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Botulinum toxin therapy in urology: historical aspect

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ABSTRACT

The review article shows the main stages of studying botulinum toxin and its use in medicine. The possibilities of using botulinum toxin for the treatment of urological patients are similarly described. Furthermore, the most significant studies on the use of botulinum toxin in patients with neurogenic detrusor c, idiopathic overactive bladder, detrusor sphincter dyssynergia, chronic pelvic pain, benign prostatic hyperplasia, erectile dysfunction, and premature ejaculation are presented.

Keywords: botulinum toxin therapy; botulinum toxin; detrusor overactivity; overactive bladder; detrusor sphincter dyssynergia.

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Ботулинотерапия в урологии. Исторические аспекты

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АННОТАЦИЯ

В обзорной статье показаны основные этапы изучения ботулинического токсина и его использования медицине. Подробно описаны возможности его применения для лечения больных урологического профиля. Представлены наиболее значимые исследования, относящиеся к использованию ботулинического токсина у пациентов с нейрогенной детрузорной гиперактивностью, идиопатическим гиперактивным мочевым пузырем, детрузорно-сфинктерной диссинергией, хронической тазовой болью, доброкачественной гиперплазией предстательной железы, эректильной дисфункцией и преждевременной эякуляцией.

Ключевые слова: ботулинотерапия; ботулинический токсин; детрузорная гиперактивность; гиперактивный мочевой пузырь; детрузорно-сфинктерная диссинергия.

Как цитировать

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BACKGROUND

Botulinum toxin (BT) therapy refers to the therapeutic use of BT. This toxin is a protein produced by the anaerobic bacteria *Clostridium botulinum* and has a powerful neurotoxic effect. This effect is attributed to the ability of BT to block the release of the neurotransmitter acetylcholine from synaptic vesicles and thereby disrupt the transmission of impulses from nerve endings to muscles. BT is one of the most powerful natural poisons. BT has eight different serotypes, coded as A, B, C, D, E, F, G, and H. BT type A (BT-A) is most widely used in various fields of medicine with its three subtypes, namely, onabotulinumtoxin (onaBT-A), abobotulinumtoxin (aboBT-A), and incobotulinumtoxin (incoBT-A).

History of the study of BT

Humanity has been familiar with BT since prehistoric times. Food storage conditions often contribute to the development of *Clostridium botulinum*. Despite reports of many cases of fatal poisoning, the connection between them and food consumption was not recognized in ancient times. Reports of food poisoning increased significantly in the late 18th and early 19th centuries. This was due to the decline in hygienic standards for food production and storage during the Napoleonic Wars. The number of fatal food poisoning cases increased, particularly in southern Germany, which was most affected by military activities. The burden of food poisoning reached such a level that government officials conducted a special investigation and in their report in July 1802 warned of the "harmful effects of consuming smoked blood sausage" [1]. The University of Tübingen joined the study of food poisoning. Wilhelm Gottfried Ploucquet (1744–1814), a senior lecturer at the Faculty of Medicine, suggested that the poisonings were caused by an unknown animal toxin, and Johann Heinrich Ferdinand von Autenrieth (1772–1835), a professor of medicine, initiated an appeal to the government asking for reports from district doctors on all food poisoning cases. Justinus Kerner (1786–1862), who was 29 years old at that time, also submitted his report, which was considered significant and led to its publication as a scientific article [2]. J. Kerner continued to investigate food poisoning and concluded that it was caused by a potentially fatal toxin present in spoiled meat products. He indicated that the toxin is active under anaerobic conditions, disrupts nerve conduction in skeletal muscles, inhibits parasympathetic nervous system function, and can be fatal even in very small doses [3]. Moreover, Kerner anticipated the advent of BT therapy, indicating that the paralytic properties of this toxin could be used to treat diseases that manifest as movement disorders, such as chorea [3].

