Review

Use of botulinum toxin in urology: a literature review

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ABSTRACT
Botulinum neurotoxin (BoNT) is currently preferred as a minimally invasive treatment for lower urinary tract pathologies. Although BoNT injections have become widespread globally for the past 5 years, today, the urological use of BoNT Type A (BoNT-A) is only licensed for the treatment of neurogenic detrusor overactivity and overactive bladder. Despite the relative evidence for the use of BoNT-A in benign prostatic enlargement, there is no high-level evidence data for the use in detrusor sphincter dyssynergia, interstitial cystitis/bladder pain syndrome, and chronic pelvic pain. In this comprehensive review, we mention the mechanism of action and efficacy of BoNT in various urological disorders, present the reliability, and evaluate the literature data supporting its use.
Keywords: Botulinum toxin, neurogenic detrusor overactivity, overactive bladder, detrusor sphincter dyssynergia, benign prostatic enlargement, interstitial cystitis

INTRODUCTION

Botulinum neurotoxin (BoNT), a protein produced by *Clostridium botulinum*, an anaerobic gram-positive bacterium, is a potent neurotoxin. Clinical manifestations are caused by infection through contaminants (particularly canned food prepared at home), meat, sausage, and gastrointestinal tract infection or gastrointestinal colonization in infants with open bruises (1). After discovering that food poisoning in the nineteenth century was usually caused by homemade sausages, this toxin was named as "Botulinum toxin" after the Latin term "Botulus" meaning sausage (2).

Toward the mid-1900s, BoNT Type A (BoNT-A) was injected in a hyperactive muscle, and it blocked the motor nerve stimulation by inhibiting acetylcholine release from the presynaptic end thus causing paralysis (3, 4). These developments inspired the use of BoNT in the treatment of various other diseases resulting in an increasing number of studies exploring the effectiveness of this treatment method. In 1973, Scott (5, 6) published a study of the effects of BoNT on rectus lateralis in monkeys, and in 1981, he reported the first administration of the toxin on human subjects by treating patients with strabismus. Following the Food and Drug Administration (FDA) approval of the use of BoNT-A in the treatment of eye disorders in 1989, the use of BoNT for initial treatment was successfully implemented for strabismus, benign essential blepharospasm, and hemifacial spasm (7).

Botulinum neurotoxin was subsequently used in a wide range of indications, including urological pathologies. The use of BoNT injections on the external urinary sphincter in patients with detrusor sphincter dyssynergia (DSD) who had spinal cord injury (SCI) was first diagnosed by Dykstra (8) in 1988. The use of BoNT-A by

Schurch et al. (9) in the same group of patients accelerated the work in this area and opened the way for further developments.

Currently, BoNT can be used in urological pathologies, such as overactive bladder (OAB), neurogenic detrusor overactivity (NDO), interstitial cystitis (IC)/bladder pain syndrome (BPS), DSD, benign prostatic hyperplasia (BPH), and chronic pelvic pain (CPP; Table 1). However, the FDA approval of BoNT treatment for only OAB and NDO has been obtained from these pathologies (10-12). In this comprehensive review, we mention the mechanism of action and efficacy of BoNT in various urological disorders, present its reliability, and evaluate the literature data supporting its use.

CLINICAL AND RESEARCH CONSEQUENCES

Types of Botulinum Toxin
Botulinum neurotoxin is a neurotoxin secreted by *Clostridium botulinum*, which is a gram-positive, anaerobic, spore-forming, rod-shaped bacterium. Immunologically, 7 active subtypes of A, B, C, D, E, F, and G have been identified. Today, the most commonly used subtypes are BoNT-A and Type B. Numerous comparative studies have demonstrated that Type A is more potent and long-acting than Type B (10-14).

The commercial forms containing BoNT-A used in clinical practice are onabotulinumtoxin A (Botox®; Allergan, Dublin, Ireland), abobotulinumtoxin A (Dysport®; Ipsen-Biotech, Paris, France), incobotulinum toxin A (Xeomin®; Merz Pharmaceuticals, Frankfurt, Germany). The dose equivalency of Botox® and Dysport®, the 2 preparations used in our country, is approximately 1 to 3-5 (15, 16).

