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THE ROLE OF BOTULINUM TOXIN IN CHRONIC MIGRAINE: A NARRATIVE REVIEW

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ABSTRACT

BACKGROUND

Migraine is a chronic and highly disabling neurological disorder and one of the leading causes of years lived with disability worldwide. Chronic migraine is associated with substantial impairment of quality of life, social functioning and mental health, and remains a major therapeutic challenge due to limited efficacy and tolerability of many preventive treatments.

AIMS

The aim of this narrative review was to synthesize current evidence on the role of botulinum toxin type A in the management of migraine, with a primary focus on chronic migraine, in order to support rational, evidence based and individualized preventive treatment strategies.

METHODS

A narrative literature review was conducted using the PubMed database. English language full text publications published between March 2010 and December 2025 were screened. Meta analyses, randomized controlled trials, cohort studies, original research articles and review papers addressing the use of botulinum toxin in adult migraine populations were considered. A total of 46 publications meeting predefined inclusion and exclusion criteria were included in the qualitative synthesis.

RESULTS

Randomized controlled trials PREEMPT 1 and PREEMPT 2, together with subsequent meta analyses and real world studies, consistently demonstrate the efficacy of onabotulinumtoxinA in chronic migraine. Treatment is associated

with a reduction in the number of migraine days, decreased frequency, intensity and duration of attacks, improvement in health related quality of life and a reduction in medication overuse. No clinically relevant benefit has been demonstrated in episodic migraine. Compared with oral preventive therapies, onabotulinumtoxinA shows better tolerability and lower rates of treatment discontinuation due to systemic adverse effects.

CONCLUSIONS

The available evidence supports onabotulinumtoxinA as an effective and well tolerated preventive treatment option for chronic migraine. Its local mechanism of action and favorable safety profile make it particularly relevant for patients who do not respond to or cannot tolerate oral preventive medications. Further research is required to clarify long term outcomes and to refine clinical predictors of treatment response.

Keywords: botulinum toxin, migraine, onabotulinumtoxinA, headache, chronic migraine

INTRODUCTION

Migraine is a debilitating and chronic neurological disorder, [1] recognized by the World Health Organization as one of the most disabling diseases in the world. [2] It is a complex and devastating condition that is traditionally associated with characteristic pain in the head. Patients struggling with migraine present a wide range of clinical symptoms.

In addition to pain, they often experience nausea, phonophobia (hypersensitivity to sound), osmophobia (hypersensitivity to smells) and neuro-otological manifestations (such as dizziness). [3]

The occurrence of these symptoms is particularly burdensome for patients and translates into a deterioration in everyday functioning, disrupting their professional and personal lives. According to the Global Burden of Disease Study 2023, headache disorders rank sixth among the most disabling groups of conditions worldwide, as indicated by the 2.9 billion people affected by them in 2023. For headache disorders, the standardized Years Lived with Disability (YLD) rate is 541.9 per 100,000 population, of which 90% were attributable to migraine. [4]

Migraine prophylaxis remains a clinical challenge due to the heterogeneity of disease mechanisms, variability of treatment response and frequent intolerance or insufficient efficacy of standard oral preventive therapies. Despite the availability of multiple pharmacological options, a substantial proportion of patients with chronic migraine fail to achieve adequate symptom control or discontinue treatment because of systemic adverse effects.

In this context, botulinum toxin type A has emerged as a distinct preventive strategy with a mechanism of action that differs fundamentally from traditional oral medications. Its targeted peripheral administration and neuromodulatory effects have led to its specific approval for chronic migraine and to increasing use in clinical practice. Over the past decade, a growing body of randomized trials, meta analyses and real world studies has expanded knowledge on its efficacy, safety profile and potential predictors of treatment response.

Given the accumulation of new clinical data, advances in the understanding of migraine pathophysiology and the development of novel preventive therapies, a focused synthesis of current evidence on the role of botulinum toxin type A in chronic migraine is warranted. This review therefore concentrates primarily on chronic migraine, while episodic migraine is addressed for comparison where relevant.

