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THE USE OF BOTULINUM TOXIN IN THE TREATMENT OF MIGRAINE

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ABSTRACT

Introduction: Migraine is a chronic neurological disorder marked by recurrent moderate to severe headaches with symptoms such as nausea, photophobia, and phonophobia. Chronic migraine, occurring on 15 or more days per month for over three months, significantly impairs daily functioning and creates a substantial health burden. Botulinum toxin type A (BoNT-A) is an effective preventive option for patients who do not respond to standard treatments.
Aim of the study: The aim of this review is to summarize current evidence on the mechanism of action, clinical efficacy, safety profile, and practical use of botulinum toxin type A in the prevention of chronic migraine.
Materials and methods: A literature search was mostly performed in PubMed and Google Scholar for studies published between 2015 and 2025, using the keywords: migraine, chronic migraine, botulinum toxin, onabotulinumtoxinA, PREEMPT trials, CGRP. Priority was given to randomized controlled trials, long-term observational studies, clinical guidelines, and mechanistic research.
Discussion: OnabotulinumtoxinA (BoNT-A) is a well-established preventive treatment for chronic migraine supported by evidence from the PREEMPT trials and long-term studies such as COMPEL. BoNT-A significantly reduces headaches, improves quality of life and decreases disability with benefits sustained over multiple treatment cycles. Its mechanism blocking the release of CGRP, substance P, and glutamate from sensory nerves and modulating nociceptive receptors targets both peripheral and central sensitization, which distinguishes it from traditional oral medication.
Injection protocols vary worldwide. The PREEMPT paradigm is evidence-based and standardized, while alternative approaches, such as the Saudi 5/20/100 protocol, offer lower doses and fewer injections but lack of large-scale validation. The safety profile is generally positive. Following recommended dosing intervals minimizes the risk of neutralizing antibodies.
Emerging CGRP-targeting therapies provide additional options, and early data suggest potential benefits of combination therapy for refractory cases. Economic analyses indicate that despite higher upfront costs, BoNT-A reduces healthcare use and disability, making it cost-effective in the long term. Future research should focus on identifying predictors of response, optimizing injection protocols, and evaluating combination strategies with biologics.
Results: Evidence from large randomized trials (PREEMPT 1 and 2) demonstrates that BoNT-A significantly reduces the number of headache days, improves quality of life, and decreases disability in patients with chronic migraine. Long-term studies show sustained benefits over multiple treatment cycles with a favorable safety profile. BoNT-A reduces peripheral and central sensitization by inhibiting the release of pain-related neuropeptides and modulating sensory nerve activity.
Conclusion: OnabotulinumtoxinA is an effective and well-tolerated preventive treatment for chronic migraine. Standardized injection protocols and appropriate patient selection optimize therapeutic outcomes. Further research is needed to identify predictors of treatment response and to explore the potential of combination therapy with CGRP (calcitonin gene-related peptide)-targeting agents.

KEYWORDS
Migraine, Chronic Migraine, Botulinum Toxin, Onabotulinumtoxina, PREEMPT Trials, CGRP

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Abbreviations: *CGRP - calcitonin gene-related peptide, BoNT-A / BTA - Botulinum toxin type A, FHM - familial hemiplegic migraine, CSD - cortical spreading depression, e.g - exempli gratia (for example), SNAP-25 - Synaptosome-Associated Protein-25, SNARE - Soluble NSF Attachment Protein REceptor, TRPV1 - Transient Receptor Potential Vanilloid 1, PREEMPT - Phase III REsearch Evaluating Migraine Prophylaxis Therapy, MIDAS - Migraine Disability Assessment, HIT-6 - Headache Impact Test, COMPEL - Chronic Migraine OnabotulinumtoxinA Prolonged Efficacy open Label, NICE - National Institute for Health and Care Excellence, Nabs - neutralizing antibodies, NAPs - non-toxic accessory proteins, FDA - Food and Drug Administration, EMA - European Medicines Agency, RCT - randomized controlled trial*

Definition and Clinical Features of Migraine

Migraine is a chronic neurological disorder characterized by recurrent episodes of moderate to severe headache, usually pulsating and on one side of the head and often accompanied by nausea, photophobia or phonophobia. It is one of the most prevalent neurological conditions worldwide, affecting over one billion people and representing a significant global health burden [1]. The overall global prevalence of migraine is approximately 14–15% [2].