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Mechanism of Action

Acetylcholine is one of the most important molecules in neural transmissions. Various fusion proteins [Synaptosomal-associated protein 25 (SNAP-25), vesicle-associated membrane protein (VAMP), and Syntaxin) are involved in the release of acetylcholine molecules into the presynaptic domain. Although the different subtypes of botulinum toxin are structurally the same, they differ with regard to serological and antigenic properties. This is because the presynaptic site binds to different fusion proteins. The toxin affects nerves presynaptically by inhibiting the release of acetylcholine at cholinergic nerve endings (17).

Botulinum toxin reaches the cholinergic nerve terminal, exhibiting typical selectivity when injected into a target tissue. The toxin is then internalized into the structure where it breaks down the rings of an important protein chain that carries acetylcholine from the intracellular domain to the synaptic region. This carrier protein is the soluble N-ethymaleimide-sensitive factor attachment protein receptor (SNARE) protein and is the target of various BoNT serotypes (18). The inhibition of motor neurons following injection of toxin into the bladder inhibits involuntary contractions by reducing acetylcholine release. The significant decrease in phasic contractions, increase in cystometric capacity, and improvement in urinary incontinence (UUI) are due to this mechanism of inhibition in motor neurons. Through sensory neuronal effects, there is also a significant reduction in sensation, degree of compression, nerve receptor, and nerve growth factor levels in the bladder. It has been reported that the frequency of UUI, nocturia, and pollakuria decreases after injection. In these cases, the number of daily pad usage was decreased or complete dryness was achieved, consequently improving the quality of life (10-12, 18, 19).

The attachment of the toxin to the presynaptic membrane is irreversible creating a lasting paralytic effect. It may take up to 24-48 hours for the toxin to take effect. However, after 3-6 months, the axons regenerate leading to the reversal of the effects of denervation (10-12, 18).

Injection Techniques

The procedure can be performed under local, spinal, or general anesthesia. Prior to injection, local anesthesia with intravesical 30 mg 2% lidocaine is administered. After 15-20 minutes, a rigid or flexible cystoscope is inserted into the bladder. BoNT-A 100 IU is diluted with 10 mL saline for OAB and BoNT-A 200 IU is diluted with 20 mL saline for NDO. The bladder is injected with 0.5-1 mL at each point into the base or the bladder walls at a distance of 1-1.5 cm from each point (10-12, 18, 19) (Figure 1). Injection to the bladder dome is not recommended to avoid intestinal injury. The knowledge that BoNT-A also affects the sensory nerves resulted in administering BoNT-A injections into the trigone and suburethral area; consequently, vesicoureteral reflux was not observed after trigonal injections. In a recent meta-analysis comparing trigonal and extratrigonal injections in patients with NDO and idiopathic detrusor overactivity, there were no significant differences between the 2 methods in terms of side effects and short-term efficacy. The authors reported that patient-related factors and dosing were the major contributors to BoNT-A injections (10-12, 20).

Although the use of a higher concentration of the BoNT ensured improved results, it also causes urinary retention, voiding dysfunction, increased postvoiding residual urine volume (PVR), and requirement of clean intermittent catheterization (CIC). Another important point is the possibility of developing tolerance due to neutralizing agents against BoNT. For individuals with high initial and recurrence doses, the initial dose of BoNT should be as low as possible, since tolerance development is rapid. The efficacy covers a certain period and re-injections are often necessary after an average of 6-9 months (10-12, 18). After BoNT injection, urinary tract infection (UTI) may occur between 3.6% and 44%, PVR levels of up to 100-150 cc (0%-75%) and urinary drainage needed through CIC are reported as high as 43%, as a side effect (21).

Use in Urology

Although BoNT injections have become widespread globally for the past 5 years, today, the urological use of BoNT-A is only licensed for the treatment of NDO and OAB. Despite the relative evidence for the use of BoNT-A in BPH, there is no high level of evidence data for the use of BoNT-A in DSD and IC/BPS (10-12, 18).