In the search for effective preventive interventions, the use of botulinum toxin type A (BoNT-A) has been proposed. [1] Botulinum toxin is a neurotoxin that is approved by the Food and Drug Administration (FDA) for the treatment of chronic migraine. [5] The therapeutic effect of botulinum toxin in migraine results from its ability to bind to cholinergic nerve endings and inhibit the release of acetylcholine at the neuromuscular junction, which disrupts signal transmission. [6] Currently, knowledge about migraines and their accompanying symptoms continues to develop, evolving toward a concept that is clinically much more complex than previously imagined. [4]

AIMS

The main purpose of this study is to compile current data on the role of botulinum toxin in migraine management in order to promote a holistic approach to its treatment and improve the quality of individual patient care. The following research objectives have been set to achieve this aim:

- Evaluation of current literature on the use of botulinum toxin type A in the prophylactic treatment of migraine in adults.
- Analysis of the effectiveness of therapy in relation to chronic and episodic migraine.
- Elucidation of the pathophysiology of the condition and the mechanisms of action of the neurotoxin.
- Comparison of BoNT-A with other preventive methods, such as traditional oral pharmacological drugs, in terms of their effects and patient tolerance.

- Identification of clinical prognostic factors that may indicate a positive patient response to treatment.
- Provision of arguments supporting the rational and evidence-based use of botulinum toxin in clinical practice.

The scientific novelty of the study lies in the synthesis of the latest reports on the identification of clinical prognostic factors, consideration of the impact of sexual dimorphism on nociception mechanisms and analysis of innovative therapeutic strategies, such as the synergism of botulinum toxin with monoclonal antibodies and the use of new neurotoxin serotypes.

METHODS

This study is a narrative review of the literature.

The review was conducted using data retrieved from the PubMed database in order to summarize and synthesize published evidence on the role of botulinum toxin in the treatment of migraine.

The literature search was performed in December 2025. Publications published between March 2010 and December 2025 were considered.

The search strategy was based on the combination of the following keywords: "botulinum toxin", "migraine", "onabotulinumtoxinA", "headache", "chronic migraine". The search was limited to English language, full text articles concerning adult populations.

Inclusion criteria were predefined and comprised meta analyses, prospective cohort studies, original research articles, systematic reviews and narrative reviews addressing the use of botulinum toxin in migraine. Exclusion criteria included articles not available in English, publications without full text access and case reports.

The selection of articles was performed by screening titles and abstracts, followed by full text assessment for eligibility based on the inclusion and exclusion criteria. A total of 46 publications met the predefined criteria and were included in the narrative synthesis.

Data extraction focused on study design, patient population, type of migraine, intervention characteristics and reported clinical outcomes. The extracted information was summarized descriptively to allow qualitative comparison of the effects of botulinum toxin with other pharmacological treatments and to distinguish its role in chronic and episodic migraine.

RESULTS

PATHOPHYSIOLOGY OF MIGRAINE

The pathophysiology of migraine is still under debate. It is complex and results from a primary disorder of the central nervous system that leads to abnormal sensory processing. [7] Migraine, especially in its chronic form, is associated with anomalous activation of the trigeminal-vascular system in the meninges, which causes neurogenic inflammation. [8] The onset of a migraine attack may be connected with the activation of C-fiber nociceptors in the dura mater. [7] This activation may be triggered by the diffusion of neuropeptides and neurotransmitters (such as calcitonin gene-related peptide, CGRP) from the cerebral cortex during the phenomenon of spreading cortical depression. The nociceptors of C fibers and A-delta pain fibers are activated, followed by the second-order sensory neurons of the trigeminal-cervical complex in the brainstem. Triggering factors include exogenous factors (such as peripheral stress, food products, environmental changes) which activate sensory afferents, as well as endogenous factors (depression, hormonal fluctuations and demodulated brain networks). [9] TRPV1 and TRPA1 ion channels play an important role in the peripheral terminals of nociceptive trigeminal neurons. [10] Activation of these channels by agonists such as cigarette smoke components for TRPA1 can lead to the release of CGRP. [11]

TYPE OF MIGRAINE

Migraine is classified into two main types depending on the frequency of headaches: chronic migraine (CM) and episodic migraine (EM). The table below summarizes the key features and diagnostic criteria for these two forms, based on information from sources, in particular the International Classification of Headache Disorders (ICHD-3). [6]

Table 1. Comparison of chronic and episodic migraine.

