

BOTULINUM TOXIN, TREATMENT OPTION FOR NEUROGENIC DETRUSOR OVERACTIVITY

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Abstract

Botulinum toxin is a potent neurotoxin that inhibits acetylcholine neurotransmitter release into the synaptic cleft of the neuromuscular junction. This leads to flaccid paralysis of the affected muscles. Neurogenic detrusor overactivity (NDO) patients benefit from this treatment because it reduces or abolishes urinary incontinence episodes and improves bladder capacity. Neurogenic detrusor overactivity is the underlying condition of the overactive bladder in neurologic patients. Its management includes medical treatment but when it fails to improve urodynamic parameters and the patient's quality of life, minimally invasive treatment with botulinum toxin injected in the detrusor is a safe and effective option. This paper aims to review important information regarding pharmacokinetics, pharmacodynamics, the safety profile, and the mechanism of action of botulinum toxin, its medical uses, and its results when used for NDO.

Rezumat

Toxina botulinică este o neurotoxină foarte puternică ce inhibă eliberarea neurotransmițătorului acetilcolină în fanta sinaptică a joncțiunii neuromusculare. Acest lucru determină paralizia flască a mușchilor afectați. Pacienții cu hiperactivitate detrusoriană neurogenă beneficiază de acest tratament cu potențial de reducere sau remitere completă a episoadelor de incontinență urinară și creștere a capacității vezicii urinare. Hiperactivitatea detrusoriană neurogenă este patologia ce stă la baza sindromului de vezică hiperactivă la pacienții cu afectare neurologică. Abordarea terapeutică include tratament medicamentos, dar când acesta nu îmbunătățește parametrii urodinamici și calitatea vieții, tratamentul minim invaziv cu toxina botulinică injectată în detrusor este o alternativă sigură și eficientă. În acest articol sunt prezentate informațiile principale legate de farmacocinetica, farmacodinamica, profilul de siguranță și mecanismul de acțiune al toxinei botulinice, precum și despre utilizarea sa în domeniul medical și efectele dovedite în cazul hiperactivității detrusoriene neurogene.

Keywords: botulinum toxin, neurogenic detrusor overactivity, overactive bladder

Introduction

The overactive bladder (OAB) is a common condition that affects both men and women, with a high negative impact on quality of life. The diagnosis is a clinical one and is based on urinary urgency, accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection (UTI) [10] or other obvious pathology, according to the International Continence Society (ICS) [3]. OAB symptoms affect the patient's everyday life, even on psychological levels. Certain clinical trials have shown higher levels of anxiety, depression, and shame, impact on social life and sexual activities, and an overall lower QoL (Quality of Life) score than people without OAB. A meta-analysis of the results obtained in trials that examined patients taking oral anticholinergic therapy suggests that alleviation of OAB symptoms correlates with higher HRQoL (Health-Related Quality of Life) than placebo [15]. Forming a vicious cycle,

the anxiety generated by OAB leads to symptoms of increased severity [19].

Often, the urodynamic correspondent of OAB is the overactive detrusor. ICS defines detrusor overactivity as involuntary detrusor contractions during the filling phase, either spontaneously or provoked. If the aetiology is a documented neurological disease, the condition is called neurogenic detrusor overactivity (NDO). Otherwise, the term used is idiopathic detrusor overactivity (IDO). The prevalence of NDO in the United States ranges from 40% to 90% in multiple sclerosis patients, from 37% to 72% in Parkinson's disease patients, and is approximately 15% after stroke. Almost 81% of spinal cord injuries result in urinary dysfunctions, and out of the adults who survive with spina bifida, close to 61% complain of urinary incontinence [11]. NDO is also found in conditions such as transverse myelitis, diabetes mellitus, Guillain Barré syndrome, alcoholism, Huntington disease, sarcoidosis and several others.

