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The role of botulinum toxin in the treatment of diseases beyond aesthetics: migraine, hyperhidrosis and bruxism - literature review

Rola toksyny botulinowej w leczeniu schorzeń poza medycyną estetyczną: migrena, nadpotliwość i bruksizm - przegląd literatury

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Streszczenie

W XIX wieku toksyna botulinowa była postrzegana wyłącznie jako silna trucizna. Późniejsze badania umożliwiły jej użycie w praktyce medycznej. Obecnie znajduje szerokie zastosowanie przede wszystkim w medycynie estetycznej. Jej potencjał terapeutyczny wykracza jednak daleko poza zabiegi kosmetyczne. Niniejszy artykuł przeglądowy analizuje zastosowanie toksyny botulinowej w leczeniu migreny, bruksizmu oraz nadpotliwości. W wymienionych schorzeniach toksyna botulinowa wykorzystywana jest głównie jako terapia objawowa, szczególnie w przypadkach, gdy leczenie pierwszego rzutu okazuje się nieskuteczne. W celu zapewnienia kompleksowego podejścia omówiono w artykule patofizjologię tych zaburzeń, standardowe schematy leczenia oraz mechanizmy działania toksyny botulinowej w łagodzeniu objawów. Przedstawiono również aktualne wytyczne towarzystw naukowych dotyczące lokalizacji iniekcji oraz ich częstotliwości. Dodatkowo omówiono rodzaje stosowanych preparatów toksyny botulinowej, odpowiednie dawkowanie, koszty terapii, możliwe działania niepożądane oraz wyzwania związane z trwałością efektów terapeutycznych. Z uwagi na wysokie koszty leczenia i konieczność wielokrotnych iniekcji w stosunkowo krótkich odstępach czasowych, dalsze badania nad optymalizacją terapii są w pełni uzasadnione. W celu zwiększenia dostępności tej metody

terapeutycznej, należy rozważyć opracowanie nowych protokołów leczenia, które zmniejszyłyby częstotliwość podawania toksyny botulinowej, bądź wprowadzenie preparatów o wydłużonym czasie działania.

Abstract

In the 19th century, botulinum toxin was recognized solely as a poison. Subsequent research led to its medical applications, and today, it is predominantly utilized in aesthetic medicine. However, its therapeutic potential extends beyond cosmetic procedures. This review examines the use of botulinum toxin in the management of migraine, bruxism, and hyperhidrosis. In these conditions, botulinum toxin primarily serves as a symptomatic treatment, often considered when first-line therapies fail. To provide a comprehensive understanding, this article discusses the pathophysiology of these disorders, standard treatment protocols, and the mechanisms by which botulinum toxin alleviates symptoms. Guidelines from scientific societies regarding injection frequency and anatomical sites are outlined. Additionally, the type of botulinum toxin, dosage, treatment costs, potential adverse effects, and challenges related to treatment durability are reviewed. Further research on botulinum toxin is warranted, as the therapy is associated with high costs and necessitates multiple injections in close succession. To improve accessibility, therapeutic protocols that reduce the number of injections should be developed, or formulations with an extended duration of action should be introduced.

Słowa kluczowe: Toksyna Botulinowa, migrena, bruksizm, nadpotliwość, użycie pozakosmetyczne, BoNT A

Keywords: Botulinum toxin, migraine, bruxism, hyperhidrosis, beyond cosmetics, BoNT A

1. Introduction

Botulinum toxin (BoNT) is a neurotoxin produced by the bacterium *Clostridium botulinum*.(Phan K et al. 2022) It was first described by Justinus Kerner in 1820 as 'sausage poisoning.' The bacterium responsible for its production was isolated in 1895 by van Ermengem from a piece of ham that had poisoned 34 individuals.(Watson NA et al. 2021) The initial medical application of botulinum toxin was pioneered by Alan B. Scott, who injected it into the oculomotor muscles to treat strabismus. Subsequently, the U.S. Food and Drug Administration (FDA) approved BoNT for therapeutic use in 1989. This approval catalyzed significant advances in BoNT research, developing new therapeutic formulations and expanding indications for its use.(Choudhury S et al. 2021)