	Chronic migraine	Episodic migraine
Frequency of headaches	Occurs for at least 15 days per month for more than 3 months. [12]	Appears less than 15 days per month. [12]

Characteristics	For at least 8 days a month, the headache meets the criteria for migraine (with or without aura) or respond to migraine-specific treatment [13]	Does not apply [2]
Prevalence	It affects approximately 1.4% to 2.2% of the population. [2]	The incidence of episodic migraine in the adult population ranges from 3.3 to 21.9% among women and from 0.7 to 16.1% among men. [6]
Response to the treatment with botulinum toxin	Botulinum toxin type A has been approved by the FDA for the preventive treatment of chronic migraine. [13] BoNT-A is more effective than placebo in reducing migraine days (average reduction of 1.8 to 2.0 days per month compared to placebo). [8, 14]	Meta-analyses indicate that patients do not derive therapeutic benefit from BTX-A. [15] In the EM subgroup, the reduction in migraine days was not statistically significant. [14]
Pharmacological therapy for severe attacks	Nonsteroidal anti-inflammatory drugs (NSAIDs), dihydroergotamine, triptans and antiemetics may be used for acute treatment, but use of opioids should be avoided due to the high risk of medication overuse headache (MOH) and drug dependence. [16]	Urgent management involves usage of triptans, nonsteroidal anti-inflammatory drugs (NSAIDs), and antiemetics. [16]
Risk of headaches caused by medication overuse (MOH)	Patients are at increased risk of developing MOH due to the frequency of attacks. [17] For this reason, it is recommended that strong medications should be used no more than twice a week. [16]	The risk of MOH is lower, but overuse of medication can lead to chronic migraine.[3]

BoNT-A is effective in reducing migraine days and improving health-related quality of life in chronic migraine, as confirmed by the randomized controlled trials PREEMPT 1 and PREEMPT 2. [18] No therapeutic benefit was observed in patients with episodic migraine. [15] The lack of beneficial effects in EM may be due to the absence of advanced central sensitization, which is the main target of BoNT-A. [8] Despite their effectiveness, traditional oral medications are often associated with systemic side effects, leading to a higher treatment discontinuation rate compared to BoNT-A. [12] Acute treatment is less effective in CM and carries a higher risk of developing MOH. [16]

MECHANISM OF ACTION OF BOTULINUM TOXIN

BoNT-A is a strong neurotoxin produced by Clostridium botulinum. [19] The mechanism of action of botulinum toxin type A in the preventive treatment of chronic migraine is complex and based on sensory and neuromodulatory effects that go beyond its traditional role as a muscle relaxant. [10] The basic mechanism of action of the toxin, which applies to both motor and sensory nerves, involves interference with the release of neurotransmitters. [8] The toxin binds to receptors on peripheral nerve endings and is then endocytosed into the cytoplasm of the sensory neuron. [9] Inside the neuron, a light chain of BoNT-A (zinc-dependent metalloprotease) cleaves the SNAP-25 protein, which is a critical component of the SNARE complex that is essential for the fusion of synaptic vesicles with the cell membrane. [10] SNAP-25 dissection permanently inhibits regulated exocytosis of sensory and motor neurochemicals and proteins, leading to transient reduction in neurotransmitter release. [18] Blockade of the SNARE mechanism in sensory nerve endings prevents the release of key migraine pain mediators from afferent fibers. [8] Calcitonin gene-related peptide (CGRP) is a key nociceptive neuropeptide whose release is blocked. [11] OnabotulinumtoxinA (OnaBoNT-A) also inhibits the release of other excitatory and proinflammatory neurotransmitters and neuropeptides from primary afferent fibers, such as substance P and glutamate. [7] Inhibition of the release of these neurotransmitters is associated with a reduction in neurogenic inflammation in the trigeminal vascular system, which is part of the pathophysiology of CM. [6] BoNT-A affects unmyelinated C fibers. [20]

The action of the toxin leads to a reduction in the excitability of nociceptors, which is crucial for reducing chronic pain. OnaBoNT-A also reduces the insertion into the cell membrane of pain-sensitive receptors such as TRPV1 and P2X3 ion channels. [8] The process of embedding these receptors in the membrane is dependent on the SNARE complex. [11]

