needed to evaluate the effects of onabotulinumtoxinA in adults with spinal dysraphism.

Another possibly unique and interesting use of BTX-A in neuropathic patients could be in the setting of history of prior augmentation cystoplasty. Augmentation cystoplasty has been used in the treatment of refractory overactive or neurogenic bladder for decades. In a very small number of patients, symptoms persist or recur after the surgery and there is little guidance on the management of these patients. At our institution, we reviewed the efficacy of intra-detrusor and intra-augment onabotulinumtoxinA injections in this setting. We identified 13 (9 females, 4 males) patients with the mean age of 31.61 and history of prior augmentation cystoplasty. The indications for onabotulinumtoxinA injections were urinary incontinence and refractory storage (irritative) symptoms in 12 (92.3%) and 1 (7.6%) patients respectively. All patients completed urodynamic studies prior to treatment. Intra-detrusor and intra-augment injections were done in 10 patients and 3 patients just received intra-detrusor injections. 10 patients (77%) reported improvement in all subjective parameters (frequency, urgency, incontinence). One patient with history of ileocystoplasty and Mitrofanoff appendicovesicostomy continued to have incontinence per urethra. Video urodynamic testing in this patient following onabotulinumtoxinA injection showed persistence detrusor overactivity, decreased compliance, and hourglass configuration and the patient underwent a repeat augmentation cystoplasty. Therefore, we propose that intra-detrusor and intra-augment injection of BTX-A may improve refractory storage symptoms and continence after augmentation cystoplasty in the carefully selected patients. However,

prospective studies are needed to better evaluate the efficacy and ideal sites of injection of BTX-A in the setting of augmentation cystoplasty.

Follow-up following botulinum toxin-A—Currently there are no guidelines available for management for neurogenic bladder patients or their follow-up after intravesical BTX-A therapy. Since neuro-urological disorders are usually progressive we recommend obtaining a Videourodynamic and validated questionnaires at baseline. If patient is high risk based on his/her UDS findings, as measured by vesicoureteral reflux, elevated detrusor pressures, and decreased bladder compliance, worsening of upper urinary tracts (hydronephrosis or renal function) we would also recommend repeating UDS following BTX-A therapy despite its clinical outcome. However, in a setting of low risk patient where baseline UDS demonstrates low detrusor storage pressures and appropriate compliance, and other clinical evaluations also suggest stable lower and upper urinary tracts in a non-progressive neurological disease where the patient clinically responds to BTX-A treatment, we may delay the repeat UDS following treatment.

Conclusion

There is level I evidence that intradetrusor injection of onabotulinumtoxinA is beneficial for the treatment of refractory NDO in patients with MS and SCI - and provides significantly better results than a placebo. BTX-A use is also supported by pilot studies for patients with Parkinson's disease (PD). Current data indicate that BTX-A might have a limited efficacy in patients with CVA. In addition, the morbidity of urinary retention and urinary tract infection must be given serious consideration in this chronically ill and fragile group of patients. Intradetrusor injections of BTX-A could be effective in children with MMC, but this possibility is not supported by a high level of evidence. Cost, adverse events associated with BTX-A, including the need for de novo CIC, and the failure to adhere to therapy by some patients, especially patients who do not already perform CIC, requires careful consideration during shared decision making regarding management of NDO.

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References

1. Ruffion A, Castro-Diaz D, Patel H, et al. Systematic review of the epidemiology of urinary incontinence and detrusor overactivity among patients with neurogenic overactive bladder. Neuroepidemiology. 2013; 41(3-4):146–155. [PubMed: 23942583]
2. Haab F. Chapter 1: The conditions of neurogenic detrusor overactivity and overactive bladder. Neurourology and Urodynamics. 2014; 33(S3):S2–S5.
3. Drake MJ, Apostolidis A, Cocci A, et al. Neurogenic lower urinary tract dysfunction: Clinical management recommendations of the Neurologic Incontinence committee of the fifth International Consultation on Incontinence 2013. Neurourol Urodyn. 2016; 35(6):657–665. [PubMed: 27176559]
4. Buser N, Ivic S, Kessler TM, Kessels AG, Bachmann LM. Efficacy and adverse events of antimuscarinics for treating overactive bladder: network meta-analyses. European urology. 2012; 62(6):1040–1060. [PubMed: 22999811]