Table 1. Use of botulinum toxin A in the treatment of urological disorders

Overactive Bladder/Non–Neurogenic Detrusor Overactivity
Neurogenic Detrusor Overactivity
Interstitial Cystitis/Bladder Pain Syndrome
Detrusor Sphincter Dyssynergia
Benign Prostatic Hyperplasia
Chronic Pelvic Pain

Figure 1. a-c. The endoscopic image of the bladder before intradetrusor botulinum toxin injection (a), the endoscopic image of the bladder during intradetrusor botulinum toxin injection (b), the endoscopic image of the bladder after intradetrusor botulinum toxin injection (c)

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1- Overactive Bladder-Non Neurogenic Detrusor Overactivity
Overactive bladder is defined as a syndrome characterized by urinary urgency with or without urgency-associated UUI. It is often associated with pollakuria and nocturia without a diagnosed pathology or infection (10-12). Nearly 12%-17% of the population is affected by this syndrome. Behavioral therapies are recommended as the first-line of treatment, and pharmacological therapy in the form of antimuscarinics and beta-3 agonists are recommended as a second-line of treatment (11, 22). Patients who have been using one or more different antimuscarinic agents for 3 months, often without adequate benefit and/or inability to tolerate the side effects of the drug, are considered as refractory OAB patients (10-12). Onabotulinum toxin A (onaBoNT-A) injections are presented as the standard therapy for the treatment of refractory OAB, according to the European Urology Association (EUA) and American Urology Association guidelines (11, 23).

In a phase 3 study by Nitti et al. (24), 557 patients were treated with 100 IU of onaBoNT-A or placebo. The authors reported a significant decrease in UUI episodes was noted and demonstrated a significant reduction in OAB symptoms compared to the placebo. The urinary retention rate was reported as 5.4%. In another phase 3 trial by Tincello et al. (25) involving 240 female patients with refractory OAB, 200 IU BoNT-A was injected in 122 patients and placebo in 118 patients. The patients were followed-up for 6 months, a significant reduction in urgency and UUI were observed and complete continence was also reported in one-third of cases. The most common adverse effect was UTI (31%), and the rate of patients that required CIC was reported as 16%.
Onem et al. (26) prospectively evaluated 80 patients with resistant OAB in the first multicentric study in Turkey. The mean urinary frequency, UUI episodes, urgency episodes were decreased (all at p<0.05), and the bladder capacity was increased both at the third and ninth month postoperatively. There was a 57.1% increase in quality of life scores of the patients, and there was no significant change in the mean PVR and maximum flow rate (Qmax). Three (3.75%) patients had urinary retention and 5 (6.25%) had urinary infection and transient hematuria. It has been reported that re-injection requirement rates were 20% in the third postoperative month and 63% in the ninth postoperative month. In the article published by Leong Randall et al. (27), there was a reduction in the symptoms of approximately 80% of patients after injection, a reduction of 12%-53% in daily urinary frequency, 28%-70% in urgency, 35%-87% in UUI episodes, and an average 45% increase in maximum cystometric capacity (MCC). In addition, the authors noted a decrease of 54%-57% in the Impact Questionnaire-Short Form Score and 38%-64% in the Urogenital Distress Inventory Score.

In a recent review by Mangera et al. (10), there was a 29% decrease in daily frequency, 38% in urgency, and 59% in incontinence episodes with BoNT-A injection (all at p<0.02). Urodynamically, an increase of 58% in MCC and a 42% decrease in maximum detrusor pressure (MDP) were reported (p<0.04, p<0.02, respectively). However, UTI rates (21% vs. 7%, p<0.01) and requirement of CIC (12% vs. 0%, p<0.01) were increased when compared to the placebo. The EAU guidelines have shown that injection of 100 IU BoNT-A into the bladder wall is superior to placebo in terms of UUI and improvement in quality of life. There is no evidence of decreased efficacy with recurrent injections. However, it is emphasized that patients should be warned about possible urinary system infections and the potential necessity of CIC (11).

2- Neurogenic Detrusor Overactivity
Neurogenic detrusor overactivity is a type of voiding disorder, accompanied by decreased bladder capacity, increased intravesical pressure, and reduced bladder compliance with or without incontinence. The association with vesicoureteral reflux may cause damage to the upper urinary tract. The main goals of treatment are to reduce involuntary contractions of the bladder, partially block the efferent parasympathetic innervation of the bladder, and administer CIC. The treatment method chosen varies for each patient group. Pudendal nerve stimulation or sacral root nerve stimulation in spinal cord injury patients may present great benefit in cases with urgency (10-12, 28). Auto-augmentation enterocystoplasty and ileal conduit are complicated surgical interventions and are considered as the last option. Intravesical capsaicin and resiniferatoxin are currently in the evaluation phase, and research needs to be improved in this regard (18, 29).