Inhibition of CGRP release and TRPV1/P2X3 insertion leads to reduced excitability of sensory neurons and peripheral desensitization of nociceptors, resulting in an increase in the migraine pain threshold. [8] Injections of OnaBoNT-A to cranial sutures inhibit the response of meningeal nociceptors to stimulation of TRPV1 and TRPA1 channels. [21]

Although OnaBoNT-A injections are administered extracranially (according to the PREEMPT protocol), the toxin may exert a central effect through transport along the nerves. [11] It is considered that OnaBoNT-A is transported retrograde along peripheral nociceptive pathways. [9] This transport allows the toxin to reach neurons in the trigeminal ganglion and trigeminal-cervical complex, enabling it to affect the central mechanisms responsible for the development of migraine pain. [11] This action leads to central desensitization of the neural pathways involved in the pathogenesis of migraine pain. Some reports indicate that OnaBoNT-A may affect central pain generation mechanisms, including reducing the duration of spreading cortical depression. [13]

TECHNIQUE OF PERFORMING THE PROCEDURE

Treatment of chronic migraine with botulinum toxin type A is performed according to a standardized protocol known as the PREEMPT (Phase 3 Research Evaluating Migraine Prophylaxis Therapy) Injection Paradigm, which is the only approved injection protocol for OnaBoNT-A for this indication. [13] The toxin action involves reaching the sensory nerve endings of the trigeminal-occipital-cervical complex, which allows for the inhibition of pain neurotransmitter release (such as CGRP) and the reduction of peripheral and central sensitization. [8]

Treatment with OnaBoNT-A involves administering the drug in regular cycles, usually every 12 weeks. [22] The toxin is injected into 31 to 39 consistent injection sites in the head and neck area. [13] The minimum dose of BoNT-A in the PREEMPT protocol is 155 units (U), which corresponds to 31 fixed injection points. [15] Five units of OnaBoNT-A are injected at each fixed point. [18] Unlike aesthetic applications, injections for CM treatment should be administered shallowly under the skin rather than deeply into the muscle. This is to reach the nerve endings directly rather than to relax the muscles. [13]

Injections are administered in seven key areas of the head and neck. [18]

Table 2. Sites and doses of botulinum toxin injections according to the PREEMPT protocol.

Muscle area	Number of injection points	Dose (unit)	Injection division
Temporal muscles	8	40 U	4 points per side
Frontalis muscle	4	20 U	2 points per side
Corrugator supercilii muscles	2	10 U	1 point per side
Procerus muscle	1	5 U	1 point
Occipital muscles	6	30 U	3 points per side
Cervical paraspinal muscle group	4	20 U	2 points per side
Trapezius muscles	6	30 U	3 points per side
In total	31	155 U	

The PREEMPT protocol allows the addition of injections in areas where the patient feels the most severe pain. [6] It is possible to add up to 40 U of OnaBoNT-A, which represents an additional 8 points, in 8 specific areas of the head or neck muscles. This results in a total maximum dose of 195 U (39 injection points), which is the maximum dose registered in Europe. [13] It happens that other protocols are used, for example, the "5/20/100 protocol" in one of the centers in Saudi Arabia, where only 100 U is injected in 20 places. [23] However, PREEMPT is the only valid and verified protocol for the treatment of chronic migraine. [13]

PREDICTIVE FACTORS FOR A GOOD RESPONSE TO TREATMENT

Clinical prognostic factors that help predict which patients with chronic migraine will respond well to botulinum toxin type A treatment are the subject of clinical research. Identifying these markers is valuable because not all patients respond to OnaBoNT-A treatment. [24] A shorter duration of chronic migraine (<12 months) before starting treatment with botulinum toxin is associated with an increased likelihood of achieving a positive clinical outcome. [18] Research suggests that in patients with resistant CM, the use of OnaBoNT-A should not be delayed, as early treatment initiation may result in greater benefits. [2] The absence of medication overuse headache (MOH) is also considered as a potential prognostic factor for a good clinical response to BoNT-A. [24] Better treatment outcomes correlated with unilateral pain location, milder headache at the baseline and fewer days of disability per month. [25]