Migraine was once thought to be mostly a blood vessel problem, but now it is known it is much more complex. It actually starts with changes in the brain and nervous system, involving both the brain, but also the nerves around it. Recent research shows that the trigeminovascular system and certain neuropeptides, especially CGRP, play key roles in the onset and spread of migraine pain [3]. Migraine attacks often occur in a sequence of phases: the prodrome, aura (observed in some patients), the headache phase, and the postdrome. The aura phase has been linked to cortical spreading depression (CSD), a wave of neuronal and glial depolarization that spreads across the cortex and is thought to underlie sensory disturbances reported by patients [4].

Genetic studies also reveal a significant genetic predisposition to migraine, implicating genes associated with ion channels, neurotransmission, and neuronal excitability - e.g. in familial hemiplegic migraine (FHM), three ion transport-related genes (CACNA1A, ATP1A2 and SCN1A) have been implicated. Such findings help explain individual susceptibility and variability in clinical presentation [5]. Neuroimaging research, including fMRI and PET studies, supports the concept of migraine as a dysfunction of brain networks rather than a purely vascular condition. It was described that hypothalamic responses to trigeminal nociceptive stimulation increase in the 24 hours preceding a migraine. Altered functional connectivity between the hypothalamus, spinal trigeminal nuclei, and dorsal rostral pons was observed during both the preictal and pain phases. These results suggest that functional changes in hypothalamo-brainstem connectivity, rather than the brainstem alone, may drive migraine attacks [6].

Migraine can be divided into three main types:

Table 1. Clinical characteristics of migraine [7]

Feature	Migraine without Aura	Migraine with Aura	Chronic Migraine
Definition	Most common type, headache attacks without prodromal neurological symptoms	Headache accompanied by prodromal symptoms (aura)	Headache occurring ≥15 days/month for >3 months, with ≥8 days/month showing migraine features
Prevalence	About 75% of cases	Less common	About 1-3% of population
Duration of Headache	4-72 hours	4-72 hours (headache phase) 5-60 min (aura)	≥15 days/month for >3 months
Pain Characteristics	Unilateral, pulsating, moderate-severe, aggravated by physical activity	Unilateral, pulsating, moderate-severe, aggravated by physical activity	Variable - often moderate-severe, more frequent
Associated Symptoms	Nausea, vomiting, photophobia, phonophobia	Nausea, vomiting, photophobia, phonophobia + aura symptoms (visual, sensory, speech, motor)	Nausea, vomiting, photophobia, phonophobia, high disability
Aura	None	Present	May or may not occur; usually chronic headache with migraine features
Clinical Importance	Standard acute and preventive treatment	Important for diagnosis, risk assessment, treatment planning	Requires long-term management, prevention, attention to medication overuse

Given its high prevalence, substantial impact on quality of life, and socioeconomic consequences, migraine remains a major public health issue. Advances in understanding its mechanisms have opened new avenues for targeted therapies, including CGRP-based treatments, offering improved outcomes for many patients [8].

1. Definition, mechanism and history of Botulinum toxin

The scientific study of botulinum toxin began in 1820, when Justinus Kerner first documented the symptoms of botulism. In 1897, Professor van Ermengem of the University of Ghent identified and isolated the bacterium responsible for the disease, originally calling it Bacillus botulinum. The organism was later renamed Clostridium botulinum. [9]. The clinical use of BT began when Alan Scott used it in strabismus in 1977. He obtained Food and Drug Administration (FDA) approval in 1989 for BTA (Botulinum Toxin A) to treat strabismus, blepharospasm, and hemifacial spasm [9]. After being injected into the tissues, onabotulinumtoxinA blocks the Soluble NSF Attachment Protein REceptor (SNARE) system by cutting one of its key proteins, Synaptosome-Associated Protein-25 (SNAP-25). This happens in both motor and sensory nerves. Because the SNARE system is required for releasing neurotransmitters and inserting certain receptors into the cell membrane, the toxin prevents both the release of pain-related chemicals and the placement of pain-sensing receptors on nerve endings [10].

As a result, onabotulinumtoxinA reduces the release of pro-inflammatory and excitatory substances such as substance P, CGRP, and glutamate from sensory nerve fibers. These substances normally help transmit pain and contribute to peripheral and central sensitization. The toxin also decreases the insertion of pain-sensitive ion channels, such as Transient Receptor Potential Vanilloid 1 (TRPV1), into the membranes of pain-sensing neurons, which are often more active in migraine[10].

