Chapter 8

Urological Applications of Botulinum Toxin A

Said M. Yaiesh, Meshari F. Almutairi,
Abdullatif E. Al-Terki and Tariq F. Al-Shaiji

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.79555

Abstract

Botulinum toxin A (BoNT-A) has seen in the last two decades an increased level of application in urological practice, first FDA approved in 2011 for neurogenic detrusor overactivity and then later in 2013 for refractory overactive bladder. Hundreds of studies have been published in literature assessing the chemical structure of botulinum toxins and how urothelial injections in the lower urinary tract and vesical instillations can be employed in the management of a spectrum of urological conditions particularly voiding dysfunction. The consensus is still out on toxin A preparations, mode and pattern of application whether instilled or injected intradetrusally, units used, as well as time to onset and duration of effect of injections and is still a dense research topic. This is reflected in the continuously changing and differing grades of recommendations between societies of urological practitioners such as the EAU and AUA, among others. This chapter discusses both the FDA-approved and experimental applications of botulinum toxin A in urology, indications, techniques, and points of debate.

Keywords: overactive bladder, neurogenic detrusor overactivity, intradetrusor injections, voiding dysfunction

1. Introduction

Urological applications of botulinum toxins are not new, but their approval and mass use are overdue. Though it was first used safely on humans in the 1970s, the journey for emergence of the urological uses of botulinum toxin isolates was only recognized in the first decade of the twenty-first century. The introduction of the use of botulinum toxin type A (BoNT-A) in its various preparations revolutionized and extended the spectrum of conservative and minimally invasive treatment modalities of a spectrum of voiding and sexual dysfunction conditions. Despite that, and although it is being increasingly recognized in guidelines, botulinum

toxin remains of limited approval in urological applications by regulatory bodies such as the US Food and Drug Administration.

The general principles of the mechanism of action of botulinum toxins apply similarly in urological applications of the toxin. By binding presynaptically to sites on the cholinergic nerve terminals, it decreases the release of acetylcholine causing a level of neuromuscular blockade. This initially relaxes whichever muscular site is injected, commonly being the bladder intradetrusally, leading to relaxation of the target muscle injected by exerting an effect on the efferent detrusor pathways. In the case of the detrusor muscle, this will lead to a decrease in its contractions and increase in accommodative capacity. Eventually, the effect of the toxin wears off, to which the hypotheses of how are varied, and the injections are to be repeated if the desirable effect is to be achieved.

In literature, the use of botulinum toxin in urology was first described in 1988 for the treatment of detrusor sphincter dyssynergia and gained momentum in more trials in the late 1990s. The studies concentrated on the use of botulinum toxin type A, with little to no evidence showcasing the effect of other types. The experimental applications first concentrated on treating voiding dysfunction disorders, especially those of neurogenic causes such as spinal cord injury and multiple sclerosis, and later went on to include the management of lower urinary tract symptoms and chronic pelvic pain. Though first initially US FDA approved for human application in 1989, it was not until 2011 that the FDA approved onabotulinumtoxinA (BoNT-A) (BOTOX®; Allergan; Irvine, California) for the treatment of urinary incontinence and detrusor overactivity secondary to neurological conditions such as spinal cord injury where conservative therapy with anticholinergic medication was inadequate or intolerable. BoNT-A was later then approved for treatment of overactive bladder symptoms in adults with an inadequate response to anticholinergic medication [1].

Estimates of the burden of urological conditions such as overactive bladder have varied in published reports. In one review, it was estimated that around 16% of adults in the USA experienced some degree of urgency symptoms with or without incontinence, irrespective of gender [2]. This number contrasts greatly to that deduced from a Finnish study published earlier and conducted in a similar manner where the prevalence of overactive bladder symptoms among adults was estimated at around 8% of the surveyed population [3]. Irrespective of the prevalence, the US drug market for overactive bladder medication was placed at USD 3 billion, including anticholinergic medication and beta-agonists [4]. This market does not include the US reported sales of USD 1.38 billion for Botox Therapeutic, the neuroscience and urology division of Allergan which is the parent company of BOTOX concerned with the treatment of chronic migraines, urological conditions, and others [5]. With an average price tag of around USD 1300 per cycle of BOTOX injection intradetrusally on average three to four times the price of a 30-day supply of anticholinergic medication, questions had to be raised on the cost-effectiveness of this mode of intervention.

In 2006, a study from the UK demonstrated that BoNT-A injections for overactive bladder irrespective of the pathology were more cost-effective over a 1-year duration than standard care with regular office follow-ups and anticholinergic medication or clean self-intermittent catheterization. This effectiveness was reproduced by other studies from the USA, Europe, and the UK for a 5-year cost-effective and sensitivity analysis comparing BoNT-A injections to

conservative management and surgical intervention [6–9]. All of this economic evidence, coupled with numerous trials demonstrating the effectiveness of botulinum injections for treatment of overactive bladder symptoms and other emerging uses, has popularized its application among urologists and has led to its inclusion as second- and third-line management modality in numerous urology care guidelines reviewed and published by authorities such as the European Association of Urology (EAU), American Urological Association (AUA), and International Continence Society (ICS).

This chapter will review the urological applications of botulinum toxin, particularly toxin type A, the different injection modes, and FDA supported, guideline supported and emerging, experimental, or deemed "off-label" uses.

1.1. Mechanism of action of botulinum injections in the urinary tract

In general, botulinum toxin is a very potent neuromuscular blocker. Each serotype exerts the neuromuscular effect by working on a different molecular level. For example, botulinum serotype A works by cleaving SNAP-25, a presynaptic protein involved in the fusion of vesicle-containing neurotransmitters, while serotype B exerts its effects to another vesicle-associated membrane protein (VAMP). This chapter will not discuss the molecular details of each serotype, and most effects and mechanisms of action mentioned will pertain to serotype A which is the most common serotype used for intradetrusor injections.

1.1.1. Botulinum injection in the bladder

In the bladder, as in other injection sites, botulinum toxin primarily acts by binding in presynaptic targets impairing acetylcholine release and thus decreasing detrusor muscle contractions by reducing the amount of acetylcholine that binds with M2 and M3 muscarinic receptors in the detrusor muscle [10, 11]. Thus, it achieves its main function by relaxing the detrusor muscle. However, many studies have proposed and to an extent showed evidence that intradetrusor botulinum toxin injections, particularly toxin A, achieve relief from certain chronic symptoms of detrusor overactivity and pain through several other mechanisms:

1. Other than through exerting a direct effect on motor function of the bladder muscle, it has an indirect sensory effect via afferent sensory pathways of the urinary bladder. Botulinum toxin injections reduce levels of sensory reception in the bladder suburothelium and, in turn, desensitize to an extent the afferent output by unmyelinated C-fibers that arise because of the damage to the pathways consisting of myelinated Aδ fibers usually carrying signals to higher brain regions involved in micturition. This eventually results in reduction of the activity of the spinal arc pathway that through activity of C-fibers causes detrusor contractions [10, 12].
2. Researchers have demonstrated that botulinum toxin A also exerts a detrusor inhibitory effect through inhibiting ATP release as well as acetylcholine. This was supported in both animal and human bladder isolates with idiopathic detrusor overactivity [11].
3. Additionally, through inhibition of urothelial ATP release, research suggests that intradetrusor botulinum injections may have antinociceptive effects not related to their

effect on efferent nerves. In the case of chronic inflammation or neural injuries, this effect could reduce sensitization in the bladder that provokes afferent activity usually causing detrusor overactivity and, instead, leads to relaxation of the detrusor muscle [11, 13].