The reduced likelihood of a good response or complete treatment failure was indicated by coexisting mental and somatic disorders such as depression, occipital neuropathy, obstructive sleep apnea and severe obesity. [23] Some sources analyzing the causes of OnaBoNT-A treatment failure mention the presence of scalp allodynia and paracranial muscle tenderness as possible causes of therapeutic failure. [24] The patient's gender does not affect the response to OnaBoNT-A treatment in chronic migraine. [26]

ADVERSE EFFECTS

The use of botulinum toxin type A in the preventive treatment of chronic migraine is generally considered safe and well tolerated, while reported side effects are usually mild, transient and related to the injection site. [2] Nevertheless, compared to placebo, OnaBoNT-A significantly increases the risk of adverse events. [15] The most commonly observed injection-associated event is muscle pain in the head and neck, which occurred in 6,7% of patients receiving BoNT-A compared to 2,2% in the placebo group in the combined analysis of the PREEMPT studies. [26] Weakness of this muscle group was noticed in 5.5% of patients receiving OnaBoNT-A compared to 0.3% in the placebo group. [27] Temporary ptosis was observed in 3.3% of patients. [26] Pain on the injection site, reported as a procedure-related adverse event, occurred in 3.2% of patients compared to 2.0% in the placebo group. [25] In real-life studies, single cases of paresthesia and dermatitis at the injection site have been reported. [28] Adverse reactions associated with treatment are usually mild or moderate and resolve spontaneously without leaving any permanent effects. [25]

CONVENTIONAL PHARMACOLOGIC MANAGEMENT

In addition to targeted treatment with botulinum toxin type A injections for chronic migraine, oral medications with systemic effects are also used. [29] Anti-epileptic drugs such as topiramate and valproate have proven effectiveness in migraine prevention. The action of these drugs is complex. It includes, among other things, blocking voltage-dependent sodium channels, blocking T-type calcium ion channels and suppressing protein kinase C. Topiramate and valproate may also suppress spreading cortical depression, which is proposed as a useful predictive model for migraine treatment. [30] Beta-blockers, especially propanolol, are also used in the treatment of CM. [28] Its action involves modulation of trigeminal-vascular responses in the ventromedial nucleus of the thalamus, suggesting involvement in the central mechanism of migraine relief. [14] Angiotensin-converting enzyme inhibitors and monoclonal antibodies targeting CGRP are also used in pharmacological treatment. [29]

Oral prophylactic medications, such as topiramate, cause a significantly higher incidence of systemic adverse effects than botulinum toxin type A therapy. [31] Treatment-related adverse events occurred in 70% of patients treated with topiramate and in 17% of patients treated with botulinum toxin. The overall rate of discontinuation of treatment due to adverse events is significantly lower for onaBT-A than for oral therapies. [26] OnaBoNT-A is administered locally and is considered to have minimal systemic absorption. [25] For this reason, OnaBoNT-A is particularly indicated for patients who may not tolerate systemic medications, such as elderly patients or those receiving polypharmacy. [27] The use of OnaBoNT-A every 12 weeks, in accordance with the PREEMPT protocol, translates into a higher degree of compliance with medical recommendations. [32] Adherence to oral prophylactic medication in CM is often low (according to the literature, it is less than 25% after 1 year), mainly due to burdensome and generalized side effects. [28] OnaBoNT-A is particularly useful for patients in whom at least three previous oral prophylactic therapies have been ineffective or intolerable. [33] OnabotulinumtoxinA is effective in patients with chronic migraine, regardless of whether they abuse acute pain medications. This is a key advantage, as MOH often compromises the effectiveness of oral medications and requires discontinuation of pain medications before starting other preventive treatments. [34]

Table 3 summarizes key studies on the use of OnabotulinumtoxinA in the treatment of chronic migraine, including randomized clinical trials, meta-analyses and clinical practice data. Sources consistently recognize botulinum toxin type A as a safe and effective drug for the prevention of chronic migraine. The efficacy of the drug observed in rigorous clinical trials is clearly reflected in everyday medical practice, as confirmed by studies conducted by Ahmed and Castrillo Sanz. Despite positive results, some studies face problems such as high placebo response, lack of control groups in observational studies or small study groups when testing new dosing protocols. [2][12][23][35-39]

Table 3. Summary table of key studies on OnabotulinumtoxinA in chronic migraine.