5. Gray SL, Anderson ML, Dublin S, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. JAMA Intern Med. 2015; 175(3):401–407. [PubMed: 25621434]
6. Risacher SL, McDonald BC, Tallman EF, et al. Association Between Anticholinergic Medication Use and Cognition, Brain Metabolism, and Brain Atrophy in Cognitively Normal Older Adults. JAMA Neurol. 2016; 73(6):721–732. [PubMed: 27088965]
7. Khavari R, Fletcher SG, Liu J, Boone TB. A modification to augmentation cystoplasty with catheterizable stoma for neurogenic patients: technique and long-term results. Urology. 2012; 80(2): 460–464. [PubMed: 22704181]
8. Krebs J, Bartel P, Pannek J. Functional outcome of supratrigonal cystectomy and augmentation ileocystoplasty in adult patients with refractory neurogenic lower urinary tract dysfunction. Neurourol Urodyn. 2016; 35(2):260–266. [PubMed: 25524480]
9. Cruz F. Targets for botulinum toxin in the lower urinary tract. Neurourol Urodyn. 2014; 33(1):31–38. [PubMed: 23775898]
10. Behr-Roussel D, Oger S, Pignol B, et al. Minimal effective dose of dysport and botox in a rat model of neurogenic detrusor overactivity. European urology. 2012; 61(5):1054–1061. [PubMed: 22341129]
11. Schurch B, de Seze M, Denys P, et al. Botulinum toxin type a is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-month study. The Journal of urology. 2005; 174(1):196–200. [PubMed: 15947626]
12. Herschorn S, Gajewski J, Ethans K, et al. Efficacy of botulinum toxin A injection for neurogenic detrusor overactivity and urinary incontinence: a randomized, double-blind trial. The Journal of urology. 2011; 185(6):2229–2235. [PubMed: 21497851]
13. Duthie JB. Botulinum toxin injections for adults with overactive bladder syndrome. Cochrane Database of Systematic Reviews. 2011; (12)
14. Zhou X, Yan HL, Cui YS, Zong HT, Zhang Y. Efficacy and safety of onabotulinumtoxinA in treating neurogenic detrusor overactivity: a systematic review and meta-analysis. Chin Med J (Engl). 2015; 128(7):963–968. [PubMed: 25836619]
15. Cui Y, Zhou X, Zong H, Yan H, Zhang Y. The efficacy and safety of onabotulinumtoxinA in treating idiopathic OAB: A systematic review and meta-analysis. Neurourol Urodyn. 2015; 34(5): 413–419. [PubMed: 24676791]
16. Lopez Ramos HE, Torres Castellanos L, Ponce Esparza I, Jaramillo A, Rodriguez A, Moreno Bencardino C. Management of Overactive Bladder with Onabotulinumtoxina: Systematic Review and Meta-Analysis. Urology. 2016
17. Carlson JJ, Hansen RN, Dmochowski RR, Globe DR, Colayco DC, Sullivan SD. Estimating the cost-effectiveness of onabotulinumtoxinA for neurogenic detrusor overactivity in the United States. Clin Ther. 2013; 35(4):414–424. [PubMed: 23522658]
18. Moore DC, Cohn JA, Dmochowski RR. Use of Botulinum Toxin A in the Treatment of Lower Urinary Tract Disorders: A Review of the Literature. Toxins. 2016; 8(4):88. [PubMed: 27023601]
19. Cruz F, Nitti V. Chapter 5: Clinical data in neurogenic detrusor overactivity (NDO) and overactive bladder (OAB). Neurourol Urodyn. 2014; 33(Suppl 3):S26–31. [PubMed: 25042140]
20. Santos-Silva A, da Silva CM, Cruz F. Botulinum toxin treatment for bladder dysfunction. International Journal of Urology. 2013; 20(10):956–962. [PubMed: 23634720]
21. 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. European urology. 2011; 60(4):742–750. [PubMed: 21798658]
22. Schurch B, Carda S. OnabotulinumtoxinA and multiple sclerosis. Annals of Physical and Rehabilitation Medicine. 2014; 57(5):302–314. [PubMed: 24953702]
23. Ginsberg D, Gousse A, Keppenne V, et al. Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity. The Journal of urology. 2012; 187(6):2131–2139. [PubMed: 22503020]
24. Rovner E, Dmochowski R, Chapple C, Thompson C, Lam W, Haag-Molkenteller C. OnabotulinumtoxinA improves urodynamic outcomes in patients with neurogenic detrusor overactivity. Neurourol Urodyn. 2013; 32(8):1109–1115. [PubMed: 23389824]