In contemporary practice, BoNT is often associated with aesthetic medicine due to its widespread use in cosmetic procedures, which are frequently covered by the media. BoNT-based treatments are among the most commonly performed aesthetic interventions.(Hong SO 2023) However, botulinum toxin has several other clinical applications that offer substantial therapeutic benefits. The FDA has approved its use for conditions such as eyelid spasm, hemifacial spasm, strabismus, torticollis, migraine, hyperhidrosis, limb spasticity, and

overactive bladder. Additionally, numerous off-label uses, including the treatment of bruxism and postherpetic neuralgia, have been reported.(Choudhury S et al. 2021)

This article reviews recent scientific literature concerning the therapeutic applications of botulinum toxin beyond aesthetic medicine. It highlights its potential role in minimally invasive therapies, particularly in cases where conservative treatments have proven ineffective. Furthermore, the article explores BoNT as an alternative or adjunctive treatment, with a specific focus on conditions such as migraine headaches, hyperhidrosis, and bruxism.

2. Division of BoNT Types

BoNT consists of two peptide chains connected by a disulfide bond. The complete protein structure comprises three distinct domains—two located within the heavy chain and one in the light chain. The C-terminal domain of the heavy chain facilitates toxin binding to receptor sites, while the N-terminal domain is responsible for translocation.(Kumar R. et al. 2016) The light chain functions as a catalytic unit. The toxin molecule is surrounded and stabilized by naturally occurring proteins, enhancing its stability.(Jabbari B. 2017)

Based on serological properties, BoNTs are classified into seven serotypes, designated A through G. Among these, BoNT A, BoNT B, BoNT E, and BoNT F are known to cause botulism in both humans and animals. Conversely, BoNT C and BoNT D primarily affect domestic animals. BoNT G-producing organisms have been isolated from soil but have not been implicated in causing botulism. The U.S. FDA has approved at least six BoNT formulations for clinical use. Notably, for various indications, BoNT A and BoNT B are utilized in medical treatments.(Choudhury S et al. 2021)

3. Mechanism of Action of BoNT at the Cellular Level

After injection, BoNT enters the extracellular space, where its heavy chain binding domain attaches to polysialogangliosides on the cell surface. The toxin is subsequently internalized through binding to another surface receptor, such as synaptotagmin or glycosylated synaptic vesicle proteins, and enters synaptic vesicles. Acidification of these vesicles, facilitated by proton pumps, activates proteins responsible for transporting acetylcholine from the cytosol into their interior.

In the absence of BoNT, synaptic vesicles fuse with the presynaptic membrane, releasing acetylcholine into the synaptic cleft. BoNT inhibits this process by translocating its light chain into the cytoplasm, which is activated by heat shock proteins and the thioredoxin reductase system. The active light chain cleaves and inactivates the transmembrane SNARE proteins, including vesicle-associated membrane protein (VAMP), synaptosomal-associated protein 25 (SNAP-25), and syntaxin. These proteins are critical for vesicle fusion with the synaptic membrane, and their inactivation prevents acetylcholine release into the synaptic space.(Jabbari B. 2018)

Beyond blocking acetylcholine release, BoNT also inhibits the release of other substances carried by small synaptic vesicles, such as glutamate. Additionally, it affects large dense-core vesicles, preventing the release of calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating polypeptide 38 (PACAP-38), and substance P. BoNT also disrupts the transport of proteins and receptors, including transient receptor potential vanilloid 1 (TRPV1), transient receptor potential ankyrin 1 (TRPA1), and purinergic receptor P2X3, which are crucial for nociception.(Choudhury S et al. 2021)(Jabbari B. 2017)

4. Migraine

Migraine is a genetically determined neurological disorder characterized by unilateral headaches of moderate to severe intensity. These headaches are frequently accompanied by nausea and heightened sensitivity to light. Migraine attacks can last from several hours to several days, significantly impacting patients' quality of life.(Pescador Ruschel MA et al. 2024) Migraines can be classified into the following categories: migraine without aura, migraine with aura, chronic migraine, probable migraine, and migraine-related episodes.