The urinary tract alternates between bladder filling and voiding phases. Normally, the nervous control integrates information from the sacral micturition centre (S2-S4), the pontine centre (Barrington's nucleus) and the cortex. Any disturbance of the pathways between them determines urinary dysfunctions following a certain pattern according to their location.

Suprapontine lesions affect cortical inhibition and result in detrusor overactivity but intact sphincter activity. Thus, these lesions should not generate high intravesical pressure.

Suprasacral lesions below the pons are characterised by the loss of voluntary inhibition, spastic overactive bladder and detrusor sphincter dyssynergia in complete lesions. This leads to high sustained intravesical pressures that over time generate recurrent urinary tract infections difficult to treat [20], hydronephrosis and kidney damage. The changes consist of the replacement of A δ fibre afferences with C fibres, inefficient detrusor contractions, detrusor sphincter dyssynergia, and detrusor or sphincter activity related to formerly indifferent stimuli in the perineal and penis area [28]. In lesions above T6 extra caution should be taken because of the potentially lethal autonomic dysreflexia, triggered by a sympathetic overreaction to stimuli below the lesion.

S1-S4 lesions are characterised by detrusor hypo-activity, paralyzed sphincter and absent micturition reflex. Sensitivity is abolished with the possibility of partially preserved pain sensitivity.

Methods

Our aim was to overview the scientific literature regarding the current knowledge and usage of botulinum toxin in treating the neurogenic overactive detrusor.

We performed a PubMed search using the terms "botulinum toxin" and one of the following: "mechanism of action", "pharmacokinetics", "pharmacodynamics", "technique of injection", "pharmacovigilance", "clinical results", "retreatment", "antibodies". The search was limited to papers written in English and, where applicable, studies on human subjects and randomised trials. We evaluated the results and selected a total of 29 papers which were chosen as fundamentals for our paper. Where applicable, our personal experience was included to provide unbiased work, discussing different points of view.

Current Treatment Alternatives

The management of patients with NDO follows several steps. The European Association of Urology (EAU) sets as a first priority of the therapy the upper urinary tract protection, and as secondary ones achieving urinary continence, improving quality of life and rehabilitating lower urinary tract function. This way,

mortality by urological causes dropped significantly, and the patient can be socially integrated again.

There is evidence that decreased intensity of symptoms can be achieved through factors that are not curative themselves: lowering the coffee intake, moderate physical activity, and weight loss. As first-line treatment, EAU, American Urological Association (AUA) and The National Institute for Health and Care Excellence (NICE) recommend bladder training and pelvic floor muscle training as an intensive course lasting at least 3 months [21].

Medication for this condition is unfortunately not a sole, optimal therapy, but rather a combination of therapies with the goal of maximizing the effect (Level of Evidence 1a, according to EAU guidelines). Oral medication offers antimuscarinics as a first-line treatment. Propiverine, trospium chloride, oxybutynin, propantheline, solifenacin, darifenacin and tolterodine used for NDO show urodynamic benefits, and clinical data suggests even greater efficacy and more durable results than for IDO [9]. The challenge with this medication is patient adherence, approximated at around 8% - 25% at 12 months, due to side effects (dry mouth, constipation, abdominal pain, blurred vision, headache, sleepiness and dizziness) and lack of expected results [7]. Alpha-blockers have proved useful in combined therapy with antimuscarinics, and beta-3 agonists (mirabegron) are recommended when a satisfactory response to antimuscarinics is not achieved or if side effects overshadow the response. Mirabegron has increased patient adherence due to side effect manageability and low occurrence rates, similar to placebo [2].

The gold standard in minimally invasive treatment is clean intermittent catheterisation, which reduces the risk of UTIs and complications associated with indwelling catheters. The EAU recommends 4 to 6 catheterisations daily.