25. Kennelly M, Dmochowski R, Ethans K, et al. Long-term efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: an interim analysis. Urology. 2013; 81(3):491–497. [PubMed: 23290144]
26. Rovner E, Kohan A, Chartier-Kastler E, et al. Long-Term Efficacy and Safety of OnabotulinumtoxinA in Patients with Neurogenic Detrusor Overactivity Who Completed 4 Years of Treatment. The Journal of urology. 2016; 196(3):801–808. [PubMed: 27091236]
27. Apostolidis A, Thompson C, Yan X, Mourad S. An exploratory, placebo-controlled, dose-response study of the efficacy and safety of onabotulinumtoxinA in spinal cord injury patients with urinary incontinence due to neurogenic detrusor overactivity. World journal of urology. 2013; 31(6):1469–1474. [PubMed: 23160758]
28. Hui C, Keji X, Chonghe J, et al. Combined detrusor-trigone BTX-A injections for urinary incontinence secondary to neurogenic detrusor overactivity. Spinal Cord. 2016; 54(1):46–50. [PubMed: 26261074]
29. Abdel-Meguid TA. Botulinum toxin-A injections into neurogenic overactive bladder--to include or exclude the trigone? A prospective, randomized, controlled trial. The Journal of urology. 2010; 184(6):2423–2428. [PubMed: 20952003]
30. Phe V, Chartier-Kastler E, Panicker JN. Management of neurogenic bladder in patients with multiple sclerosis. Nat Rev Urol. 2016; 13(5):275–288. [PubMed: 27030526]
31. Dillon BE, Lemack GE. Urodynamics in the evaluation of the patient with multiple sclerosis: when are they helpful and how do we use them? The Urologic clinics of North America. 2014; 41(3): 439–444. ix. [PubMed: 25063600]
32. Khalaf KM, Coyne KS, Globe DR, et al. The impact of lower urinary tract symptoms on health-related quality of life among patients with multiple sclerosis. Neurourology and urodynamics. 2016; 35(1):48–54. [PubMed: 25327401]
33. Ginsberg D, Cruz F, Herschorn S, et al. OnabotulinumtoxinA is effective in patients with urinary incontinence due to neurogenic detrusor overactivity [corrected] regardless of concomitant anticholinergic use or neurologic etiology. Adv Ther. 2013; 30(9):819–833. [PubMed: 24072665]
34. Chartier-Kastler E, Rovner E, Hepp Z, Khalaf K, Ni Q, Chancellor M. Patient-reported goal achievement following onabotulinumtoxinA treatment in patients with neurogenic detrusor overactivity. Neurourol Urodyn. 2016; 35(5):595–600. [PubMed: 25846869]
35. Kalsi V, Gonzales G, Popat R, et al. Botulinum injections for the treatment of bladder symptoms of multiple sclerosis. Annals of neurology. 2007; 62(5):452–457. [PubMed: 17890635]
36. Prieto J, Murphy CL, Moore KN, Fader M. Intermittent catheterisation for long-term bladder management. The Cochrane database of systematic reviews. 2014; (9) CD006008.
37. Phe V, Pakzad M, Curtis C, et al. Urinary tract infections in multiple sclerosis. Multiple sclerosis. 2016; 22(7):855–861. [PubMed: 26892318]
38. Metz LM, McGuinness SD, Harris C. Urinary tract infections may trigger relapse in multiple sclerosis. Axone. 1998; 19(4):67–70. [PubMed: 9849133]
39. Tauber SC, Nau R, Gerber J. Systemic infections in multiple sclerosis and experimental autoimmune encephalomyelitis. Archives of physiology and biochemistry. 2007; 113(3):124–130. [PubMed: 17922308]
40. Leitner L, Guggenbuhl-Roy S, Knupfer SC, et al. More Than 15 Years of Experience with Intradetrusor OnabotulinumtoxinA Injections for Treating Refractory Neurogenic Detrusor Overactivity: Lessons to Be Learned. Eur Urol. 2016
41. da Silva CM, Chancellor MB, Smith CP, Cruz F. Use of botulinum toxin for genitourinary conditions: What is the evidence? Toxicon. 2015; 107(Pt A):141–147. [PubMed: 26235907]
42. Mehta S, Hill D, McIntyre A, et al. Meta-analysis of botulinum toxin A detrusor injections in the treatment of neurogenic detrusor overactivity after spinal cord injury. Archives of physical medicine and rehabilitation. 2013; 94(8):1473–1481. [PubMed: 23632286]
43. Fougere RJ, Currie KD, Nigro MK, Stothers L, Rapoport D, Krassioukov AV. Reduction in Bladder-Related Autonomic Dysreflexia after OnabotulinumtoxinA Treatment in Spinal Cord Injury. Journal of neurotrauma. 2016; 33(18):1651–1657. [PubMed: 26980078]