In the Russian Empire in the 19th century, poisoning cases similar to botulism were also repeatedly described; however, they were associated with fish consumption. In Russia, E.F. Sengbusch (1807–1867) made the first detailed study of these cases. In 1844, he published an article "On Fish Poison," where he summarized fish poisoning cases with clinical manifestations similar to botulism.

Fig. 1. Emile van Ermengem (1851–1932)
Рис. 1. Эмиль ван Эрменгем (1851–1932)

An important scientific step in the study of botulism was the discovery of botulism-producing bacteria in 1895. On December 14, 1895, in the small Belgian village of Ellesel, mass poisoning affecting 34 people occurred, of which three died. All victims had symptoms of botulism (mydriasis, diplopia, dysphagia, and dysarthria with subsequent increase in motor impairment) [4]. The source of the poisoning was considered poor-quality ham, which was sent for examination to Emile van Ermengem, a bacteriologist (Fig. 1). During a microbiological study of the tissues of the deceased and the eaten products, van Ermengem detected anaerobic Gram-positive rod-shaped bacteria, which were named *Bacillus botulinus* (from the Latin *botulus*, which means "sausage"). Van Ermengem published the results of his discovery in 1897 [5].

In 1910, the German microbiologist Julius Leuchs identified different strains of *Bacillus botulinus* [6], and in 1919, Georgina Burke proposed designating them as types A and B [7]. In the late 1910s and early 1920s, the mechanism of biological action of BT received significant research attention. In 1924, studies established that BT caused a complete curare-like blockade of the motor nerve endings in striated muscles, causing their paralysis [8]. Early damage to the diaphragmatic muscles leading to respiratory depression and death was also detected. In the same year, at the suggestion of bacteriologist Ida Bengstrom, the name of the botulism pathogen *Bacillus botulinus* was changed to *Clostridium botulinum* (from the Greek word "kloster," which means "spindle").

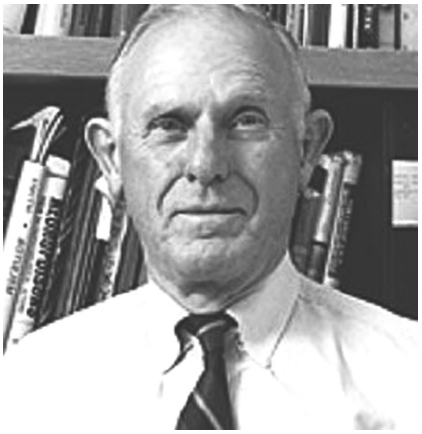

Fig. 2. Alan Scott (1932–2021)
Рис. 2. Алан Скотт (1932–2021)

Use of BT in medicine

Significant progress in the study of botulism was made during World War II, when both the possibility of using BT as a biological weapon and protection methods against it were studied. American researchers Carl Lamanna and Richard Duff developed a method for obtaining and crystallizing BT, and Edward J. Schantz proposed a technology for obtaining purified BT in a volume sufficient for use in clinical trials.

In 1949, the English pharmacologist Arnold Burgen (1922–2022) established that the paralytic effect of BT is caused by its effect on neuromuscular synapses by blocking the release of acetylcholine [9]. In 1964, American neurologist Daniel B. Drachman (1932–2022) demonstrated for the first time, through an experiment, that BT-A injections can cause muscle weakness and muscle atrophy [10]. The results of D. Drachman's research attracted the attention of ophthalmologist professor Alan Scott (1932–2021; Fig. 2), who was involved in the treatment of strabismus. In 1973, he presented the results of experimental studies where he demonstrated that BT injection into the extraocular muscles leads to a decrease in their tone [11]. In 1980, A. Scott published the results of a study involving 67 patients with strabismus, in whom BT administration into certain muscle fibers of the eye was accompanied by a significant clinical effect [12]. Later, in the 1980s, A. Scott et al. showed that BT injections into the facial muscles were also effective in the treatment of blepharospasm and hemifacial spasm.