Treatment can also be delivered intravesical, its effect targeting the afferences and efferences of the micturition reflex. Vanilloids, capsaicin and resiniferatoxin desensitise afferent C fibres for some months post-instillation, resiniferatoxin being less painful and very efficient even in patient's refractory to capsaicin. Efference modulation through intradetrusor injection of botulinum toxin A yields a greater clinical efficiency than the methods above, being considered by the EAU the most effective minimally invasive treatment for NDO (Grade A recommendation – strong evidence). Even so, injecting botulinum toxin is an option reserved only for patients refractory to antimuscarinics and should not be used as a first-line treatment.

Botulinum Toxin

The botulinum toxin is produced by *Clostridium botulinum*, and it is the most potent natural-occurring

toxin known to date. Since there is no vaccination available for botulism, it is considered an agent that could become a biological weapon. The lethal dose for humans is 1 µg/kg for the oral route, 10 ng/kg when inhaled and 1 ng/kg when administered intravenously or intramuscularly, being far more toxic than potassium cyanide [27]. There are seven types of toxins depending on the antigenic differences, A through G, similar in structure, molecular weight and mechanism of action; only types A and B are used in medicine due to a satisfactory duration of their effect. They induce flaccid paralysis, which is useful in the cases of hyperfunction of peripheral cholinergic nerve terminals, such as the overactive detrusor, as well as dystonia, achalasia, hyperhidrosis, glabellar lines, and numerous others.

There is vast experience in using onabotulinum toxin A (Botox®) and abobotulinum toxin A (Dysport®) as NDO treatment, although the latter is not FDA (Food and Drug Administration) approved for this condition. The recommended doses are 200 Allergan Units for Botox and 500 Speywood Units for Dysport, with a therapeutic effect lasting up to 9 months [29]. 1 U (unit) is the equivalent of 1 LD50 (median lethal dose) for mice and correlates with a few picograms of substance. The potency units are not identical between subtypes, and products are not interchangeable.

Botulinum Toxin Mechanisms of Action

The toxin acts on the reflex arc efference at the neuromuscular junction, where it blocks the release of acetylcholine, thus preventing contraction. It is considered that its direct effect is augmented by an indirect effect on the sensitivity of afferent C fibres. Since the mechanism does not involve apoptosis, the effect of the toxin is irreversible only until the sprouting of nerve terminals and formation of new synaptic contacts occur.

At the molecular level, the botulinum toxins impair the exocytosis of the neurotransmitter into the synaptic cleft. Studying their mechanism of action led to major discoveries in terms of proteins involved in membrane fusion and exocytosis generally. We now know that the process is mediated by SNARE (soluble N-ethylmaleimide sensitive factor attachment protein receptor) proteins, more precisely VAMP2 (vesicle-associated membrane protein 2), syntaxin 1A and SNAP-25 (synaptosomal-associated protein, 25kDa). VAMP2 is present on the vesicle, while syntaxin 1A and SNAP-25 are present on the membrane. For the exocytosis to occur, these proteins must intermediate vesicle docking to the membrane, form a fusion pore, and then the fusion of the two membranes. VAMP2 has a higher affinity for the SNARE complex that results from syntaxin 1A and SNAP-25 coupled, rather than for each protein taken separately. The complex formed by the 3 proteins combined is very

stable and involves a zipper mechanism that allows membrane remodelling. All botulinum toxins exert their effect by cleaving SNARE proteins due to their metalloprotease activity. However, they target different portions of the proteins. The SNARE proteins consist of a C-terminal closer to the membrane and an N-terminal that is distal. The zipper mechanism starts from the N-terminal. In particular, the botulinum toxin type A acts on the C-terminal and allows effective docking of the vesicle but interferes with the exocytosis in a further step, before the fusion pore is supposed to open. This is why the treatment with high amounts of Ca²⁺ has good results in restoring fusion activity for botulinum toxin type A but has no effect on other types of botulinum toxin that do not allow the docking of the vesicles [14].