44. Elkelini MS, Bagli DJ, Fehlings M, Hassouna M. Effects of intravesical onabotulinumtoxinA on bladder dysfunction and autonomic dysreflexia after spinal cord injury: role of nerve growth factor. BJU international. 2012; 109(3):402–407. [PubMed: 21733076]

45. Anderson RU, Orenberg EK, Glowe P. OnabotulinumtoxinA office treatment for neurogenic bladder incontinence in Parkinson's disease. Urology. 2014; 83(1):22–27. [PubMed: 24231202]

46. Sakakibara R, Panicker J, Finazzi-Agro E, Iacovelli V, Bruschini H. A guideline for the management of bladder dysfunction in Parkinson's disease and other gait disorders. Neurourol Urodyn. 2016; 35(5):551–563. [PubMed: 25810035]

47. 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(8):e105989. [PubMed: 25148378]

48. Kuo HC. Therapeutic effects of suburothelial injection of botulinum a toxin for neurogenic detrusor overactivity due to chronic cerebrovascular accident and spinal cord lesions. Urology. 2006; 67(2):232–236. [PubMed: 16442605]

49. Hassouna T, Gleason JM, Lorenzo AJ. Botulinum toxin A's expanding role in the management of pediatric lower urinary tract dysfunction. Curr Urol Rep. 2014; 15(8):426. [PubMed: 24903352]

50. Game X, Mouracade P, Chartier-Kastler E, et al. Botulinum toxin-A (Botox) intradetrusor injections in children with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic literature review. Journal of pediatric urology. 2009; 5(3):156–164. [PubMed: 19264554]

51. Hascoet J, Manunta A, Brochard C, et al. Outcomes of intra-detrusor injections of botulinum toxin in patients with spina bifida: A systematic review. Neurourol Urodyn. 2016

Key points

- There is level I evidence that intradetrusor injection of onabotulinumtoxinA for the treatment of refractory neurogenic detrusor overactivity (NDO) in patients with multiple sclerosis (MS) and spinal cord injury (SCI) is associated with a significantly greater achievement of patients' goals and better performance in urodynamic studies (UDS) when compared with use of a placebo. Pilot studies also support this intervention for patients with Parkinson's disease (PD).
- Studies in patients with cerebrovascular accident (CVA) are relatively insufficient. Current data indicate that botulinum toxin A (BTX-A) might be effective in this setting but the results might not be as favorable as in patients with SCI or MS. In addition, the possibility of urinary retention following injection must be given serious consideration in this chronically ill and fragile group of patients.
- BTX-A seems to be effective in children with MMC (low level of evidence).
- The cost, morbid adverse events associated with BTX-A such as the possibility of needing to initiate clean intermittent catheterization (CIC), increased risk of urinary tract infections, and the failure to adhere to therapy by some patients, especially patients who do not perform CIC at the baseline, need to be considered during shared decision making in management of NDO.