The results of these studies were the basis for regulatory agencies to recognize BT as a drug. On December 29, 1989, BT-A was approved by the FDA for the treatment of strabismus, blepharospasm, and hemifacial spasm in patients aged ⩾12 years. Subsequently, the indications for the BT therapy were significantly expanded, and it began to be used to treat migraines, axillary hyperhidrosis, limb spasticity, and muscle dystonia and in cosmetology.

Use of BT in urology

The first report on the use of BT therapy for urological diseases dates back to 1988. That year, Dennis Dykstra et al. published the results of a study on the efficiency of onaBT-A injections into the external urethral sphincter in patients with detrusor–sphincter dyssynergia caused by a result of spinal injury [13]. Twelve years later, in 2000, Swiss researchers from the University of Zurich demonstrated the effectiveness of intradetrusor injections of onaBT-A in 31 patients with spinal cord injury and **neurogenic detrusor overactivity (NDO)** [14]. The administration of onaBT-A in doses of 200 and 300 U led to an increase in the maximum capacity of the bladder and a significant decrease in the maximum detrusor pressure in the emptying phase. For a long time, the possibilities of BT therapy were studied specifically in patients with NDO [15, 16]. In 2005, the results of the first randomized, placebo-controlled study of the efficacy and safety of intradetrusor injections of onaBT-A (200 or 300 U) in patients with urgent urinary incontinence caused by NDO were published [16]. The use of onaBT-A led to significant reductions in the frequency of urinary incontinence, increases in maximum cystometric capacity, and improvement in the quality of life compared with the control treatment. The results of subsequent phase III clinical trials [17, 18], which involved 691 patients with NDO caused by spinal injury or multiple sclerosis, confirmed the efficacy and safety of onaBT-A, and a dose of 200 U was considered optimal for use in these patients. These results were the basis for the FDA to approve the use of onaBT-A at a dose of 200 U in August 2011 for the treatment of NDO-related urinary incontinence in patients in whom anticholinergic therapy was ineffective or its tolerance was unsatisfactory. In 2022, based on the results of multicenter phase III clinical trials CONTENT1 and CONTENT2, which involved 485 patients [19], regulatory approvals were received in many countries, including Russia, for the use of aboBT-A in doses of 600 and 800 U in patients with neurourological problems. The drug is indicated for NDO-related urgent urinary incontinence in patients with spinal injury or multiple sclerosis who undergo intermittent bladder catheterization [20].

In 2001, P. Radziszewski et al. reported the first experience of BT therapy for **idiopathic detrusor overactivity** and urge urinary incontinence [21]. In 2007, the results of the first randomized placebo-controlled study were published, which compared the efficiency of 200 U onaBT-A and placebo in patients with idiopathic detrusor overactivity [22]. Patients who received intravesical onaBT-A injections showed a significant decrease in the frequency of urination and severity of urge urinary incontinence, which was accompanied by an increase in the maximum cystometric capacity. In 2010, the results of a randomized, placebo-controlled study were presented, which assessed the outcomes of using several doses of onaBT-A

(50, 100, 150, 200, and 300 U) and placebo in 313 patients with idiopathic overactive bladder (IOB) refractory to standard anticholinergic therapy [23]. The administration of onaBT-A, regardless of its dose, showed a significant advantage over placebo, whereas the administration onaBT-A at a dose of 100 U was recognized as optimal in terms of the ratio of efficacy and safety. The results of other clinical studies also indicated the advisability of administering onaBT-A at a dose of 100 U for idiopathic IOB [24–28]. The data obtained were the basis for the FDA to approve onaBT-A administration at a dose of 100 U in patients with IOB in January 2013. Subsequently, onaBT-A administration in the indicated dose for the treatment of patients with IOB was approved by regulatory authorities in other countries, including Russia, and included in clinical guidelines for the treatment of urinary incontinence. Currently, BT therapy has become widespread in clinical practice as an effective and well-tolerated method for the treatment of neurogenic and non-neurogenic IOB [29].