The etiology of migraine is complex and involves polygenic inheritance, with migraines occurring three times more frequently in genetically related individuals.(de Vries B et al. 2016) Additionally, migraines may be triggered by factors such as stress, hormonal fluctuations, irregular meals, specific foods, or weather changes.(Pavlovic 2014) While the exact pathophysiology of migraines remains incompletely understood,

several theories have been proposed. These include activation of afferent fibers of the trigeminal nerve associated with the brain's soft pia mater, cortical spreading depression as described by Leão, secretion of vasoactive neuropeptides such as substance P, calcitonin gene-related peptide (CGRP), and neurokinin A, as well as alterations in serotonin levels.(Karatas H et al. 2013)(Matsuda M et al. 2019)(Deen M et al. 2018)

Migraines affect approximately 12% of the population, with a higher prevalence in women than men. The peak incidence occurs between the ages of 35 and 39.(Pescador Ruschel MA et al. 2024)

Treatment of migraines is divided into two main approaches:

1. Acute treatment of migraine attacks.
2. Preventive treatment to reduce attack frequency, severity, and duration.

Acute treatment involves the use of analgesics such as paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen, naproxen, and diclofenac, for mild to moderate pain. For more severe cases or those unresponsive to NSAIDs, triptans, such as sumatriptan and zolmitriptan, are considered first-line therapies. Studies indicate that approximately 75% of patients benefit from triptan therapy.(Singh RBH et al. 2020) These medications can be administered via multiple routes, including intranasally, which is advantageous for patients experiencing nausea or vomiting. Adjunctive antiemetics, such as metoclopramide or chlorpromazine, may also be used in these patients. Newer agents such as gepants (CGRP antagonists) and ditans (selective serotonin 1F receptor agonists) may be effective for refractory cases. Ergotamine and dihydroergotamine are still available but are associated with more side effects.(Pescador Ruschel MA et al. 2024)

Preventive treatment aims to reduce migraine frequency, intensity, and duration by identifying and avoiding triggers.(Ha H et al. 2019) Medications used for prevention include beta-blockers, antidepressants (e.g., amitriptyline, venlafaxine), anticonvulsants (e.g., valproic acid), calcium channel blockers, CGRP antagonists, and BoNT.(Pescador Ruschel MA et al. 2024)

5. BoNT A in Migraine

BoNT A is indicated for the treatment of chronic migraine, defined as headaches occurring at least 15 days per month for more than three months, with migraine features present on at least eight days per month.(Cephalalgia 2018) In 2016, the American Academy of Neurology recommended BoNT A for chronic migraine treatment. In 2018, the European Headache Federation endorsed its use following the failure of two to three prophylactic medications.(Simpson D.M et al. 2016)(Bendtsen L. et al. 2018)

During migraine attacks, C-type fibers in the dura are activated by cortical spreading depression. These fibers release CGRP, which increases sensitization and can activate A-type pain fibers. Signals are transmitted to the trigeminocervical complex in the brainstem, activating second-order neurons in trigeminal sensory pathways, ultimately resulting in headaches.(Becker WJ 2020)

Several mechanisms of action of BoNT A in migraine therapy have been proposed. Sensory neurons in the head have branches terminating both at the dura mater and extracranially through cranial sutures or emissary canals. BoNT A injections into these extracranial sites may modulate pain signaling from intracranial sources.(Zhang X. et al. 2016) Additionally, BoNT A reduces CGRP release, diminishing sensitization of C- and A-type fibers and lowering blood CGRP levels, thus reducing migraine frequency. Peripheral blockade of extracranial nerve conduction may also contribute to pain relief.(Cernuda-Morollón E. et al. 2015)(Pellesi L. et al. 2020)