4. Inhibition of other neurotransmitter molecules and sensory receptors such as glutamate, substance P, calcitonin gene-related peptide (CGRP), and TRPV1 has been demonstrated in basic research and clinical trials, contributing to the sensory effect of botulinum bladder injections [14].

5. A number of studies addressed the effects of botulinum injections on muscular composition in general and in the detrusor muscle specifically. In one study on injections of botulinum toxin for cervical dystonia, repeated type A injections lead to some minor muscle fiber alterations proposed to later cause muscle weakness [15]. In the urinary bladder specifically, botulinum type A injections reduced fibrosis and bladder nerve growth factor levels, but not necessarily the level of inflammation or edema [16, 17].

Cumulatively, botulinum injections in urothelial tissue result in relaxation of the detrusor muscle. This effect is not immediate and is time-restrained by the induction and the slow recovery of the neuromuscular junction plate from the paralytic effects of the injection. As the recovery begins, the detrusor relaxation effects begin to decrease. For a maintained and sustained effect, repeated injections are necessary. Unfortunately, recipients of repeated intradetrusor injections do not always continue to exhibit similar responses to consecutive injections. A hypothesized "secondary failure" phenomenon [18] has been addressed in literature for injections in the bladder and in other sites, and the theoretical reasons attributed include the following:

1. Botulinum toxin injections have been shown to induce an immune response that results in the production of antibodies that counter the effect of the toxin [19, 20].

2. Animal studies have demonstrated a reactive increase in production of intracellular proteins after repeated injections of the toxin, possibly in a cellular effort to counter the effect of the injections [21].

3. Microscarring of injection sites, hypothetically, though recent literature rebutted this theory by demonstrating no significant detrusor muscle ultrastructure alterations after injections [22].

It is worth mentioning that there also are several studies that counter the hypothesis of diminished effect on repeated injections. The EAU guidelines side with such studies based on randomized controlled trials (RCTs) that showcased sustained efficacy on repeated injections of onabotulinumtoxin A [23]. The frequency of subsequent intradetrusor injections will be discussed onward in this chapter.

1.1.2. Botulinum injections in the urethra

BoNT-A injections in the urethra particularly at the level of the urethral sphincter have been demonstrated to reduce sphincteric tone and urethral pressure. The mechanism of action is likely similar to the action of botulinum toxin injections in detrusor muscle.

http://dx.doi.org/10.5772/intechopen.79555

1.1.3. Botulinum injections in the prostate

The effects of BoNT-A injections in the prostate have been demonstrated through a number of clinical trials in both humans and animals. In rats, botulinum toxin injections resulted in activation of apoptosis inducing prostatic atrophy. This was also demonstrated in clinical trials where apoptosis was identified at both the stromal and epithelial levels of prostatic tissue after BoNT-A injections, which reduced prostatic tissue mass, and was shown to reduce prostatic urethral pressure [24–27].

1.2. Botulinum toxin serotypes and preparations in urology

There are seven different serotypes of botulinum toxins with several different properties and preparations. Commercially available preparations of serotypes A and B have been approved for human use, but their urological application has been limited. These include, but are not limited to, two botulinum toxin type A preparations, onabotulinumtoxinA commercially known as BOTOX® and distributed in the USA and abobotulinumtoxinA more widely known as Dysport® (Galderma; Ipsen; Paris, France). These two preparations have been extensively studied in literature and trials of urological applications. There are a few reports that compared the potency and efficacy of these two preparations of serotype A.

It should be noted there are other BoNT-A preparations and, along with other serotypes except for one preparation of serotype B, have not been in significant trials for application in urological conditions. The reasons may be the unavailability of these serotypes in abundant commercial quantities or, in some cases like serotype F which has a short duration of action, may be deemed impractical or ineffective for intradetrusor injections, especially when considering the desired durable neuromuscular effect by botulinum injections in the bladder detrusor muscle [11, 28]. Similarly, one preparation of serotype B has been shown to exhibit effects of a shorter duration than onabotulinumtoxinA and abobotulinumtoxinA, though not in direct comparison [29].

BOTOX® is FDA approved for use in neurogenic detrusor overactivity and refractory overactive bladder where anticholinergic medication failed to resolve symptoms of frequency, urgency, and urge urinary incontinence satisfactorily or were intolerable by patients. In contrast, Dysport® is yet to be FDA approved for any urological application or included in the guidelines [30]. However, that has not limited its inclusion in a substantial number of trials for different applications including overactive bladder, idiopathic and neurogenic, as well as bladder pain syndrome, among others. Though both formulations are toxin A serotypes, they differ in their preparation and extraction methods and molecular characteristics. Hence, there are differences in quantitative dosage and potentially potency, which will be covered in a subsequent section of this chapter.

There are also other commercially available formulations of BoNT-A: incobotulinumtoxinA, marketed as Xeomin® by the German company Merz Pharmaceuticals and Chinese BTX-A marketed as Prosigne®, among others. These preparations, along with botulinum toxin B preparation rimabotulinumtoxinB (Myobloc®, Solstice Neurosciences Inc., San Francisco, USA), are much less extensively investigated in urology literature and research but have been

utilized experimentally for certain applications. Additionally, two more new preparations of botulinum toxin A are on the horizon, including Evolus' DWP-450 (Irvine, California, USA), expected to undergo review by the FDA in 2018 and Revance Therapeutics' RT-002 (Newark, California, USA) whose FDA application filing is expected in 2019 [5]. Though yet far from being introduced commercially, research into their urological uses would not be surprising.

Recently, BoNT-A preparations have been augmented with added substances thought to improve the delivery and potency of the injections. Of these preparations were liposomal activated preparations, which have been experimented for different urological applications. The consensus is still not drawn, but data suggests no difference in efficacy or potency or need for repeat injections.

1.3. Dosage and potency

Research has extensively investigated the different dosages and regimens for botulinum toxin A injections in the urinary bladder. Differences were identified according to the preparation, as is the case between onabotulinumtoxinA and abobotulinumtoxinA, as well as the quantity of toxin per unit of each preparation measured using different modalities and the clinical implication this may have. Difference in dosing also exists for each condition and in recommendations and guidelines by different advisory bodies. It should be noted, however, that most guidelines only describe injection doses of onabotulinumtoxinA (BOTOX®) since it is the only FDA-approved formulation for some urological uses. Nevertheless, this has not limited research into dosage and effects of abobotulinumtoxinA (Dysport®). Additionally, dilution of the toxin and amount of liquid injected has varied, as well as the number of injection sites.