Table 1

Outcomes of Intradetrusor Injection of OnabotA in Patients with NDO, 6 Weeks after Injection

		Patients (n)	UI (n)	Dry (%)	No IDC (%)	MCC (mean-mL)	PdetmaxIDC (mean-CmH2O)	UR (%)
Cruz et al	Saline	92	-13.2	7.6	17.4	6.5	+6.4	12.0
	200U	92	-21.8	38.0	64.4	+157.0	-28.5	30.0
	300U	91	-19.5	39.6	59.5	+157.2	-26.9	42.0
Ginsberg et al	Saline	149	-8.8	0.0	19.0	+16.0	-2.4	10.0
	200U	135	-21.0	36.0	64.0	+151.0	-35.1	35.0
	300U	132	-22.0	41.0	69.0	+168	-33.3	42.0
DIGNITY *	Saline	241	-10.5	9.1	18.4	+11.9	+1.1	7.1
	200U	227	-21.3	37.0	64.1	+153.6	-32.4	30.8
	300U	223	-21.3	40.4	65.1	+163.1	-30.1	44.0

* DIGNITY pooled data. Abbreviations: OnabotA, onabotulinumtoxinA; UI, urinary urge incontinence episodes per week; IDC, involuntary detrusor contractions; MCC, maximum cystometric capacity; PdetmaxIDC, maximum detrusor pressure during involuntary detrusor contraction; UR, urinary retention

Table 2

Outcomes of DIGNITY Study in Multiple Sclerosis versus Spinal Cord Injury patients

	MS			SCI		
	Placebo	**200 U**	**300 U**	**Placebo**	**200 U**	**300 U**
No of Patients	131	130	120	110	97	103
Age (year)	50.2	49.7	49.9	41.5	40.7	40.6
Male (%)	23.7	20	10.8	77.3	69.1	67
CIC (baseline-%)	32.1	31.5	24.2	88.2	80.4	85.4
UI (n)	-14.0	-22.6	-24.0	-6.4	-19.6	-18.2
Dry (%)	10.7	41.5	44.2	7.3	30.9	35.9
No IDC (%)	18.5	68	79	18.2	58.7	57.6
MCC (ml)	6.8	149.3	165.1	18.6	159.5	160.6
PdetmaxIDC (cm H2O)	10.7	-22.1	-24.1	-10.9	-42.7	-35.3
UTI	29.2	53.3	59	44.8	49.5	52.5
Urinary Retention (%)	4.6	29.5	39.3	1.9	7.2	4

Abbreviations: CIC, clean intermittent catheterization; UI, urge urinary incontinence episodes per week; IDC, involuntary detrusor contractions; MCC, maximum cystometric capacity; PdetmaxIDC, maximum detrusor pressure during involuntary detrusor contraction; UTI, urinary tract infection

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Table 3

Outcomes of BTX-A in Patients with Parkinson's Disease and Cerebrovascular Accident