The effects of intravesical BoNT-A injections on the detrusor muscle in patient with SCI were first demonstrated in a non-randomized retrospective study by Schurch et al. (30). In this study, NDO patients who were refractory to anticholinergic drugs were evaluated. Patients with low bladder compliance due to organic detrusor muscle changes or fibrosis were excluded from the study. BoNT-A 200-400 IU was injected into the detrusor muscle without trigon, and all 19 patients were followed up for 9 months with clinical evaluation and urodynamic studies. At 36 weeks, the reflex volume increased from 207 mL to 320 mL, with an increase of 54%, and MCC increased from 286 mL to 458 mL, with an increase of approximately 60% (p=0.007, and p=0.003, respectively). In addition, MDP regressed from 62 cmH$_2$O to 36 cmH$_2$O (−41.9%).

Ginsberg et al. (31) published a study including 416 patients (227 patients with multiple sclerosis [MS] and 189 patients with SCI). Overall, 135 of these patients were injected with 200 IU onaBoNT-A, 132 with 300 IU onaBoNT-A, and 149 with placebo. Following the injections, improvement of MCC and MDP in the first involuntary detrusor contraction was higher in the onaBoNT-A group than in the placebo group (p=0.001). Re-injection requirements were noted after 256 days in patients given 200 IU onaBoNT-A, after 254 days in patients given 300 IU onaBoNT-A, and after 92 days in patient given placebo. In addition, CIC was required in 10% of the placebo group, 35% of the 200 IU onaBoNT-A group, and 42% of the 300 IU onaBoNT-A group due to urinary retention. In a study including 71 MS patients, Deffontaines-Rafin et al. (32) reported that UUI disappeared in 46% of the patients, NDO was not observed in urodynamic examinations, half-and-half improvement was achieved in 31% of cases, and a significant change was not detected in 23% of the patients, with the 300 IU onaBoNT-A injections. The mean MBC was increased from 240 cc to 328 cc (p<0.001), and the MDP was decreased from 61 cmH$_2$O to 36 cmH$_2$O after injections. They also found that the duration of MS was an important factor influencing treatment success (p=0.015).

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In a recent review, a 63% decrease in daily incontinence frequency (p<0.01), 18% decrease in catheterization episodes (p <0.01), 63% increase in MCC, and 42% decrease in MDP were reported with BoNT-A injections (10). In the EAU guideline, it is stated that onaBoNT-A is a successful minimally invasive treatment method for NDO in patients with MS or SCI, where antimuscarinic treatment was ineffective. It has been emphasized that the efficacy of onaBoNT-A is proven by randomized, placebo-controlled studies, with no loss of efficacy in repeated injections (33).

3- Interstitial Cystitis/Bladder Pain Syndrome

Interstitial cystitis/Bladder pain syndrome is defined as a set of symptoms based on the exclusion of infection and other identifiable pathologies, together with symptoms, such as urgency, pollakuria, pain in the bladder or pelvic region, and the sensation of pressure (34). Despite extensive research being conducted presently, there is no definite consensus on the optimal treatment of this clinical presentation. The main goal in the treatment of IC/BPS should be to protect the quality of life at the optimal level and to minimize the severity of symptoms. Although BoNT injections together with hydrodistension is not an FDA-approved treatment for this syndrome, it is commonly used in patients because other treatment steps are not effective and worsen the symptoms (12, 35).

Giannantoni et al. (36) reported that 200 IU BoNT-A injected into the detrusor muscle in patients with BPS provided significant improvement in pain, urinary frequency, voided volume, and bladder capacity; however, all patients had recurrent basal complaints at the end of the first year. In a randomized controlled trial including 67 patients (56 females, 11 males) by Kuo and Chancellor (37), BoNT-A injections (100 IU and 200 IU) with or without hydrodistension were compared. Only patients treated with hydrodistension + BoNT-A showed improvement in bladder pain visual analog scale (VAS) and MCC. In the postoperative global response assessment at 3 months, the success of hydrodistension + BoNT-A was 80% for 200 IU, 72% for 100 IU, and 48% for patients who underwent only hydrodistension. It has been reported that the effect of BoNT-A lasted 12-24 months. Despite the same efficacy, an increase in the dysuria and PVR were more frequent in patients who received 200 IU BoNT-A. In a double-blind, placebo-controlled, multicentre study, Kuo et al. (38) compared the effects of hydrodistension + 100 IU BoNT-A injections versus hydrodistension + saline injections on 67 patients. On the postoperative eighth week, there was a significant decrease in VAS (−2.6 vs. −0.9, p=0.02) and an increase in MCC (+67.8 vs. −45.4, p=0.020) compared to the placebo group. However, no changes were observed in other urodynamic parameters and subjective symptoms, such as frequency/nocturia.