Author and year of publication	Type of study	Number of patients	Criteria for chronic migraine	Injection protocol	Main clinical outcome	Main conclusions	Study limitations
Aurora et al., 2010 (PREEMPT 1) [35]	Randomized clinical trial	679	ICHD-II: ≥15 days of headaches/ month, ≥50% of which are migraines	PREEMPT (155–195 U, 31–39 points)	Significant reduction in migraine days and headaches; improved quality of life	BoNT-A is an effective and safe prophylactic drug for CM.	No statistical significance for the primary endpoint (frequency of episodes)
Diener et al., 2010 (PREEMPT 2) [36]	Randomized clinical trial	705	ICHD-II: ≥15 days of headaches/ month, ≥50% of which are migraines	PREEMPT (155–195 U, 31–39 points)	Reduction of 9 days with headache vs. 6.7 (placebo); improvement in quality of life.	BoNT-A is statistically more effective than placebo in all endpoints.	High response to placebo (reduction of 6.7 days)
Herd et al., 2019 [37]	Meta analysis	4190	IHS classification criteria for migraine headaches	Various (doses 6–300 U); injections into the muscles of the head and neck	Reduction of 2 migraine days per month with CM vs. placebo; improvement in pain intensity by approximately 3 cm on the VAS scale	BoNT-A is effective in CM; no evidence of effectiveness in episodic migraine	Low quality of evidence for many measures; small groups in most included studies
Blumenfeld et al., 2018 (COMPEL) [38]	Real world clinical data	716	CM criteria	PREEMPT (155 U, 31 points every 12 weeks)	Reduction of 10.7 days with headache after 108 weeks; significant improvement in HIT-6 scores	Long-term efficacy and safety with regular use for 2 years	Open-label study, no control group; funded by the manufacturer
Ahmed et al., 2019 [39]	Real world clinical data	641	CM criteria	PREEMPT (as applied in practice)	Reduction in the frequency of headache days; improvement in all MSQ and EQ-5D domains	The efficacy of BoNT-A in real-world settings correlates with the results of the PREEMPT study.	Non-randomised observational study; short observation period for some parameters
Bruloy et al., 2019 [12]	Meta analysis	3646	ICHD: CM (≥15 days) and episodic	Mainly fixed-site scheme	Reduction of 1.56 migraine days in CM; significant improvement in quality of life	BoNT-A is more effective than placebo in CM after just 2 months of treatment.	No access to individual patient data (aggregated data)

Author and year of publication	Type of study	Number of patients	Criteria for chronic migraine	Injection protocol	Main clinical outcome	Main conclusions	Study limitations
Castrillo Sanz et al., 2018 [2]	Real world clinical data	69	ICHD-3: ≥15 days/ month for >3 months	PREEMPT (155 U, 31 points)	Reduction in the number of days with pain by 48.5%; decrease in pain intensity by 20.7%	BoNT-A is safe and effective; early implementation provides greater benefits.	Small sample size; no control group
Algahtani et al., 2020 [23]	Real world clinical data	30	ICHD-3: ≥15 days/ month for >3 months	Modified (100 U, 20 points – so-called "5/20/100")	Reduction of 9.47 migraine days (decrease from 15.6 to 6.1); 63% of patients reduced their use of emergency medication	A protocol with a lower dose (100 U) may be effective, cheaper, and safer.	Very small group; retrospective study from a single center