OnabotulinumtoxinA/BOTOX® comes in different dose formulations than abobotulinumtoxinA (Dysport®). BOTOX® vials are available in 100 and 200 U, whereas Dysport® vials are available in 300 and 500 U; researchers have, however, used higher doses of BOTOX® of up to 300 U. The units for each preparation are not the same nor are they interchangeable. In general, 1 U of BOTOX® is equivalent approximately to 3 U of Dysport®. However, these units are no indication of the potency of either drug. Potency of BoNT-A has rather been described using other units, including mouse units (MU) and median paralysis units (MPU), and the results of different studies have not been successful in concluding which preparation is more potent than the other, especially for bladder injections. It should be of note that the only FDA-approved doses for BOTOX® are 100 U per setting for idiopathic overactive bladder and 200 U for neurogenic detrusor overactivity. Higher doses of BOTOX® have not demonstrated clinically significant efficacy in relation to a higher incidence of adverse effects [1, 31–34].

1.4. Injection modes and sites

Botulinum toxin injections have been described to be delivered to different tissues along the lower urinary tract. In the bladder, literature investigated both intravesical instillations and intradetrusor injections, with the latter proving to be more effective in achieving the therapeutic effect of botulinum in the bladder. BoNT-A can also be delivered intrasphincterically to the urethral sphincter, either periurethrally or even transperineally as some research describes, as well as injected into the prostate.

http://dx.doi.org/10.5772/intechopen.79555

Literature and guidelines alike have described different numbers of injection sites in a technique called "mapping." This entails injecting the toxin in a well-spread manner to a specific number of sites on the cystoscopy. Of recent, the most commonly utilized number of injection sites varies between 20 and 30 mapped sites, equally spread between the right and left posterolateral walls of the bladder, with some sites injected more caudally. However, there has been an avoidance for injection of botulinum toxin in the bladder trigone as hypothesis suggests it may contribute to the development of retrograde ascension of urine from the bladder to the kidney, known as vesicoureteric reflux. The consensus is out on whether this hypothesis is valid; however, trigonal injections have been applied in botulinum injections for bladder pain syndrome/interstitial cystitis with no reported occurrence of reflux [35, 36].

1.5. Injection techniques

1.5.1. Preparation of the toxin

To inject the botulinum toxin preparation, it must be first dissolved and diluted from its powdered preparation in the storage vial. It is a surgeon's preference for the dilutional amount of normal saline solution to be used and depends on the number of injection sites the surgeon plans on delivering the toxin through. In order to prepare 100 U of onabotulinumtoxinA for injection, the surgeon usually injects 10 ml of sterile normal saline into the toxin vial and gently swirls the vial to ensure completely dissolving the toxin powder. If 200 U are to be used, the surgeon could use 5 ml for each 100 U vial or 10 ml for each vial [35, 36].

1.5.2. Endoscopic delivery

The toxin is delivered using an ultrafine needle placed through an introductory channel element of the cystoscope device. Generally, the patient is under sedation or general anesthesia, but injections under local anesthesia have been reported. A rigid or flexible cystoscope can be used with equal effectiveness. The bladder is filled with irrigation fluid, and the needle is mapped across the bladder urothelium to deliver a specific amount of the diluted toxin per injection site. The amount delivered is dependent on the number of sites and amount of toxin applied. Traditionally, injecting 100 U of onabotulinumtoxinA diluted in 10 ml of normal saline over 20 sites yields an amount of 0.5 ml per injection, delivering 5 U of the toxin at each site, delivered into the suburothelium or detrusor muscle.

Figure 1 provides a schematic presentation of the posterolateral view of the urinary bladder on cystoscopy, 20 injection sites equally spread in a mapped scheme in each half of the wall. The trigonal area, which stretches between the right and left ureteric orifices along an interorifice ridge, is labeled and is usually spared unless indicated [35, 36].

1.6. Safety and adverse effects

Ever since its initial approval and application, the safety of botulinum injections has been front and center and in a continuous debate. Botulinum toxin is considered one of the most potent toxins to humans and, as such, the level of caution in utilizing it is understood. However, the FDA and other regulatory bodies have approved its clinical application supported by a myriad of clinical trials demonstrating both its safety and efficacy.

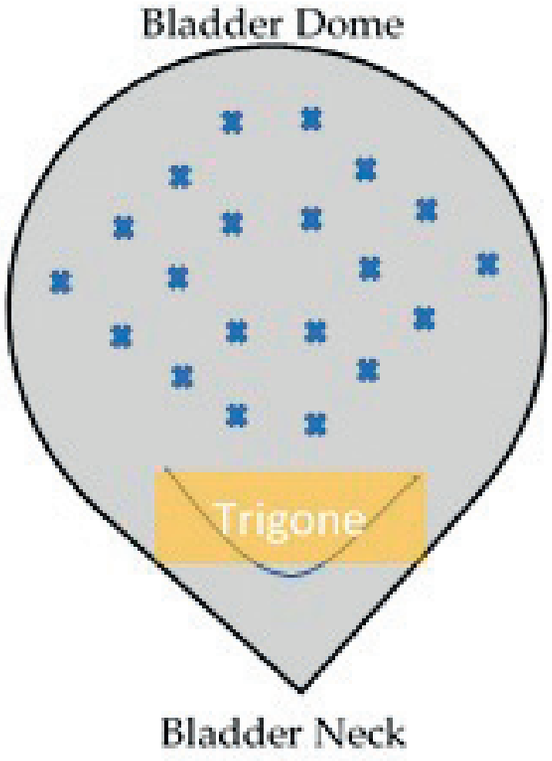

Figure 1. Twenty mapped injection sites over the bladder urothelial posterolateral walls.

In urological application, it has demonstrated to be a safe modality of treatment regardless of which condition it is being utilized for. Numerous trials have proven that the toxin does not seem to systemically spread. One concern was spinal diffusion of the toxin after detrusor injection, which has been debunked. It has also been proven that it does not cause any fibrotic or spastic changes in the urothelium, which was hypothesized as a result of injections earlier on in its application.

Though declared safe toxicologically, injection of the botulinum toxin A into the bladder urothelium does result in certain adverse events, depending on the amount or dose injected and on the disorder being treated. Common reported adverse events from the literature and acknowledgment in guidelines include:

1. Bacteriuria and urinary tract infections. However, septic illness is not significantly reported.
2. Acute urinary retention in the setting of detrusor injections in rather incontinent patients. Patients are usually counseled and consented prior to injection to the development of urinary retention postinjection that it is probable, transient, and will require temporary self-intermittent catheterization for an estimated period and a maximum of 2 weeks. In subsequent repeat injections, some practitioners may opt to lower the injectable dose below to what has resulted in urinary retention.
3. Limited hematuria.

http://dx.doi.org/10.5772/intechopen.79555

1.7. Efficacy and follow-up

To deem botulinum injections as a viable treatment option for any urological condition with established treatment modalities, it had to prove its efficacy, durability, and comparative benefit. For each urological application, botulinum toxin A injections have been compared to established standardized modalities of treatment. In the case of treatment for overactive bladder, for example, intradetrusor BoNT-A injections provided a more cost-efficient and tolerable treatment method according to some reviews. However, the injections had questions of durability.