Safety Data

Little is known about the pharmacokinetics of botulinum toxin. Since more and more medical applications have been discovered, efforts have been made to clarify important information. The LD50 for botulinum toxin type A is approximately 5 pg for a 25 g rat. Recent studies on mice estimated the half-life of the lethal dose of the toxin in blood to range between 230 and 240 min. Blood cells do not bind, alter or metabolise the toxin, but act as a delivery system for the toxin to the targeted organs [25]. For intramuscular injections, flaccid paralysis occurs in 2 - 5 days and slowly diminishes after 2 - 3 months. Dose-effect correlations seem to follow a curve, but the dose-duration saturates at 3 months [8].

Pharmaceutical Formulation

Botulinum toxin A is commercialised in vials containing a sterile, lyophilised powder that should be stored in refrigerators at 2 - 8°C for up to 2 years. Once reconstituted with saline, it should be stored in the refrigerator for a maximum of 24 hours. Each concentration should be reconstituted with the exact amount of saline indicated by the leaflet. The final solution should be clear, colourless, and free from particulate matter. It should only be manipulated while wearing gloves.

Intradetrusor Injection Technique

Onabotulinum toxin and abobotulinum toxin A are proven safe and efficient for intradetrusor injecting. Delivery is achieved endoscopically, using a rigid or flexible cystoscope and a flexible injection needle. Injection techniques vary slightly, but recent findings suggest no difference in the result. The reconstituted solution is injected in 20 to 30 sites, each with 1 mL of the solution, corresponding to 6.7 Allergan Units of onabotulinum toxin A for 30 sites and 25 Speywood Units abobotulinum toxin A for 20 sites. The agreed

bioequivalence Botox: Dysport ranges between 1:2 and 1:3 [26]. Results from a randomised placebo-controlled phase IIa study, show that a reduction from 30 to 15 injection sites does not affect the efficacy of the treatment [6]. The injection into the detrusor is approximately 2 mm deep in the dome and posterior and lateral bladder walls. Depending on the technique, the trigone area may or may not be avoided, and the main risk considered is the development of vesico-ureteral reflux. Abdel-Meguid TA compared the results of the procedure in two similar groups, the main difference being the inclusion of the trigone in the targeted treatment areas; the results yield that vesico-ureteral reflux has not developed or aggravated in none of the patients and that the result of the therapy is significantly better when the trigone is included in the treatment areas [1]. Controversy also exists between intradetrusor *versus* submucous injection. Suburothelial injection could have the advantage of direct action on the sensitive nerves in the lamina propria, but most protocols favour the intradetrusor technique. J Krhut *et al.* conclude that there are no significant differences between the two techniques regarding results while noting that the intradetrusor group has shown an increase in post-procedural detrusor compliance, but also a case of transient muscle weakness as a side effect [17]. Nonetheless, determining the precise localisation during the procedure is difficult in many cases.

Clinical Data from the Literature

Results of trials show post-procedure improvement in all urodynamic parameters. Stoehrer *et al.* report an increase of mean maximum capacity (MCC) from 294 mL to 392 mL at 6 weeks, a decrease of maximum detrusor pressure (MDP) from 33.7 cmH₂O to 24.6 cmH₂O, an increase of detrusor compliance from 23.1 mL/cmH₂O to 40.0 mL/cmH₂O, and an increase in reflex volume from 168 mL to 240 mL at 6 months. Continence is reported by approximately 80% of the patients undergoing 5 to 6 catheterisations daily. The mean duration of the therapeutic effects is similar for both types of toxins, i.e. 8.9 months for Botox 300 U and 7.6 months for Dysport 750 U [29]. Deffontaines-Rufin *et al.* studied the effect of botulinum toxin in patients with NDO due to multiple sclerosis. MCC increased from 240 mL to 328 mL and MDP decreased from 61 cmH₂O to 36 cmH₂O at 3 months. 46% of the patients were fully continent, and 31% reported improvement [5].