In urology, BT therapy was first applied in patients with **detrusor-sphincter dyssynergia** in 1988 [13]. However, the first randomized, double-blind, placebo-controlled study of the effectiveness of BT therapy in such patients was completed only in 2005 [30]. It compared the efficiency of onaBT-A administered at a dose of 100 U and placebo, which were administered transperineally into the external urethral sphincter of 86 patients with multiple sclerosis. On day 30 after injection, the onaBT-A group showed an increase in the voided volume and a decrease in the maximum detrusor pressure and detrusor opening pressure; however, no difference in the residual urine volume was registered. Subsequently, several observational studies have shown the effectiveness of transurethral, transrectal, or transperineal injections of onaBT-A at a dose of 100 U into the external urethral sphincter in patients with detrusor-sphincter dyssynergia [31–34]. In some of these studies, the residual urine volume decreased in patients with spinal cord injury after onaBT-A injections, which has not been previously reported in patients with multiple sclerosis. In general, studies evaluating the efficiency of BT therapy in patients with detrusor–sphincter dyssynergia reported contradicting results, which is apparently due to differences in the research design, participant characteristics, and injection techniques. These circumstances limit the wider use of BT in these patients and require further research in this field.

The use of BT to treat patients with **benign prostatic hyperplasia** (BPH) was first reported in 2003 [35]. In a randomized placebo-controlled study, 30 men with symptomatic BPH received transperineal injections of onaBT-A at a dose of 200 U or placebo. After 2 months, the onaBT-A group demonstrated a significant clinical improvement in the parameters. A multicenter 12-week phase II clinical trial compared the efficacy and safety of transrectal injections of onaBT-A at doses of 100 and 300 U in 134 patients with BPH [36]. A positive effect was registered in 73% of patients in the 100 U group and 81% in the 300 U group. However, no significant changes in the prostate volume or prostate-specific antigen levels were revealed.

The results of the first studies were very promising, which was the basis for two large randomized placebo-controlled studies, which involved 492 patients with BPH [37, 38]. M. Marberger et al. [37] injected onaBT-A into the prostate transperineally and transrectally at doses of 100, 200, and 300 U; and K.T. McVary et al. [38] conducted transrectal injections at a dose of 200 U. In both studies, after onaBT-A injections, a significant clinical improvement was noted compared with the baseline level; unexpectedly, no differences were noted between the treatment and placebo groups. A subsequent meta-analysis of placebo-controlled studies also confirmed a pronounced placebo effect [39]. Thus, from the point of view of evidence-based medicine, the efficiency of BT in patients with BPH is not confirmed; therefore, this treatment method is not included in clinical recommendations. Moreover, the use of BT therapy for BPH is still the focus of several recent studies [40, 41].

In 2004, the results of the first study on the possibility of using intravesical BT therapy in patients with **painful bladder syndrome/interstitial cystitis (PBS/IC)** were first published [42]. Of the 13 total patients (all women) who participated in the study, seven received aboBT-A injections into the submucosal layer of the bladder wall, and six received onaBT-A. In this study, 5–7 days after the injections, the patients noted a decrease in pain severity, and the average duration of the effect was 3.7 months. The encouraging results gave rise to other studies in this field. In 2006, A. Giannantoni et al. achieved a positive result in 85.7% of patients with PBS/IC who received onaBT-A injections at a dose of 200 U into the submucosal layer of the triangle and body of the bladder [43]. The effectiveness of BT therapy was noted in patients with both non-ulcerative and ulcerative PBS/IC [44], with injections only into the bladder triangle [45], as well as in combination with bladder hydrodistension [46].