Author (Year)	Diagnosis	Method (Level of Evidence)	No of pts	Mean Age (yr)	Toxin Type	Clinical Outcomes	UDC after Tx	MCC after Tx (mL)	UR (%)
Anderson (2014)	PD	Prospective No control (4)	20	70.4	OnabotA (100 U)	50% ↓ in UI in 59% of pts	NR	NR	0
Knüpfer (2016)	PD	Retrospective No control (4)	10	67.9	OnabotA (200U)	Pad use/d = 1 ±0.94 (2.8 ±2.35)*	20% of pts (90%)*	332.6 (196.2)*	0
Jiang (2014)	PD	Retrospective No control (4)	9	73.6	OnabotA (100U)	UI/ 3 days = 9.6† (10.8)*	NR	283 (266)*	11.1
Kulaksizoglu (2010)	PD	ProspectiveNo control (4)	16	67.2	AbobotA (500U)	No UI= 6 pts Other pts = 1† of UI/1-3 days	Mean pressure M 40‡ (68)* F 29‡ (41)*	319 (198.6)*	0
Giannantoni (2011)	PD	Prospective No control (4)	8	66	OnabotA (100U)	No UI = 3 pts	First vol** ↑ significantly	↑** significantly	0
Giannantoni (2009)	PD	Prospective No control (4)	4	76.25	OnabotA (200U)	No UI	First vol 385 (158)*	468.25 (241.5)*	0
Kuo (2006)	CVA	Prospective No control (4)	12	72.4	OnabotA (200U)	8.3% became dry UI improved in 41.7%	First vol 328.1 (188.2)*	343.2 (198.3)*	25
Jiang (2014)	CVA	Retrospective No control (4)	23	73.6	OnabotA (100U)	UI/ 3 days =5.7† (13.5)*	NR	358 (198)*	17.4

Notice: Studies outlined here have used different variables as their clinical and UDS outcomes. Data in this table were put as is. Abbreviations: d, day; yr, year; pts, patients; Tx, treatment; No, number; ↓, decrease(d); ↑, increase(d); NR, not recorded; mL, milliliter; vol, volume; M, male; F, female; UI, urinary incontinence; UDC, uninhibited detrusor contractions; MCC, maximum cystometric capacity; UR, urinary retention; PD, Parkinson's disease; CVA, cerebrovascular accident; OnabotA, onabotulinumtoxinA; AbobotA, abobotulinumtoxin A;

* values before treatment;

** only graphs have been used in this manuscript;

† episode(s);

‡ cm H2O

Table 4

Outcomes of BTX-A in Patients with Myelomeningocele

Author (Year)	Method (Level of Evidence)	Number of Patients	Mean Age (yr)	Toxin Type	Dry after Tx	DO after Tx	Pdetmax before Tx (cm H2O)	Pdetmax after Tx (cm H2O)	MCC before Tx (ml)	MCC after Tx (ml)
Tiryaki (2015)	Retrospective No control (4)	16	9	OnabotA	55%	No	NR	NR	NR	NR
Tarcan (2014)	Prospective No control (4)	31	7.95	NR	96%	No	64.6	30.1	53.9	233.3
Marte (2013)	Retrospective No control (4)	47	10.7	OnabotA	100%	No	NR	NR	NR	NR
Zermo (2012)	Retrospective No control (4)	28	6.45	OnabotA	32%	Yes	60.2	33.14	120	153
Horst (2011)	Retrospective No control (4)	11	6.7	OnabotA	NR	NR	56	46	208	279
Safari (2010)	Prospective With control * (2)	60	6.65	AbobotA	63%	Yes	133	62.53	176.2	246.3
Neel (2010)	Prospective No control	13	5.3	NR	87%	NR	58	36	75	150
Deshpande (2009)	Prospective No control (4)	7	16	OnabotA	NR	NR	NR	NR	257	344
Kajbafzadeh (2006)	Prospective No control (4)	26	6.9	OnabotA	73%	Yes	139	83.2	102.8	270.2
Altaweel (2006)	Prospective No control (4)	20	13	NR	65%	NR	43 (40.1)†	21.6 (40.1)†	215.6 (146)†	338.3 (164)†
Riccabona (2004)	Prospective No control (4)	15	5.8	NR	87%	NR	78.8	42.76	136.3	297
Schulte-Baukloh (2002)	Prospective No control (4)	17	10.8	OnabotA	NR	Yes	58.9	39.7	137.5	215

Abbreviations: yr, year; Tx, treatment; DO, detrusor overactivity; MCC, maximum cystometric capacity; Pdetmax, maximum detrusor pressure; OnabotA, onabotulinumtoxinA; AbobotA, abobotulinumtoxin A; NR, not recorded

* Data of control group has not been shown

† Data in and out parenthesis, refer to incontinent and continent patients respectively