Understanding the chemical effect of the injectable toxin, it was well understood that it was time limited, and repeated injections will be required to attain and sustain the effect of the injection. Questions of the safety of repeated injections were satisfactorily addressed in both clinical trials and guidelines, with no evidence to warrant against it. However, reports of a decreased effect after subsequent injections of the same preparation emerged on longer follow-up trials, described as "secondary failure." The rates of this failure are not high, and the data is inconsistent. It should also be noted that urological conditions where botulinum toxin is applied are mostly of a chronic nature, and repeated injections are associated with a higher financial burden and operative morbidity for the patients; thus, it is reasonable to assume that patients may opt for more definite treatment modalities even if they were more invasive.

It has been demonstrated that a positive response to botulinum toxin could be reachieved after secondary failure by applying different preparations of BoNT-A or even using BoNT-B in certain circumstances. However, this is all experimental and not endorsed or approved by the FDA or any urological association.

Intradetrusor BoNT-A injections have been demonstrated to have an initial, subjectively, and objectively reported effect starting at 2 weeks after the injection. Numerous studies demonstrate a peak effect at 6 weeks postinjection. The effect is sustained variably, with reports extending to 9 months or even a year, but the accepted consensus is that the effect does regress at around 6 months postinjection. However, the frequency of reinjection to attain the effect is not mandated by these numbers rigidly and shows interpatient differences. Thus, most practitioners perform reinjections of the toxin on a patient-request basis. The time of onset and length of the effect of intrasphincteric, paraurethral, and intraprostatic injections differ from detrusor injections.

2. Urological applications

The urological applications of botulinum toxin A and B are numerous. As previously described, the FDA approved the use of onabotulinumtoxinA for neurogenic detrusor overactivity in cases of spinal cord injury or multiple sclerosis, idiopathic overactive bladder, and urge urinary incontinence [1]. However, the guidelines and experimental uses have extended to include numerous other urological conditions.

2.1. Neurogenic detrusor overactivity

Neurogenic detrusor overactivity (NDO) is defined as a spectrum of lower urinary tract dysfunction symptoms that result from disruption of the neural control of the bladder, and the term "neurogenic bladder" applies to the urinary bladder malfunction that ensues neural dysfunction resulting from conditions affecting the nerves, including trauma as with spinal cord injury, of which NDO is one entity and detrusor areflexia is another. The range of symptoms includes bladder overactivity, urinary retention, or even both.

Symptoms of neurogenic detrusor overactivity vary according to the onset and cause, as well as the level of the insult in the nervous system. They are generally divided into suprapontine lesions, spinal cord lesions, and peripheral neuropathies. **Table 1** lists the different common causative entities of neurogenic bladder. Each disease results in a different combination of symptoms of bladder dysfunction as a result of the neural pathway it affects and may result in overactivity. Botulinum injections are indicated only when the detrusor muscle is overactive as a result of the neural disease secondary to suprapontine and spinal cord injuries.

Whichever the causative neurological insult, quality of life measurement tools utilized in clinical research unveil a debilitating entity of bladder overactivity encountered by NDO patients. When the suprapontine neural pathways are affected, primitive voiding reflex arcs of the lower urinary tract remain intact, and the bladder becomes overactive. Overactive bladder and spasticity can result in frequency of urination, urgency, and urge urinary incontinence. If the external urinary sphincter is affected and becomes hypotonic by the neural condition, stress urinary incontinence or mixed urge-stress urinary incontinence may also occur.

Anticholinergic medications are the first line of therapy for neurogenic detrusor overactivity. However, the use of these medications is sometimes limited by patient tolerability and requirement for high doses to achieve satisfactory results, and that is often accompanied by a higher level of side effects. The EAU and ICS both recommend the use of botulinum toxin A injections as a second line of management in agreement with the FDA approval. The recommendations of the EAU are based on several randomized controlled trials that proved the efficacy of intradetrusor injections of BoNT-A for the treatment of neurogenic bladder overactivity [36]. A summary of a number of these studies can be reviewed in **Table 2**.

The FDA recommends the injection of a maximum of 200 U of onabotulinumtoxinA intradetrusally in the bladder for NDO. However, trials have reported injections of up to

Suprapontine lesions	Spinal cord lesions	Peripheral neuropathies
Cerebrovascular accidents (stroke)	Spinal cord trauma above or below T6 level	Diabetes mellitus
Parkinson's disease	Multiple sclerosis	Neurosyphilis
Brain tumors		Herpes zoster
Shy-Drager syndrome		Lumbar disk herniation and surgery
		Radical pelvic surgery

Table 1. Causes of neurogenic bladder.

Author	Year	Toxin	Patient population	Outcome	Notes
Denys et al.	2017	Abobotulinum, 750 U, 15 or 30 injections, trigone sparing	NDO and incontinence from SCI or MS	Fifteen injection sites as effective as 30 injection sites compared to placebo	
Kennelly et al.	2017	Onabotulinum, 200 or 300 U, trigone sparing	NDO patients	Safe outcomes, similar effects for both doses	Four-year follow-up study
Apostolidis et al.	2013	Onabotulinum, 50, 100, and 200 U, trigone sparing	NDO patients with urge incontinence	200 U dose most effective and durable effect	Placebo controlled. Effect reported at week 6 postinjection, measured for 52 weeks
Rovner et al.	2013	Onabotulinum, 200 and 300 U, trigone sparing	NDO due to MS or SCI with urgency incontinence	Both doses achieved comparable results in improving urodynamic outcomes of patients	Placebo-controlled phase III trials
Sussman et al.	2013	Onabotulinum, 200 and 300 U, trigone sparing	NDO due to MS or SCI with urgency incontinence	Both doses achieved comparable results in improving health-related quality of life outcomes of patients	Placebo-controlled, double-blinded. Maximal effect gained at week 6 postinjection compared to placebo
Šámal et al.	2013	Onabotulinum, 300 U, submucosally or intradetrusorally	NDO patients	Submucosal injections equally effective	
Ginsberg et al.	2012	Onabotulinum, 200 or 300 U	NDO due to MS or SCI with urgency incontinence	Both doses equally improved the number of incontinence episodes, cystometric parameters, and quality of life	Placebo-controlled, double-blinded, 52-week follow-up
Cruz et al.	2011	Onabotulinum, 200 or 300 U, trigone sparing	NDO due to MS or SCI with urgency incontinence	Both doses equally improved the number of incontinence episodes, cystometric parameters, and quality of life	Placebo-controlled, double-blinded. First effect documented at 2 weeks postinjection

Table 2. Summary of RCTs utilizing botulinum toxin in treatment of neurogenic detrusor overactivity [34, 37–43].

300 U for the control of the overactivity. Reports of higher dose efficacy being clinically insignificant considering a higher level of adverse events and complications have steered the consensus toward the FDA set dosage.

2.2. Idiopathic overactive bladder

Idiopathic or non-neurogenic overactive bladder (OAB) describes a syndromic set of symptoms of increased daytime and nighttime urination urgency and frequency with or without urgency urinary incontinence in the absence of a causative pathology. In ICS definition, OAB is a syndrome of urgency, a compelling sensation to urinate, frequency, or urinating more than eight times during waking hours, and nocturia, waking up once or more to urinate at night;

whether urinary incontinence occurs as a result of the urgency (wet OAB) or does not (dry OAB) is not essential for the clinical diagnosis.