Although the FDA approval requires extensive patient-populated, placebo-controlled studies, these studies show the efficacy of 100 IU onaBoNT-A in the treatment of IC/BPS. The AUA recommends onaBoNT-A at the fourth step of the IC/BPS treatment by starting at 100 IU (35).

4- Detrusor Sphincter Dyssnergia

Detrusor sphincter dyssnergia is a voiding disorder resulting from spinal lesions between the pontin and sacral voiding centers. DSD causes voiding dysfunction with external sphincter spastic or uncoordinated contraction in patients with MS or SCI during voiding. The treatment is based on the removal of obstruction. Although it is not effective, anticholinergic agents, alpha blockers, and spasmolytic agents are used. In addition, treatment methods, such as CIC, permanent urethral and suprapubic catheters, sphincterotomy, dorsal rhizotomy, are among the modalities performed (10-12, 18, 39).

Dykstra et al. (8) explained that reversible chemical sphincterotomy could be performed with BoNT injections to reduce DSD in SCI patients for the first time. BoNT was injected transurethrally or transperineally into the patients through cystoscopy under electromyographic examination. It was performed to 2/3 different regions of injection sites on the sphincter. Urethral pressure profile and PVR were used as the main parameters to follow the effect of toxin. Eight of 11 patients showed improvement. Urethral pressure profiles decreased by an average of 27 cmH_2O, and PVR decreased by an average of 146 mL. The duration of the efficiency was maintained approximately 50 days, and no side effects were observed. In a double-blind study, Dykstra and Sidi (40) evaluated the efficiency of BoNT injections or saline in the treatment of DSD in 5 male patients with SCI. In 3 patients administered BoNT injections, an average of 30 cmH_2O in the urethral pressure, 122 mL in PVR, and 30 cm H_2O in the bladder pressures decreased after treatment. No improvement was observed in these parameters, in 2 patients injected with saline.

In a prospective study including 24 SCI patients, Schurch et al. (41, 42) compared the efficacy of onedose BoNT injections (100 IU in 1 mL) versus once-monthly BoNT injections for 3 months. In 21 of these patients, maximum urethral pressure, duration of DSD, and urethral pressures were reduced by 48%, 47%, and 20%, respectively. There was a significant reduction in PVR (130 mL). In 8 cases, detrusor hypoactivity and bladder neck dyssynergia completely reduced voiding. No improvement in autonomic dysreflexia was observed. Also, in this study, single injections were observed to have a shorter duration (2-3 months) of efficacy on voiding dysfunction when compared to repeated injections (9-13 months).

Today, BoNT activity in DSD is demonstrated in quadriplegic men who cannot undergo catheterization and in MS patients (8, 18, 39-42). The new and standardized trials should be performed due to lack of protocol data, differences on BoNT doses, and insufficient long-term outcomes.

5- Benign Prostatic Hyperplasia

Benign prostatic hyperplasia is a common condition in older men. The goal of treatment is to reduce BPH-related lower urinary tract symptoms and improve quality of life. Alpha-adrenergic blockers and 5-a reductase inhibitors used in therapy are not always effective and side effects may be seen. Currently, the gold standard surgical procedure of BPH treatment is the transurethral resection. However, BoNT may be offered as a treatment alternative in patients who are unfit for operation, whose general condition is impaired, have multiple comorbidities, or do not admit operation.

BoNT-A toxin is efficacious by inhibiting autonomic efferent nerve effects on prostate growth and contractions (12, 18).