The PREEMPT protocol (Phase III Research Evaluating Migraine Prophylaxis Therapy) recommends 31 injections of 5 units each into the frontal, temporal, occipital, upper neck, and trapezius regions. An additional eight injections may be administered based on pain localization (“follow the pain” approach). Treatments are

repeated every 12 weeks. Proper injection technique is critical to minimize adverse effects. Treatment response is evaluated four weeks before and after therapy. Discontinuation is advised if headache frequency decreases to fewer than 10 days per month for three consecutive months. Patients should be reassessed after 4-5 months to monitor for recurrence of chronic migraine.(Blumenfeld A.M et al. 2020)

According to Ching J et al., early intervention during the clinical course of chronic migraine may improve the likelihood of achieving remission and discontinuing BoNT therapy.(Ching J. et al. 2019) BoNT treatment may be particularly beneficial for patients who are unresponsive to first-line therapies or have contraindications to oral medications.(Hoffmann J et al. 2014)

In the PREEMPT trials, BoNT A improved quality of life by 44% at week 25 and by 59% at week 56. Among 688 participants, 49.3% reported at least a 50% reduction in headache frequency following the first injection cycle.(Silberstein et al. 2013) BoNT A has also demonstrated synergistic effects with triptans, enhancing their efficacy.(Eren OE et al. 2020)

Despite its benefits, BoNT A lacks specificity, affecting both sensory and motor neurons. To avoid paralytic side effects, low doses are required. Developing BoNT formulations targeting only sensory fibers could enhance therapeutic efficacy and allow higher dosing.(Becker WJ 2020) Transdermal BoNT formulations are also under investigation.(Fonfria E. et al. 2018)

BoNT therapy is costly, with an estimated annual expense of $3,000.(Fonfria E. et al. 2018) Side effects, although infrequent, include eyelid ptosis (2%), neck pain (4%), and muscle weakness (3%). Overall, BoNT A is well tolerated and considered a viable treatment option for chronic migraine.(Yalinay Dikmen P. et al. 2018)(Pallapothu MR et al. 2023)

6. Bruxism

Bruxism is a common disorder characterized by excessive activity of the masseter muscles, resulting in clenching or grinding of the teeth. It presents in two forms: sleep bruxism and awake bruxism. Approximately 20% of the population experiences daytime bruxism, while 10% are affected by nocturnal bruxism.(Malcangi G et al. 2023)

The primary symptoms include headaches, temporomandibular joint pain, masseter muscle pain, excessive mechanical wear of the teeth, prosthetic complications, tooth fractures, hypertrophy of the masticatory muscles, and restricted mouth opening.(Fernández-Núñez T et al. 2019)(Lal SJ et al. 2024) The etiology of bruxism is multifactorial and may involve genetic predisposition, psychological factors (e.g., stress, emotional tension), anatomical abnormalities of the oral cavity, and alterations in central nervous system function.(Matusz K et al. 2022)

The diagnosis of bruxism requires a comprehensive evaluation, including a detailed medical history, standardized questionnaires, clinical examination, and supplementary diagnostic tests such as electromyography (EMG) and polysomnography to assess masticatory muscle activity during sleep. EMG recordings of masticatory muscle activity serve as an objective diagnostic tool, and when combined with polysomnography, they represent the gold standard for diagnosis. Diagnostic criteria include the presence of clenching and grinding of teeth during sleep, accompanied by at least one additional symptom, such as excessive tooth wear, grinding sounds reported by household members, or increased muscle tension in the facial and cervical regions.(Lobbezoo F et al. 2018)

Treatment is indicated when bruxism leads to detrimental effects on oral structures or when patients report pain-related symptoms.(Lal SJ et al. 2024) The primary treatment objective is muscle relaxation, which can be achieved through various interventions. First-line therapy includes behavioral modifications, psychotherapy (focusing on stress reduction and lifestyle adjustments), and relaxation techniques aimed at alleviating muscle tension. Occlusal splints are commonly prescribed to prevent mechanical damage to the dentition. In cases where conservative measures are insufficient, pharmacological therapy, such as clonazepam (0.5 mg) or clonidine (0.1 mg), may be considered; however, due to limited evidence supporting their efficacy, these medications are not routinely recommended. An alternative treatment option is BoNT A injection, which has been shown to

significantly reduce muscle spasm intensity, thereby improving patient-reported outcomes, including sleep quality and overall satisfaction.(Ali SM et al. 2021)(Choudhury S et al. 2021)(Lal SJ et al. 2024)