The first double-blind, placebo-controlled multicenter study of the effectiveness of BT therapy in patients with non-ulcerative PBS/IC refractory to standard therapy was completed in 2016 [47]. The study involved 60 patients, randomized into two groups of 30 people each, who received suburothelial onaBT-A injections at a dose of 100 U and placebo, respectively. After 8 weeks, the main group, compared with the control group, showed a significant decrease in the severity of pain syndrome and an increase in the maximum cystometric capacity. Another study confirmed the effectiveness of

the onaBT-A dose of 100 U in the treatment of patients with PBS/IC [48]. Currently, BT therapy is included in the clinical guidelines for the treatment of PBS/IC by many urological associations [49, 50].

The efficiency of BT therapy in the treatment of patients with **chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)** was first noted in 2000 in a small study that demonstrated pain reduction in the prostate gland and urethra after transurethral injections of onaBT-A at a dose of 200 U into the perisphincteric area [51]. In another study, a positive effect was achieved after onaBT-A injections at a dose of 100 U into the perineal muscles [52]. In the case of CP/CPPS accompanied with impaired urine outflow from the bladder, good results were obtained after onaBT-A administration at a dose of 100 U into the external urethral sphincter [53]. The results of the first double-blind, placebo-controlled clinical trial of the efficacy of BT therapy in patients with CP/CPPS refractory to traditional drug therapy were published in 2015 [54]. Patients received transurethral onaBT-A injections at a dose of 100 U or placebo into the prostate gland. Compared with the control group, the main group showed significant pain reduction, a decrease in the frequency of urination, and an improvement in the quality of life. In another study, the transrectal administration of BT into the prostate in patients with CP/CPPS led to better clinical results than the transurethral route [55].

The first report on BT therapy in women with CPPS due to the hypertonicity of the pelvic muscles dates back to 2004. S.K. Jarvis et al. revealed that onaBT-A administration at a dose of 40 U to the *m. levator ani* resulted in reduced pain severity [56]. In 2006, the results of the first double-blind, placebo-controlled, randomized clinical trial of the effectiveness of BT in these patients were published [57]. Women who received onaBT-A injections at a dose of 80 U into the pelvic diaphragm noted not only a decrease in pain compared with the control group but also a decrease in the severity of dyspareunia and an improvement in sexual function compared with the placebo group.

In recent years, the possibilities of BT therapy in patients with erectile dysfunction that is poorly or unresponsive to standard treatment have attracted great interest. Randomized controlled [58–60] and uncontrolled [61, 62] clinical studies have shown the effectiveness of single intracavernous injections of BT-A in such patients (onaBT-A in doses of 50 and 100 U, aboBT-A in doses of 250 and 500 U, and incoBT-A in a dose of 100 U); thus, this treatment method may be very promising.

The possibilities of using BT therapy in the treatment of **premature ejaculation** are being studied. In 2010, E.C. Serefoglu et al. reported the effectiveness of BT injections into the *m. bulbospongiosus* in these patients [63]. However, further studies, including those conducted in recent years, have yielded less clear results [64, 65]; thus, the effectiveness of BT therapy in patients with premature ejaculation is still unclear.

CONCLUSION

The history of the development of BT therapy is a unique event in clinical medicine and pharmacology. This is one of the most dangerous toxins that has been proven to be extremely effective and relatively safe for the treatment of several diseases. Currently, BT is present in the arsenal of doctors of various specialties, including urologists. Numerous studies have demonstrated the therapeutic capabilities of BT in urology, providing a reliable evidence base for its clinical use. BT therapy is most widely used in the treatment of detrusor overactivity and IOB, and the potential of this treatment method is much wider. Further studies on the effectiveness and safety of BT in the treatment of chronic pelvic pain, detrusor–sphincter dyssynergia, BPH, erectile dysfunction, premature ejaculation, etc., for which BT therapy may be very useful are warranted.

ADDITIONAL INFORMATION

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. Personal contribution of each author: G.G. Krivoborodov, M.N. Slesarevskaya, N.S. Efremov, A.A. Gontar — search and analysis of literary data, editing the text of the manuscript; I.V. Kuzmin — search and analysis of literary data, writing the text of the manuscript.

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Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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