In a prospective, randomized, placebo-controlled, double-blind trial conducted by Maria et al. (43), which supports the therapeutic properties of BoNT-A in BPH, 200 IU BoNT-A was intraprostatically injected to 15 patients in 4 mL saline,. The procedure was performed using the transrectal ultrasound guideline perineally with 2 mL per prostate lobe. Patients were followed for 19.6±3.8 months, the authors reported prostate specific antigen (PSA) reduction in 51% of the patients and a 65% reduction in the American Urological Association Prostate Symptom Score in the BoNT-A group, while no significant change was observed in the saline group. In the study by Chuang et al. (44), the BoNT-A doses were adjusted to the measured prostate volume as 200 IU BoNT-A for those with prostate tissue above 30 mL, and 100 IU BoNT-A for those below 30 mL and injected by perineal transrectal ultrasound guidance. The International Prostate Symptom Scores (IPSS), Qmax values, and PVR values were compared with the preoperative values. There was a 30% improvement in lower urinary tract symptoms and quality of life scores in both groups. The improvement period started from the first week and maintained to the twelfth month. No local or systemic side effects were observed in any of the patient. Four of the 5 patients had urinary retention, and they voided spontaneously after 1 week.

Guercini et al. (45) administered 300 IU BoNT in patients with prostate volume >80 cc and Qmax <10 mL/s. After a 1-month follow-up, improvement rates were 38.7% in prostate volume, 45.8% in average IPSS, 38.4% in PSA levels, and 64.1% in PVR. In addition, patients' Qmax increased to 87.8%. Park et al. (46) reported symptomatic improvement in 39 of 52 patients injected with BoNT at different doses (100-300 IU) transperineally. A decrease of 30.3% in IPSS, 34.4% in quality of life index, and 13.3% in prostate volume and an increase of 15.5% in Qmax values were observed. Currently, BoNT-A is not routinely used in BPH therapy and has not been approved by the FDA. The EAU guidelines also state that BoNT injection should not be recommended in male patients lower urinary tract symptoms (level of evidence: 1a) (47). However, as shown in the studies conducted, developments are positively directed.

6- Chronic Pelvic Pain

Investigation of prostatitis began in 1998 by the National Institutes of Health (NIH) by classifying it into 4 groups: acute bacterial prostatitis, chronic bacterial prostatitis, CPP syndrome, and asymptomatic inflammatory prostatitis. Of these, type 3 chronic prostatitis is the most common cause (95%) of CPP syndrome (48). Due to the inadequacy of different treatment modalities, physicians treating this group of patients have started to seek different methods of treatment.

It was reported in 1998 for the first time by Maria et al. (49) that there was improvement in urinary symptoms after intraprostatic injections of BoNT in 4 patients with nonbacterial prostatitis. A 30 IU BoNT was injected to the proximal apex of these patients in a single transperineal dose. The uroflowmetric examinations showed significant improvement in 3 patients. None of these pa-

tients had symptoms for the following 12 months. In 2000, 11 patients with CPAS diagnosed by Zermann et al. (50) showed a significant decrease in pain after transurethral BoNT injection. The authors administered 200 IU BoNT-A injection transurethrally to the perisphincteric region. In 9 of the 11 patients, subjective pain reduction was observed, and the mean pain level (1: no pain, 10: unbearable pain) was reduced from 7.2 to 1.6 on the VAS. In urodynamic examinations performed before and after injections, a decrease in functional urethral length, urethral closure pressure, and PVR and an increase in mean and maximum flow rates were observed.

Although the number of patients is limited, it is promising that BoNT may be an effective treatment for CPP during preliminary studies. In these studies, injection localization, methods, and dosages vary widely. In large-scale randomized controlled trials, the introduction of standardized treatment methods is an important need in this regard.

CONCLUSION

Botulinum toxin is currently preferred as a minimally invasive treatment in the treatment of lower urinary tract pathologies. The FDA approval was received for OAB and NDO, and it is widely applied throughout the world. In these patients, a significant decrease in bladder phasic contractions and an increase in cystometric capacity were observed urodynamically; moreover, a significant decrease in the frequency of urgency, nocturia, and pollakuria were noted. In this regard, it is stated that the number of daily pad usage decreased or full dryness was provided thus improving the quality of life. Patients administered with BoNT injections should be warned about urine retention and requirement of CIC. Patients should be informed that the effect of botulinum toxin injection is temporary, repeated injections may be necessary, and their efficacy may continue after repeated injections.

Current studies are suspicious about BoNT injection in BPH and do not clearly support it. BoNT injections are promising in CPP and IC/BPS due to limited evidence. Similarly, although the efficacy and reliability of BoNT in DSD has been shown in small studies, extensive, well-designed, randomized controlled trials are needed.

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