Often, investigations for these presenting symptoms include performing a urodynamic evaluation of the bladder, where a urinary catheter connected to pressure transducers is used to fill the bladder with a saline solution in order to reproduce the urinary complaints of the patient; uninhibited involuntary bladder contractions witnessed as a result of the filling or after the patient has voided are defined as detrusor overactivity, which occurs with the majority of OAB patients. Nevertheless, many patients with idiopathic OAB do not require urodynamic assessment when the symptoms are clear-cut, and a number of clinical tools and scores can aid in diagnosing, assessing severity, and following up of treatment efficacy of the syndrome. Refractory OAB is when symptoms fail to resolve on conservative management with nonsurgical noninvasive modalities.

Botulinum toxin A for the treatment of idiopathic refractory OAB was approved by the FDA in 2013, but only in the onabotulinumtoxinA/BOTOX preparation [1]. Clinical trials on both onabotulinumtoxinA and abobotulinumtoxinA for the treatment of refractory OAB have preceded this approval, and to date, there is continuous investigation into the optimal dosage, dilution, and frequency of injections to achieve optimal relief of the symptoms.

Though the ICS recommendations for the use BoNT-A for OAB refrain from specifying a certain preparation, both the EAU and American Urology Association/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (AUA/SUFU) guidelines specifically mention onabotulinumtoxinA injections only. While the EAU guidelines mention that abobotulinumtoxinA and incobotulinumtoxinA are neither licensed nor interchangeable for onabotulinumtoxinA, the AUA guidelines go a step further in adding a note on the use of abobotulinumtoxinA compared to onabotulinumtoxinA. Citing one clinical trial that compared the efficacy of the two preparations, the AUA/SUFU guidelines on management of non-neurogenic overactive bladder declare that although abobotulinumtoxinA is of equal clinical efficacy, it is reported with a higher incidence of postinjection adverse events when compared to onabotulinumtoxinA, particularly with regard to the development of postinjection urinary retention requiring self-catheterization [44].

The recommended dose of onabotulinumtoxinA intradetrusor injection for idiopathic overactive bladder in both the EAU and AUA guidelines is 100 U diluted in normal saline and mapped across 20 injection sites. Both sets of guidelines discuss the possible rates of bacteriuria postinjection, cautions of injection in elderly patients with OAB, and necessity of repeated injections to sustain a desirable effect. The grade of recommendation for onabotulinumtoxinA injection per the EAU guidelines is listed as grade A recommendation, supported by a compelling set of randomized clinical trials, while the AUA gives the same treatment modality a standard level of recommendation with a grade B strength of evidence where the benefits of the injection outweigh the risks.

2.3. Detrusor sphincter dyssynergia

Normally, when the bladder contracts, there is a synergistic neural communication that relaxes the sphincter responsible for control of the bladder outlet. This coordination allows the bladder to perform its storage and emptying functions. However, any disruption to this synergy causes

http://dx.doi.org/10.5772/intechopen.79555

voiding dysfunction. Certain neurological conditions affecting the suprasacral micturition centers, such as some of the causes listed in **Table 1** like spinal cord trauma below the vertebral level of T6, could lead to an entity of voiding dysfunction known as detrusor sphincter dyssynergia (DSD). In DSD, the detrusor sphincter pathologically contracts simultaneously with the detrusor muscle of the urinary bladder instead of relaxing to allow bladder emptying. Thus, instead of free urinary flow during attempts of voiding, patients only pass small amounts of urine, if any. Multiple sclerosis affecting the spinal cord could also result in DSD.

Botulinum toxin injection for the management of DSD was the first published urological application of the toxin. Since its first description in 1988 by Dykstra, intrasphincteric botulinum injections for the management of DSD have been the focus of many researchers and urologists [45]. However, the clinical guidelines such as those published by the ICS and EAU do not dive into details for recommending this modality of managing DSD in neurogenic bladder patients since it is not registered for such an application, but rather mention it as a possible entity of treatment and make no specifications on the dosage or frequency of injections. The EAU based its limited recommendation on a Cochrane review that concluded that more RCTs are necessary before further recommending intrasphincteric botulinum injections for DSD but acknowledged reports stating its effectiveness. It should be mentioned, however, that the literature describes different techniques for intrasphincteric and periurethral injections of BoNT-A for the treatment of DSD, including transurethral endoscopic injections and imaging-assisted transperineal approaches, with variable reported outcomes.

2.4. Other neurogenic and non-neurogenic voiding dysfunctions

Lower urinary tract symptoms can also be attributed to asynchrony between the detrusor and sphincteric muscles and over- or underactivity of either the bladder detrusor muscle or urethral sphincter. This may be an entity of dysfunction voiding, idiopathic or even neurogenic, such as the peripheral neuropathy causes listed in **Table 1**. Successful treatment of DSD with sphincteric BoNT-A injections allowed an insight into the treatment of these voiding dysfunction entities. It has been demonstrated to decrease patient reliance on self-catheterization and improve voiding efficiency. However, the data is experimental, and the modes, dosage, and frequencies vary, in the absence of a consensus or clear recommendation by regulatory bodies like the EAU or AUA.

2.4.1. Fowler's syndrome

Fowler's syndrome is a unique entity of voiding dysfunction. Usually affecting young women, it is defined as a disorder of urethral sphincter relaxation and urinary retention in volumes reaching up to 1 l of urine, often in the absence of sensation of bladder fullness. Though its etiology is not well understood, the introduction of sacral neuromodulation has provided a means for restoring the normal voiding function in patients of Fowler's syndrome. Guidelines on the treatment of this syndrome with intrasphincteric injections of botulinum toxin are not available, nor is there any consensus or panel discussion. However, an open-label study in 2015 reevaluated this modality of treatment after an unsuccessful trial 20 years prior. This recent trial reignited interest into a less invasive modality of treatment of this syndrome compared to sacral neuromodulation.

2.5. Bladder pain syndrome/interstitial cystitis

This chronic debilitating condition was first described over 200 years ago. The hallmark of this condition is "bladder pain" or suprapubic pain that the patient can specifically attribute its sensation in the bladder. Different terms have been used to describe the combination of suprapubic pain, urgency, and frequency, in the absence of an infective pathology. Originally named interstitial cystitis only, the term bladder pain syndrome was added to further describe this disease entity where macroscopic findings may be absent on cystoscopic examination of the bladder. Similarly, the disease has been also termed hypersensitive bladder for the same reason. Nevertheless, a subgroup of the disease exhibits positive cystoscopic findings of what is known as "Hunner's lesions." These lesions, originally thought to be ulcers in the bladder mucosa but proven otherwise, constitute what is more known as the "classic" or "ulcerative" type of bladder pain syndrome/interstitial cystitis (BPS/IC), and although first described in women, the disease afflicts both genders.

Treatment of this disease is as complex as its pathology. With an unknown cause, the aim of treatment for the most part has concentrated on symptomatic relief and prolonged periods of remission of the pain in between flares of the disease. Different modalities have been described for the treatment of the disease, with varying degrees of success, ranging from oral amitriptyline to surgical interventions. In the presence of Hunner's lesions, there are numerous reports of achievement of some degree of pain relief on resection and ablation of these lesions. However, the other lower urinary tract symptoms may not be limited.