7. BoNT A in Bruxism

BoNT A can be administered via intramuscular or intradermal injection. When delivered intramuscularly, the toxin induces proteolysis of SNAP-25, thereby inhibiting acetylcholine release at the neuromuscular junction. This results in a reduction in muscle contraction strength and partial, temporary muscle paralysis, typically lasting for several months until repeat therapy is required. BoNT-A affects neurotransmission at chemical synapses within both the peripheral and central nervous systems.[Choudhury S et al. 2021)(Malcangi G et al. 2023)

During BoNT A administration, small doses are used to localize the effect to the targeted area. The maximum therapeutic effect is typically observed 2–6 weeks post-injection and persists for approximately 2–4 months. BoNT A reduces the force exerted by the masseter muscles, as measured at the point of contact between antagonist teeth during occlusion.(Matusz K et al. 2022) In cases of sleep bruxism, BoNT A decreases the intensity of muscle contractions without altering their frequency. This approach is considered effective in reducing the intensity of masticatory muscle contractions, particularly when combined with occlusal splints.(Shim YJ et al. 2020)

The administration of approximately 12–18 units of BoNT A into the ventral portion of the masseter muscle effectively reduces hypertrophy and alleviates morning headaches.(Malcangi G et al. 2023) Reported adverse effects include pain at the injection site, xerostomia, speech difficulties, localized muscle weakness, dysphagia, and ecchymosis.(Da Silva Ramalho J.A. et al. 2023)(Ondo W.G. et al. 2018)(Yurttutan M.E. et al. 2019) Additionally, treatment with BoNT-A is associated with significant financial costs.(Malcangi G et al. 2023)

8. Hyperhidrosis

Hyperhidrosis is a chronic autonomic disorder characterized by excessive stimulation of cholinergic receptors on eccrine glands, resulting in sweat production exceeding the amount required for thermoregulatory homeostasis.(Sammons JE et al. 2017) Due to the high concentration of eccrine glands in the axillae, palms, face, and soles, these areas are the most commonly affected. Hyperhidrosis affects approximately 3% of the American population, with the highest prevalence observed in individuals aged 20 to 60 years.(Strutton DR et al. 2004)(Martina E et al. 2021)

Hyperhidrosis is classified into primary and secondary forms. The etiology of primary hyperhidrosis remains unclear, although genetic predisposition is considered a significant contributing factor. Symptoms typically manifest in younger individuals. Secondary hyperhidrosis may result from various underlying conditions, including medication use, diabetes mellitus, hyperthyroidism, Parkinson's disease, tuberculosis, pheochromocytoma, lymphoma, and menopause. The disorder is associated with excessive sympathetic nervous system activity, leading to acetylcholine release from nerve endings. Cholinergic stimulation of muscarinic receptors induces sweating. The thermoregulatory center of the hypothalamus plays a key role in the sympathetic innervation of sweat glands.(Romero FR et al. 2016)(Brackenrich J et al. 2022)(Menzinger S et al. 2017)

Diagnosis is established through clinical evaluation, supplemented by quantitative assessment scales for sweat production. Diagnostic criteria for primary hyperhidrosis include a duration of at least six months, involvement of the axillae, palms, soles, or face, bilateral and symmetrical distribution, absence of nocturnal sweating, onset before the age of 25 years, positive family history, and impairment of daily activities. In cases where a secondary cause is suspected, further investigations should be conducted to exclude infectious diseases, renal disorders, malignancies, diabetes mellitus, and thyroid dysfunction.(Brackenrich J et al. 2022)(Romero FR et al. 2016)