SEXUAL DIMORPHISM

Recent reports indicate significant gender differences in the structure of peripheral nociceptors, which may lead to the development of gender-specific dosing regimens for botulinum toxin type A in the future. Studies have shown that human nociceptors are gender-differentiated at the transcriptional, protein and functional levels. CGRP transcript expression is higher in female dorsal root ganglion cells than in male cells. In women, nociceptors are selectively sensitized by prolactin, while in men this process is associated with orexin B. [40] Estrogens modulate trigeminal neuron activity and vasomotor tone and increase CGRP receptor expression and function in women. [41] The key mechanism of action of OnaBoNT-A in migraine is to block the release of neuropeptides, especially CGRP, by cleaving the SNAP-25 protein. [42] Since CGRP plays a stronger pro-nociceptive role in women, and its release is enhanced by prolactin, the effect of botulinum toxin may be especially important therapeutically in women. [41] As for pregnant women, a growing observational database suggests that OnaBoNT-A used in chronic migraine is not associated with an increased risk of fetal malformations, as its large molecular size limits its passage through the placenta. [43] Understanding these mechanistic differences is key to implementing precision medicine in the treatment of migraine. The fact that trigeminal nociceptors are dimorphic suggests that future clinical practice and OnaBoNT-A dosing may need to take patient gender into account in order to optimize treatment outcomes and better identify individuals who will respond best to therapy. [40]

PHARMACOLOGICAL INNOVATIONS

The latest reports in regenerative medicine point to the growing potential of combining botulinum toxin type A with modern cell therapies and tissue engineering, particularly in the treatment of joint and nerve injuries. It reduces inflammation and pathological nerve activity, creating a more favorable environment for stem cell survival and function. There is evidence that BoNT-A may promote the proliferation of Schwann cells, suggesting its possible regenerative effect after nerve damage. These reports mark a shift from medicine focused solely on alleviating pain symptoms to strategies that integrate pain relief with the actual repair of damaged body structures. [44]

Research on combination therapy with botulinum toxin and monoclonal antibodies targeting the CGRP pathway indicates their potential synergistic or additive effect in the treatment of chronic migraine. [7] The theory of synergism is based on the fact that both therapies act on different types of nerve fibers; OnaBoNT-A inhibits the activation and sensitization of non-myelinated C-type fibers (by blocking the release of CGRP), while CGRP antibodies block signals from thinly myelinated A-delta fibers. [9] The combination of both methods may lead to a greater reduction in the afferent stimulus flow to the trigeminal-cervical complex in the brainstem than the use of either method alone. [8] A study involving 257 patients with chronic migraine confirmed that adding CGRP antibodies to ongoing OnaBoNT-A treatment provided additional therapeutic benefits and was well tolerated. [7] In actual clinical practice, it has been observed that patients who have not achieved full improvement with toxin alone may benefit significantly from the addition of erenumab. [9] Although the combination of drugs is safe, real-world data show that CGRP antibodies are discontinued more often (23.3%) than botulinum toxin (3.3%), most often due to lack of reimbursement or lack of effect. [7] Despite promising results, the full extent of the synergism between OnaBoNT-A

and CGRP antagonists remains an open question and requires further clinical research to develop optimal standards for combination therapy. [45]

BoNT/X is a newly identified serotype with unique properties that has been the subject of intensive structural research using cryo-electron microscopy. It exhibits a different mechanism of action from traditional serotypes A and B, as it can attack alternative SNARE proteins. Thanks to this property, BoNT/X shows promise in the treatment of conditions that are resistant to existing therapies. Despite very high catalytic activity and efficient translocation, the overall potency of this serotype in in vivo and in vitro studies remains low. [42] Work is underway on the use of DNA recombination techniques to produce toxins that would be selective only for the sensory neurons responsible for pain. [9] This approach would allow for the use of much higher therapeutic doses in the treatment of migraine without the risk of causing muscle paralysis, which is the main limitation of current preparations. [46] Research is also being conducted on the use of BoNT-F, particularly in patients who have developed resistance to serotypes A and B. [42] In addition to new serotypes, techniques for modifying proteins are being investigated to improve the precision of targeting specific subtypes of neurons or receptors, thereby minimizing the drug's impact on surrounding tissues. The development of these new variants, supported by bioengineering, aims to create a new generation of painkillers with prolonged action and reduced side effects. [44]

DISCUSSION

This narrative review summarizes published data on the use of onabotulinumtoxinA in migraine, with a primary focus on chronic migraine. The included literature consistently describes chronic migraine as a severe and disabling neurological disorder with a substantial global disease burden, repeatedly ranked among the leading causes of years lived with disability worldwide [1–4].