Regarding choosing one over the other, comparative studies do not indicate a preference. Grosse *et al.* present the results of a 56-patient clinical trial, in which the only difference between the two substances was the continence volume measured at 3 months, significantly higher in Dysport[®] (459 mL) *versus* Botox[®] (386 mL) [12]. For patients that don't achieve

results with the treatment, trials demonstrate that the majority that does not respond to Botox[®] is prone to favourable effects with Dysport[®] [4] and *vice-versa* [24].

Safety Profile, Adverse Events and Specific Precautions

Treatment with botulinum toxin carries its own risks, and both physicians and patients should be aware of them. Transient side effects include ecchymosis, hematomas, pain and erythema at the injection site. Serious adverse events are caused when the substance spreads to adjacent muscles or diffuses into deeper tissues. Botulism-like symptoms are dysphagia, muscle weakness, dysphonia and even respiratory failure. The allergic reaction spectrum can range from local oedema to anaphylactic shock. Reviews of the literature show a favourable safety profile of botulinum toxin A, with no severe adverse events reported and a rate of mild to moderate adverse events of 25%, compared to 15% in the control group. Out of these, only focal weakness had a greater incidence in the treatment group [22]. However, in 2009, the FDA released a statement regarding the side effects of botulinum toxin A and B treatments that required manufacturers to place black box warnings on their products. This is the most serious warning from FDA and was necessary because cases of product spread from the injection site were reported. The reported cases developed botulism-like symptoms and mainly were seen after treatments involving high-dose muscle injections for spasticity. The patients affected were predominantly children with cerebral palsy and adults with cervical dystonia; cases resulting in death could not be directly linked to either botulinum toxin administration or other underlying conditions [18]. For the intradetrusor injections, the known side effects of the treatment are postoperative pain, procedure-induced urinary tract infections (2 - 32%), mild haematuria (2 - 21%) and increased post-void residual with urinary retention risk (0 - 33%), where clean intermittent catheterisation becomes necessary. Most of the patients suffering from NDO are familiar with this procedure. A systemic reaction to the toxin is possible, with manifestations including generalised muscle weakness, diplopia, dysphagia and dysphonia. Theoretically, potentially lethal paralysis of the respiratory muscles can occur, although it has never been reported [13, 22].

Caution is advised when botulinum toxin is administered in patients with concomitant medication. Drug interactions are common with aminoglycosides, anticholinergic drugs, and muscle relaxants. There is not sufficient evidence for product safety during pregnancy and breastfeeding. However, a recent study showed that in mice with repeated implantation failure due to low endometrial receptivity, botulinum toxin administered

inside the uterine horns induced endometrial angiogenesis, promoting endometrial receptivity and increased embryo implantation rates with no morphologically retarded embryos [16].

For severe cases of botulism, the botulinum antitoxin can be used. It contains antibodies and antibody antigen-binding fragments that block the unbound toxin, so the outcomes are better when it is used early [23]. Unfortunately, the antitoxin is not effective on the already set effects of the toxin.

Efficacy of Retreatment

The patient requests retreatment after approximately 36 weeks due to recurring incontinence episodes in the absence of urinary tract infection. The results of reinjection indicate sustained symptomatic, as well as urodynamic efficacy [13]. The possibility of antibody formation after multiple treatments has become highly improbable after 2001. Once better-purified formulas have been developed, is estimated at 1% or less; however, it does not predict treatment failure [22].

Conclusions

Botulinum toxin is a potent neurotoxin that has become very useful in medical applications during the last years. Research shows that it is a safe and effective treatment for various conditions if used in the correct dosage and in selected patients. Starting from plastic surgery with glabellar lines reduction and hyperhidrosis and reaching more serious disorders such as focal spasticity and cerebral palsy dystonia, the medical uses of botulinum toxin are expanding. In urology, it has brought new perspectives in treating idiopathic or neurogenic detrusor hyper-activity. With increasingly more success shown by trials with off-label usage in dermatology, gastroenterology and chronic pain management, it is expected that a broader range of conditions will benefit from treatment with botulinum toxin in the near future.