Botulinum toxin injections have been extensively described in the literature as a modality of treating the symptoms of BPS/IC. First described by Smith et al. in 2004, it was reported to provide relief from the bladder pain. Research then demonstrated the effects of BoNT-A injections on the bladder in BPS/IC. On the microscopic level, BoNT-A in BPS/IC was shown to:

1. Decrease acetylcholine and noradrenaline release from nerves in the urothelium.
2. Decrease the level of TRPV1, which is typically elevated in BPS/IC in the bladder urothelium.
3. Decrease the levels of nerve growth factor (NGF).
4. Decrease the level of neurogenic inflammation.
5. Decrease the expression of P2X3 receptors and CGRP release.
6. Modulation of the release of inflammatory mediators from the bladder urothelium, typically upregulated in BPS/IC.
7. Decrease mast cell infiltration and apoptotic cell counts in the urothelium.

These cellular effects have been both demonstrated and reproduced in several studies; however, there was no consensus or standardization on the dose of BoNT-A injected and modalities employed to augment the injections. Nevertheless, the described effects included:

1. Marked decrease in bladder and suprapubic pain.
2. Decrease in daytime and nighttime urinary frequency.
3. Decrease in the ICSI symptom score, an index used to assess the severity of the symptoms of patients diagnosed with BPS/IC.

4. An improvement in the quality of life of injected patients.
5. An increase in the maximal bladder capacity of urinary storage known as cystometric capacity.
6. Decrease in urgency and desire to void.
7. Antinociceptive effect.

BoNT-A injections for bladder pain syndrome is not FDA approved. However, the data is compelling enough from many randomized control trials that the ICS, EAU, and AUA sought to include its application in their guidelines. Though the grades of recommendation differ in strength, BoNT-A injections for the symptomatic treatment of BPS/IC are recognized as a viable option. The EAU strongly recommends the use of BoNT-A injections for BPS/IC when more conservative measures have failed and lists in sequence the different modalities it can be used in. The AUA has a more modest recommendation for BoNT-A in BPS, listing it as a fourth-line management modality.

Both onabotulinumtoxinA and abobotulinumtoxinA have been utilized in trials of treatment of BPS/IC. There is no consensus in both the literature and the guidelines on the dose of BoNT-A to be used. It should be of note that many trials, along with the EAU guidelines on management of BPS/IC, describe an entity of management known as hydrodistension, used alone or in combination with BoNT-A injections. During hydrodistension, the bladder is filled with a considerable amount of irrigation fluid and left in the bladder for an amount of time ranging between 5 and 15 minutes. The EAU proposes in its treatment algorithm that hydrodistension can be tried alone, then submucosal BoNT-A injections with hydrodistension, and, finally, intradetrusal BoNT-A injections with hydrodistension, without specifying the injectable dose or duration of distension, reflecting the variance in the data. Additionally, trigonal-involving BoNT-A injections have been described in the treatment of BPS/IC without inducing vesicoureteric reflux and with a considerable efficacy.

2.6. Chronic pelvic pain syndrome

This broad term describes a spectrum of disorders including chronic prostatitis, which is dubbed in some guidelines as the male variant of bladder pain syndrome. As with BPS/IC, chronic pelvic pain syndrome (CPPS) is of a noninfective etiology with a significant effect on the quality of life of the afflicted patient. A number of trials described decreased levels of pain on both periurethral and transperineal injections of BoNT-A for the treatment of CPPS. The EAU guidelines do not specify a recommendation for BoNT-A into the pelvic floor or prostate for CPPS and describe it as having a "modest" effect, while the AUA pairs treatment of BPS/IC and CPPS modalities in its recommendations.

2.7. Benign prostatic enlargement

The effects of intraprostatic injections of BoNT-A have been demonstrated in research on both humans and animals and have supported the hypothesis that an induction in the apoptosis of the glandular tissue of the prostate could lead to its atrophy and relief from the obstructive

component of lower urinary tract symptoms that result from benign prostatic enlargement (BPE). BPE could be thought of as a disease of age in men, where continuous proliferation of the glandular tissue in the transitional zone of the prostate gland leads to an increase in its size and narrows the outlet of the bladder, obstructing urinary flow. There is no specific sizable enlargement that causes symptoms, and the degree of symptoms does not correlate to the size of the enlarged prostate.

To date, the gold standard of treatment of BPE is transurethral resection of the prostate by endoscopic measures, after standing the test of time against open prostatectomy and when compared to emerging modalities of treatment. However, this has not deterred research into less invasive modalities of treatment including pharmacological regimens using alpha-receptor antagonists and 5-alpha reductase inhibitors, both first lines of treatment for BPE that have been shown to offer symptomatic relief and delay the need for surgical intervention, and other endoscopic and interventional radiology modalities.

Trials that have investigated intraprostatic injections of BoNT-A for BPE have described different doses and modes of injection. Due to the multifactorial nature of the lower urinary tract symptoms in BPE, prostatic BoNT-A injections may not provide complete or significant results in the presence of associated bladder over- or underactivity as a result of the outlet obstruction resulting from the prostatic enlargement. However, among those trials, there were clinically significant results with injections into the prostate and the bladder neck, including:

1. Improvement in the maximal urinary flow rate of patients, known as the QMax on uroflowmetric studies.
2. Reduction in symptomatic scoring indices used to assess severity of symptoms associated with BPE.

Nevertheless, within these trials, the modes of injection and doses are different, and the results are inconsistent and in some instances contradictory, indicating the need for further assessment and more trials before a consensus could be made.

BoNT-A injections for the treatment of BPE are considered completely "off-label" and against the EAU guidelines on the management of male lower urinary tract symptoms resulting from BPE or benign prostatic obstruction. The EAU cites trials and a recent systemic review and meta-analysis that showed BoNT-A not to be superior to placebo in the management of BPE and, as such, recommends against the use of BoNT-A in BPE. The AUA, however, makes no reference to or acknowledgment of BoNT-A prostatic injections.

2.8. Erectile dysfunction

Erectile dysfunction (ED) describes a spectrum of disorders in which a male cannot attain or maintain an erection sufficient to perform penetrative intercourse or complete it to ejaculation. The application of botulinum toxin injections in the treatment of entities of ED such as premature ejaculation and vasculogenic ED is reported in the literature of recent but are limited to small clinical trials and case reports hypothesizing the effect of the toxin in improving the sexual performance of the affected male. It is an area of future research and consideration,

especially with certain animal trials showing complementation of the mechanism of action of botulinum toxins and the physiology of attaining an erection.

3. Conclusion

Botulinum toxin applications in urology have garnered much attention in the last two decades both on the research and regulatory levels. The effects of the toxin at the neurophysiological level of the bladder urothelium extend beyond the neuromuscular blockade leading to detrusor relaxation and have been proven to exert sensory, antinociceptive, and anti-inflammatory effects as well through mediation of neural, cellular, and inflammatory markers. Though limited to the use of botulinum toxin A with the exception of one preparation of botulinum toxin B, the urological applications of botulinum are categorized into FDA-approved, guideline-supported, and experimental or "off-label" uses. The FDA has approved the use of onabotulinumtoxinA only and in the setting of neurogenic detrusor overactivity and refractory overactive bladder after failed treatment with anticholinergic medications. Regulatory bodies like the EAU and AUA not only adhered to this approval but also endorsed clinically apparent beneficial applications of BoNT-A in conditions like DSD and BPS/IC. Experimental and off-label uses are not recommended but are still practiced with limited evidence.