Management options include topical and systemic therapies. First-line treatment consists of over-the-counter aluminum chloride hexahydrate 20%, applied nightly for three to four days, followed by maintenance therapy as needed. However, skin irritation may occur as an adverse effect. Recently, topical glycopyrronium tosylate has been approved for the treatment of hyperhidrosis. In patients unresponsive to topical therapy, oral anticholinergic agents such as oxybutynin (5–10 mg/day) or topical glycopyrrolate (0.5–2.0%) may be considered. For

refractory cases, botulinum toxin type A injections have demonstrated efficacy.(Brackenrich J et al. 2022)(Fujimoto T. 2016)(Delort S et al. 2017)

9. BoNT A in Hyperhidrosis

Botulinum toxin type A was approved by the U.S. FDA in 2004 for the treatment of primary severe hyperhidrosis localized to the axillary region.(Chen S. 2012) Research has demonstrated its off-label efficacy in treating hyperhidrosis affecting the hands, feet, trunk, and face.(Perez-Bernal AM et al. 2005)(Kim WO et al. 2009)(Komericki P et al. 2012)

BoNT A exerts its effect by cleaving the SNAP-25 protein, thereby inhibiting the presynaptic fusion and binding acetylcholine vesicles to nerve endings. This process prevents the release of acetylcholine and subsequently blocks neural stimulation of the sweat glands, leading to a marked reduction in sweat production within the treated area. The duration of reduced sweating ranges from six to 24 months.(Brackenrich J et al. 2022)

BoNT A is administered via intradermal injection, ensuring targeted action on the sweat glands. The injection depth varies depending on the anatomical site, with the dermal-subcutaneous junction in the axillary region reaching approximately 2 mm, while in the plantar region, it extends to 4.5 mm. The Minor's test (starch-iodine) or Ponceau Red staining may be utilized to delineate the affected area accurately. The number of injections is determined by the severity of symptoms and the surface area requiring treatment, with injection volumes typically ranging from 0.1 to 0.2 mL.

Higher injection volumes may lead to diffusion beyond the targeted area, potentially resulting in unintended denervation. Adverse effects are generally mild, including pain, hematoma, bruising, headache, myalgia, pruritus, and urticaria. Additionally, compensatory sweating occurs in approximately 5% of patients. A reduction in sweating is usually observed within 7 to 10 days post-treatment and persists for approximately 6 to 10 months. Following BoNT A injection into the axillary region, patient satisfaction rates range from 66% to 100%.(Nawrocki S et al. 2020)

The primary drawbacks of BoNT A therapy include its high cost and the necessity for repeated treatments to maintain efficacy.(Brackenrich J et al. 2022) Isla-Tejera B et al. compared the cost of treating hyperhidrosis with endoscopic thoracic sympathectomy versus BoNT A over one and five years, concluding that the cost of BoNT A treatment was higher than that of surgical intervention.(Isla-Tejera B et al. 2013)

BoNT A provides symptomatic relief by inhibiting sweat gland activity but does not address the underlying cause of hyperhidrosis. Once treatment is discontinued, symptoms typically recur. Severe hyperhidrosis significantly impairs quality of life, affecting both mental and physical well-being. Patients frequently experience stress, embarrassment, and social or professional difficulties, further diminishing their overall well-being.(Brackenrich J et al. 2022)

10. Conclusions

Botulinum toxin therapy has demonstrated efficacy in the management of various conditions beyond the scope of aesthetic medicine. It is primarily employed as an alternative therapeutic option when first-line treatments prove ineffective. The effectiveness and therapeutic potential of BoNT are supported by numerous recommendations from regulatory agencies and scientific societies.

Although botulinum toxin is among the most potent neurotoxins known, its clinical use is associated with a relatively low incidence of adverse effects. However, its primary limitations include high costs and the requirement for frequent injections at short intervals. Further research is needed to develop cost-effective strategies to improve accessibility for a broader patient population. Additionally, efforts should focus on optimizing treatment protocols to reduce the frequency of injections or extend the duration of BoNT's therapeutic effects, thereby enhancing patient convenience and compliance.

Disclosure:

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