Conflict of interest

The authors declare no conflict of interest.

References

1. Abdel-Meguid TA, Botulinum toxin-A injections into neurogenic overactive bladder—to include or exclude the trigone? A prospective, randomised, controlled trial. *J Urol.*, 2010; 184(6): 2423-2428.
2. Baka-Ostrowska M, Bolong DT, Persu C, Tøndel C, Steup A, Lademacher C, Martin N, Efficacy and safety of mirabegron in children and adolescents with neurogenic detrusor overactivity: An open-label, phase 3, dose-titration study. *Neurourol Urodyn.*, 2021; 40(6): 1490-1499.
3. Bo K, Frawley HC, Haylen BT, Abramov Y, Almeida FG, Berghmans B, Bortolini M, Dumoulin C, Gomes M, McClurg D, Meijlink J, Shelly E, Trabuco E, Walker C, An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for the conservative and nonpharmacological management of female pelvic floor dysfunction. *Neurourol Urodyn.*, 2017; 36(2): 221-244.
4. Bottet F, Peyronnet B, Boissier R, Reiss B, Prevaire JG, Manunta A, Kerdraon J, Ruffion A, Lenormand L, Perrouin Verbe B, Gaillet S, Gamé X, Karsenty G; Groupe d'Etude de Neuro-Urologie de Langue Française (GENULF) and the committee of NeuroUrology of the French Association of Urology (AFU), Switch to Abobotulinum toxin A may be useful in the treatment of neurogenic detrusor overactivity when intradetrusor injections of Onabotulinum toxin A failed. *Neurourol Urodyn.*, 2018; 37(1): 291-297.
5. Deffontaines-Rufin S, Weil M, Verollet D, Peyrat L, Amarenco G, Botulinum toxin A for the treatment of neurogenic detrusor overactivity in multiple sclerosis patients. *Int Braz J Urol.*, 2011; 37(5): 642-648.
6. Denys P, Del Popolo G, Amarenco G, Karsenty G, Le Berre P, Padrazzi B, Picaut P, Dysport Study Group, 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. *Neurourol Urodyn.*, 2017; 36(2): 457-462.
7. Drake MJ, Long-term adherence to clinical therapy of overactive bladder. *Transl Androl Urol.*, 2017; 6(3): 602-603.
8. Dressler D, Adib Saberi F, Botulinum toxin: mechanisms of action. *Eur Neurol.*, 2005; 53(1): 3-9.
9. Fowler CJ. Systematic review of therapy for neurogenic detrusor overactivity. *Can Urol Assoc J.*, 2011; 5(5 Suppl 2): S146-S148.
10. Gajdács M, Ábrók M, Lázár A, Burián K, Epidemiology and antibiotic resistance profile of bacterial uropathogens in male patients: a 10-year retrospective study. *Farmacia*, 2021; 69(3): 530-539.
11. Ginsberg D, The epidemiology and pathophysiology of neurogenic bladder. *Am J Manag Care.*, 2013; 19(10 Suppl): s191-s196.
12. Grosse J, Kramer G, Jakse G, Comparing two types of botulinum-A toxin detrusor injections in patients with severe neurogenic detrusor overactivity: a case-control study. *BJU Int.*, 2009; 104(5): 651-656.
13. Karsenty G, Denys P, Amarenco G, De Seze M, Gamé X, Haab F, Kerdraon J, Perrouin-Verbe B, Ruffion A, Saussine C, Soler JM, Schurch B, Chartier-Kastler E, Botulinum toxin A (Botox) intradetrusor injections in adults with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic literature review. *Eur Urol.*, 2008; 53(2): 275-287.
14. Khounlo R, Kim J, Yin L, Shin YK, Botulinum Toxins A and E Inflict Dynamic Destabilisation on t-SNARE to Impair SNARE Assembly and Membrane Fusion. *Structure*, 2017; 25(11): 1679-1686.e5.
15. Kinsey D, Pretorius S, Glover L, Alexander T, The psychological impact of overactive bladder: A systematic review. *J Health Psychol.*, 2016; 21(1): 69-81.
16. Koo HS, Yoon MJ, Hong SH, Ahn J, Cha H, Lee D, Park CW, Kang YJ, Non-invasive Intrauterine