Conflict of interest

None to declare.

Author details

Said M. Yaiesh[1], Meshari F. Almutairi[2], Abdullatif E. Al-Terki[2] and Tariq F. Al-Shaiji[2*]

*Address all correspondence to: tshaiji@gmail.com

1 Kuwait Urology Board, Kuwait Institute for Medical Specialization, Kuwait

2 Department of Surgery, Urology Unit, Amiri Hospital, Kuwait City, Kuwait

References

[1] US Food & Drug Administration. BOTOX. Label. Highlights of Prescribing Information [Internet]. 2018. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103000s5307lbl.pdf [Accessed: May 5, 2018]

[2] Reyonolds WS, Fowke J, Dmochowski R. The burden of overactive bladder on US public health. Current Bladder Dysfunction Reports. 2016;**11**(1):8-13. DOI: 10.1007/s11884-016-0344-9

[3] Tikkinen K, Tammela T, Rissanen A, Valpas A, Huhtala H, Auvinen A. Mint: Is the prevalence of overactive bladder overestimated? A population-based study in Finland. PLoS ONE. 2007;**2**(2): e195. DOI: 10.1371/journal.pone.0000195

[4] Fiore K, Fauber J, Wynn M. Drug firms helped create $3 billion overactive bladder market. Medpage Today and Milwaukee Journal Sentinel. 2016. Available from: https://www.jsonline.com/story/news/investigations/2016/10/16/overactive-bladder-drug-companies--helped-create-3-billion-market/92030360/ [Accessed: May 5, 2018]

[5] Lee A. Pressure may be on Allergan to strike a major deal, as Botox gets another rival. The Street. 2018. Available from: https://www.thestreet.com/story/14507282/1/will-allergan--do-major-deal-botox-rivals.html. [Accessed: May 5, 2018]

[6] Kalsi V, Popat R, Apostolidis A, Kavia R, Odeyemi I, Dakin H, Warner J, Elneil S, Fowler C, Dasgupta P. Cost-consequence analysis evaluating the use of botulinum neurotoxin-a in patients with detrusor overactivity based on clinical outcomes observed at a single UK Centre. European Urology. 2006;**49**:519-527. DOI: 10.1016/j.eururo.2005.11.006

[7] Watanabe JH, Campbell JD, Ravelo A, Chancellor MB, Kowlaski J, Sullivan SD. Cost analysis of interventions for antimuscarinic refractory patients with overactive bladder. Urology. 2010;**76**(4):835-840. DOI: 10.1016/j.urology.2010.01.080

[8] Padmanabhan P, Scarpero HM, Milam DF, Dmochowski RR, Penson DF. Five-year cost analysis of intra-detrusor injection of botulinum toxin type A and augmentation cystoplasty for refractory neurogenic detrusor overactivity. World Journal of Urology. 2011;**29**(1):51-57. DOI: 10.1007/s00345-010-0618-3

[9] Ruffa L, Bagshawa E, Araclib J, Velardb ME, Pardhananib G, Zsolt H. Economic impact of onabotulinumtoxinA for overactive bladder with urinary incontinence in Europe. Journal of Medical Economics. 2016;**19**(12):1107-1115. DOI: 10.1080/13696998.2016.1199430

[10] Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. Nature Reviews Neuroscience. 2008;**9**(6):453-466. DOI: 10.1038/nrn2401

[11] Weckx F, Tutolo M, De Ridder D, Van der Aa F. The role of botulinum toxin A in treating neurogenic bladder. Translational Andrology and Urology. 2016;**5**(1):63-71. DOI: 10.3978/j.issn.2223-4683.2016.01.10

[12] Sellers DJ, McKay N. Developments in the pharmacotherapy of the overactive bladder. Current Opinion in Urology. 2007;**17**(4):223-230. DOI: 10.1097/MOU.0b013e3281299033

[13] Khera M, Somogyi GT, Kiss S, Boone TB, Smith CP. Botulinum toxin A inhibits ATP release from bladder urothelium after chronic spinal cord injury. Neurochemistry International. 2004;**45**(7):987-993. DOI: 10.1016/j.neuint.2004.06.001

[14] Nitti VW. Botulinum toxin for the treatment of idiopathic and neurogenic overactive bladder: State of the art. Reviews in Urology. 2006;**8**(4):198-208. DOI: 10.1002/mds.27072

[15] Ansyed T, Odergren T, Mint BK. Muscle fiber atrophy in leg muscles after botulinum toxin type A treatment of cervical dystonia. Neurology. 1997;**48**(5):1440-1442

[16] Comperat E, Reitz A, Delcourt A, Capron F, Denys P, Mint C-KE. Histologic features in the urinary bladder wall affected from neurogenic overactivity—A comparison of inflammation, oedema and fibrosis with and without injection of botulinum toxin type A. European Urology. 2006;**50**(5):1058-1064. DOI: 10.1016/j.eururo.2006.01.025

[17] Giannatoni A, Di Stasi SM, Nardicchi V, Zucchi A, Macchioni L, Bini V, Goracci G, Porena M. Botulinum-A toxin injections into the detrusor muscle decrease nerve growth factor bladder tissue levels in patients with neurogenic detrusor overactivity. Journal of Urology. 2006; **175**(6):2341-2344. DOI: 10.1016/S0022-5347(06)00258-8

[18] Gaillet S, Bardot P, Bernuz B, Boissier R, Lenne-Aurier K, Thiry-Escudier I, Tournebise H, Lechevallier E, Karsenty G. Five years follow-up study and failures analysis of Botulinum toxin repeated injections to treat neurogenic detrusor overactivity. Progrès en Urologie. 2012;**22**(17):1064-1070. DOI: 10.1016/j.purol.2012.10.006

[19] Hegele A, Frohme C, Varga Z, Olbert P, Kranz J, Hofmann R. Antibodies after botulinum toxin A injection into musculus detrusor vesicae: incidence and clinical relevance. Urologia Internationalis. 2011;**87**:439-444. DOI: 10.1159/000332194

[20] Jankovic J, Vuong KD, Ahsan J. Comparison of efficacy and immunogenicity of original versus current botulinum toxin in cervical dystonia. Neurology. 2003;**60**(7):1186-1188. DOI: 10.1212/01.WNL.0000055087.96356.BB

[21] Whelchel DD, Brehmer TM, Brooks PM, Darragh N, Coffield JA. Molecular targets of botulinum toxin at the mammalian neuromuscular junction. Movement Disorders. 2004; **19**:S7-S16. DOI: 10.1002/mds.20004

[22] Haferkamp A, Schurch B, Reitz A, Krengel U, Grosse J, Kramer G, Schumacher S, Bastian PJ, Büttner R, Müller SC, Stöhrer M. Lack of ultrastructural detrusor changes following endoscopic injection of botulinum toxin type A in overactive neurogenic bladder. European Urology. 2004;**46**(6):784-791. DOI: 10.1016/j.eururo.2004.07.011