Randomized controlled trials PREEMPT 1 and PREEMPT 2, together with subsequent meta analyses and real world observational studies, report a reduction in the number of migraine days and improvement in health related quality of life in patients with chronic migraine treated with onabotulinumtoxinA [8, 14, 18, 35, 36]. Across the analyzed sources, therapeutic benefit is demonstrated in chronic migraine populations, while studies addressing episodic migraine do not show a clinically relevant effect [14, 15]. In the cited literature, this difference is attributed to the presence of peripheral and central sensitization mechanisms in chronic migraine, which are less pronounced or absent in episodic migraine [8].

Mechanistic explanations discussed in the included studies link clinical efficacy to established pathophysiological processes of chronic migraine. OnabotulinumtoxinA is described as binding to peripheral sensory nerve endings, entering the neuron and cleaving the SNAP 25 protein, which inhibits regulated exocytosis of neurotransmitters such as CGRP, substance P and glutamate [9–11, 18, 20]. These processes are associated with reduced neurogenic inflammation and decreased excitability of trigeminal nociceptors, which are central elements of chronic migraine pathophysiology described in the reviewed literature [7, 8].

Several reviewed studies compare onabotulinumtoxinA with oral preventive pharmacological therapies. These sources report lower rates of systemic adverse effects and lower treatment discontinuation rates for onabotulinumtoxinA compared with oral agents such as topiramate or beta blockers [2, 15, 25, 26, 31]. This aspect is discussed in relation to specific patient groups, including older adults and patients receiving multiple concomitant medications, as well as patients who have failed or not tolerated multiple oral preventive therapies [27, 33].

The literature also addresses variability in treatment response. Reported associations include unilateral pain, lower baseline headache severity and lower disability burden, as well as the absence of medication overuse headache [24, 25]. Conversely, comorbid conditions such as depression, obesity, obstructive sleep apnea, occipital neuropathy and scalp allodynia are described as factors associated with reduced response or treatment failure [23, 24]. These associations are presented in the cited studies as observational findings rather than definitive predictors.

Important limitations emerge from the analyzed material. First, this review is narrative in nature and does not follow a systematic review protocol, which limits reproducibility and increases susceptibility to selection bias. Second, the included literature is heterogeneous with respect to study design, patient populations, outcome measures and follow up duration, particularly among real world and observational studies [2, 12, 23, 38, 39]. Third, several observational studies lack control groups or include small sample sizes, which restricts the strength of causal inference [2, 23]. In addition, high placebo response rates reported in randomized trials complicate interpretation of treatment effects [35, 36]. The potential impact of publication bias cannot be excluded, as studies with negative or neutral results may be underrepresented in the available literature.

In summary, the reviewed evidence consistently supports the use of onabotulinumtoxinA for the prevention of chronic migraine when administered according to the PREEMPT protocol [13]. At the same time, the conclusions of this review are based on qualitative synthesis of published data, and the identified methodological limitations underline the need for further well designed studies to refine patient selection criteria, clarify long term outcomes and address unresolved questions regarding predictors of treatment response.

CONCLUSIONS

Migraine, particularly its chronic form, remains a significant global health challenge requiring effective and well tolerated preventive treatment strategies. The data presented in this article demonstrate that FDA approved onabotulinumtoxinA is an effective option for the prevention of chronic migraine. Its use leads to a reduction in the number of migraine days, a decrease in the frequency, intensity and duration of attacks, and an improvement in patients' quality of life, as confirmed by the results of the randomized clinical trials PREEMPT 1 and PREEMPT 2.

OnabotulinumtoxinA is characterized by a local mechanism of action and a favorable safety profile, which makes it a clinically relevant therapeutic option for patients with chronic migraine, particularly in cases of insufficient efficacy or poor tolerability of oral preventive medications. An additional benefit is the reduction in the risk of medication overuse.

Despite the consistent evidence supporting the efficacy and safety of onabotulinumtoxinA, further studies are required to more precisely assess long term treatment outcomes and to refine the identification of clinical factors associated with an optimal response to therapy.

DISCLOSURE

AUTHORS' CONTRIBUTIONS

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All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

USE OF ARTIFICIAL INTELLIGENCE

The authors declare that no artificial intelligence tools were used in the generation, writing, editing or revision of this manuscript. All content was created solely by the authors.

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CONFLICT OF INTEREST

Authors declare no conflicts of interest.

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