- Administration of Botulinum Toxin A Enhances Endometrial Angiogenesis and Improves the Rates of Embryo Implantation. *Reprod Sci.*, 2021; 28: 1671-1687.
17. Krhut J, Samal V, Nemeč D, Zvara P. Intradetrusor versus suburothelial onabotulinumtoxinA injections for neurogenic detrusor overactivity: a pilot study. *Spinal Cord.*, 2012; 50(12): 904-907.
 18. Kuehn BM, FDA requires black box warnings on labeling for botulinum toxin products. *JAMA.*, 2009; 301(22): 2316.
 19. Lai HH, Rawal A, Shen B, Vetter J, The Relationship Between Anxiety and Overactive Bladder or Urinary Incontinence Symptoms in the Clinical Population. *Urology*, 2016; 98: 50-57.
 20. Manciuc C, Mihai IF, Filip-Ciubotaru F, Lacatusu GA, Resistance profile of multidrug-resistant urinary tract infections and their susceptibility to carbapenems. *Farmacia*, 2020; 68(4): 715-721.
 21. Nambiar A, Lucas M, Chapter 4: Guidelines for the diagnosis and treatment of overactive bladder (OAB) and neurogenic detrusor overactivity (NDO). *NeuroUrol Urodyn.*, 2014; 33 Suppl 3: S21-S25.
 22. Naumann M, Jankovic J, Safety of botulinum toxin type A: a systematic review and meta-analysis. *Curr Med Res Opin.*, 2004; 20(7): 981-990.
 23. O'Horo JC, Harper EP, El Rafei A, Ali R, DeSimone DC, Sakusic A, Abu Saleh OM, Marcelin JR, Tan EM, Rao AK, Sobel J, Tosh PK, Efficacy of Antitoxin Therapy in Treating Patients With Foodborne Botulism: A Systematic Review and Meta-analysis of Cases, 1923-2016. *Clin Infect Dis.*, 2017; 66(suppl_1): S43-S56.
 24. Peyronnet B, Roumigué M, Castel-Lacanal E, Guillotreau J, Malavaud B, Marque P, Rischmann P, Gamé X, Preliminary results of botulinum toxin A switch after first detrusor injection failure as a treatment of neurogenic detrusor overactivity. *NeuroUrol Urodyn.*, 2016; 35(2): 267-270.
 25. Ravichandran E, Gong Y, Al Saleem FH, Ancharski DM, Joshi SG, Simpson LL, An initial assessment of the systemic pharmacokinetics of botulinum toxin. *J Pharmacol Exp Ther.*, 2006; 318(3): 1343-1351.
 26. Ravindra P, Jackson BL, Parkinson RJ, Botulinum toxin type A for the treatment of non-neurogenic overactive bladder: does using onabotulinumtoxinA (Botox®) or abobotulinumtoxinA (Dysport®) make a difference?. *BJU Int.*, 2013; 112(1): 94-99.
 27. Rossetto O, Montecucco C, Tables of Toxicity of Botulinum and Tetanus Neurotoxins. *Toxins (Basel)*, 2019; 11(12): 686: 1-12.
 28. Schick E., Corcos J, (Eds.). Textbook of the Neurogenic Bladder (2nd ed.). CRC Press. 2008; 380-383.
 29. Stoehrer M, Wolff A, Kramer G, Steiner R, Lmöchner-Ernst D, Leuth D, Steude U, Ruebben H, Treatment of neurogenic detrusor overactivity with botulinum toxin A: the first seven years. *Urol Int.*, 2009; 83(4): 379-385.