[23] Blok B, Pannek J, Castro Diaz D, del Popolo G, Groen J, Gross T, Hamid R, Karsenty G, Kessler TM, Schneider MP, 't Hoen L. EAU Guidelines on Neurourology. 2015. Available from: http://uroweb.org/wp-content/uploads/21-Neuro-Urology_LR2.pdf [Accessed: May 5, 2018]

[24] Gorgal T, Charrua A, Silva JF, Avelino A, Dinis P, Cruz F. Mint: Expression of apoptosis-regulating genes in the rat prostate following botulinum toxin type A injection. BMC Urology. 2012;**12**(1). DOI: 10.1186/1471-2490-12-1

[25] Silva J, Pinto R, Carvallho T, Coelho A, Avelino A, Dinis P, Cruz F. Mint: Mechanisms of prostate atrophy after glandular botulinum neurotoxin type A injection: An experimental study in the rat. European Urology. 2009;**56**(1):134-141. DOI: 10.1016/j.eururo.2008.07.003

[26] Lin ATL, Yang AH, Chen KK. Mint: Effects of botulinum toxin A on the contractile function of dog prostate. European Urology. 2007;**52**(2):582-589. DOI: 10.1016/j.eururo.2007.03.002

[27] Chuang YC, Chancellor MB. Mint: The application of botulinum toxin in the prostate. Journal of Urology. 2006;**176**(6):2375-2382. DOI: 10.1016/j.juro.2006.07.127

[28] Eleopra R, Tugnoli V, Quatrale R, Rossetto O, Montecucco CM. Different types of botulinum toxin in humans. Movement Disorders. 2004;**19**:S53-S59. DOI: 10.1002/mds.20010

[29] Dykstra D, Enriquez A, Mint VM. Treatment of overactive bladder with botulinum toxin type B: A pilot study. International Urogynecology Journal. 2003;**14**:424. DOI: 10.1007/s00192-003-1099-3

[30] US Food & Drug Administration. Dysport. Label. Highlights of Prescribing Information [Internet]. 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125274s109lbl.pdf [Accessed: May 5, 2018]

[31] Pearce LB, Borodic GE, Johnson EA, First ER, Maccallum R. The median paralysis unit: A more pharmacologically relevant unit of biologic activity for botulinum toxin. Toxicon. 1995;**33**(2):217-227. DOI: 10.1016/0041-0101(94)00137-W

[32] Wohlfarth K, Schwandt I, Wegner F, Jürgens T, Gelbrich G, Wagner A, Bogdahn U, Schulte-Mattler W. Biological activity of two botulinum toxin type A complexes (Dysport and Botox) in volunteers. Journal of Neurology. 2008;**255**(12):1932-1939. DOI: 10.1007/s00415-008-0031-7

[33] Ginsberg D, Cruz F, Herschorn S, Gousse A, Keppenne V, Aliotta P, Sievert KD, Brin MF, Jenkins B, Thompson C, Lam W, Heesakkers J, Haag-Molkenteller C. Onabotulinumtoxina is effective in patients with urinary incontinence due to neurogenic detrusor activity regardless of concomitant anticholinergic use or neurologic etiology. Advances in Therapy. 2013;**30**(9):819-833. DOI: 10.1007/s12325-013-0054-z

[34] Cruz F, Herschorn S, Aliotta P, Brin M, Thompson C, Lam W, Daniell G, Heesakkers J, Haag-Molkenteller C. 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. DOI: 10.1016/j.eururo.2011.07.002

[35] Al-Shaiji TF. Intradetrusor injection of botulinum toxin for the management of refractory overactive bladder syndrome: an update. Surgical Innovation. 2012;**20**(4):351-355. DOI: 10.1177/1553350612460125

[36] Apostolidis A, Dasgupta P, Denys P, Elneil S, Fowler CJ, Giannantoni A, Karsenty G, Schulte-Baukloh H, Schurch B, Wyndaele JJ. Recommendations on the use of botulinum toxin in the treatment of lower urinary tract disorders and pelvic floor dysfunctions: A European consensus report. European Urology. 2009;**55**(1):100-120. DOI: 10.1016/j.eururo.2008.09.009

[37] Denys P, Del Popolo G, Amarenco G, Karsenty G, Le Berre P, Padrazzi B, Picaut P. Efficacy and safety of two administration modes of an intra-detrusor injection of 750 units Dysport® (abobotulinumtoxinA) in patients suffering from refractory neurogenic detrusor

overactivity (NDO): A randomised placebo-controlled phase IIa study. Neurourology and Urodynamics. 2017;**36**(2):457-462. DOI: 10.1002/nau.22954

[38] Kennelly M, Dmochowski R, Schulte-Baukloh H, Ethans K, Del Popolo G, Moore C, Jenkins B, Guard S, Zheng Y, Karsenty G. Efficacy and safety of onabotulinumtoxinA therapy are sustained over 4 years of treatment in patients with neurogenic detrusor overactivity: Final results of a long-term extension study. Neurourology and Urodynamics. 2017;**36**(2):368-375. DOI: 10.1002/nau.22934

[39] 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. DOI: 10.1007/s00345-012-0984-0

[40] Rovner E, Dmochowski R, Chapple C, Thompson C, Lam W, Haag-Molkenteller C. OnabotulinumtoxinA improves urodynamic outcomes in patients with neurogenic detrusor overactivity. Neurourology and Urodynamics. 2013;**32**(8):1109-1115. DOI: 10.1002/nau.22376

[41] Sussman D, Patel V, Del Popolo G, Lam W, Globe D, Pommerville P. Treatment satisfaction and improvement in health-related quality of life with onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity. Neurourology and Urodynamics. 2013;**32**(3):242-249. DOI: 10.1002/nau.22293

[42] Šámal V, Mečl J, Šrám J. Submucosal administration of onabotulinumtoxinA in the treatment of neurogenic detrusor overactivity: pilot single-centre experience and comparison with standard injection into the detrusor. Urologia Internationalis. 2013;**91**(4):423-428. DOI: 10.1159/000350247

[43] Ginsberg D, Gousse A, Keppenne V, Sievert KD, Thompson C, Lam W, Brin MF, Jenkins B, Haag-Molkenteller C. Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity. The Journal of Urology. 2012; **187**(6):2131-2139. DOI: 10.1016/j.juro.2012.01.125

[44] Gormley EA, Lightner DJ, Burgio KL, Chai TC, Clemens JQ, Culkin DJ, Das AK, Foster HE Jr, Scarpero HM, Tessier CD, Vasavad SP. Diagnosis and Treatment of Non-Neurogenic Overactive Bladder (OAB) in Adults: AUA/SUFU Guideline. 2014. Available from: http://www.auanet.org/guidelines/overactive-bladder-(oab)-(aua/sufu-guideline-2012-amended-2014)#x3763 [Accessed: May 5, 2018]

[45] Dykstra DD, Sidi AA, Scott AB, Pagel JM, Goldish GD. Effects of botulinum A toxin on detrusor-sphincter dyssynergia in spinal cord injury patients. The Journal of Urology. 1988;**139**(5):919-922

IntechOpen