For chronic migraine prevention, the toxin is injected into 31–39 sites across seven head and neck muscles. Sensory nerve endings from the trigeminal and cervical ganglia are found throughout these muscles and tend to be overactive in people with migraine. By inhibiting these sensory nerve endings, onabotulinumtoxinA reduces the number of pain signals sent to the brain, helping to prevent activation and sensitization of central neurons involved in migraine chronification [10].

2. Clinical Evidence

2.1 PREEMPT Trials

The PREEMPT (Phase III REsearch Evaluating Migraine Prophylaxis Therapy) program consists of two multicenter, randomized, double-blind, placebo-controlled trials involving over 1,300 patients with chronic migraine [11,12].

Key findings included:

- Significant reduction in headache days per month compared with placebo [11,12].
- Improvement in Migraine Disability Assessment (MIDAS) and Headache Impact Test (HIT-6) scores [11,12].
- Sustained benefits with repeated treatment cycles [13].

These results led to FDA and European Medicines Agency - EMA approval of BoNT-A for chronic migraine prevention in 2010 [11,12].

3. Injection Protocols

The difference between Botox treatment of wrinkles and migraine is the method of dilution. In aesthetic medicine procedures the most common method of dilution is using 2,5-3 ml of NaCl [14], when in migraine treatment it is 4ml [15] Botulinum toxin is administered according to the protocols such as:

3.1 PREEMPT injection paradigm [16]:

- 155 units injected into 31 standardized sites across frontalis, temporalis, occipitalis, cervical paraspinal, and trapezius muscles [16].
- Optional additional 40 units ("follow-the-pain" approach) depending on patient symptoms [16].
- Treatments are repeated every 12 weeks [16].

Injections must be performed by clinicians trained in this protocol to ensure safety and efficacy [16].

3.2 Saudi Arabian 5/20/100 protocol

This is the local migraine-treatment protocol for botulinum toxin which consists of administering 100 units of onabotulinumtoxinA across 20 injection sites distributed among five muscle groups. The protocol was used for the first time in King Abdulaziz Medical City in Jeddah, Saudi Arabia, where a retrospective single-center observational study was conducted. It resulted in reduced frequency of using abortive medications in 63.3% of patients. The authors claim this protocol can contribute to the lower cost of Botox migraine treatment and also reduce its side effects. [17]

Table 2. Differences between protocols of injecting botox in migraine treatment [16,17]

Parameter	PREEMPT Protocol	Saudi 5/20/100 Protocol
Total Dose	155 units + optional 40 "follow-the-paint'	100 units
Number of Injection Sites	31 fixed sites (up to 39 optional sites)	20 sites
Number of muscle groups	7 muscle regions (frontalis, corrugator, procerus, temporalis, occipitalis, cervical paraspinal, trapezius)	5 muscle groups
Injection Strategy	fixed-site, fixed-dose + optional dosing	fixed distribution across 5 muscles
Interval Between Treatments	every 12 weeks	not strictly specified; used clinically as needed (typically similar intervals)

Evidence Base	validated in large randomized controlled trials (RCTs) - PREEMPT 1&2	supported by a single-center retrospective observational study
Clinical Outcomes	significant reduction in headache days and severity shown in RCTs	63,3% reduction in the use of abortive medications
Training Requirements	requires specific PREEMPT certification/training	no standardized international training;
Advantages	strong evidence base; standardized; customizable via follow-the-paint	lower total dose; fewej injections; potentially reduced side effects and lower cost
Limitation	higher total dose; more injections; higher cost	evidence based on limited data; not internationally validated

4. Indications

BoNT-A is indicated for adults with chronic migraine (≥15 headache days per month for > 3 months of which ≥8 days has the features of migraine headache) [16]. It is not recommended for episodic migraine or in tension-type headache, where evidence of benefit is lacking [16,18]. Guidelines suggest its use in patients who have failed at least two oral preventive medications or cannot tolerate them. It is recommended for patients with medication overuse to discontinue the overused drugs before starting onabotulinumtoxinA. If withdrawal is not possible, onabotulinumtoxinA may be initiated either simultaneously with withdrawal or even prior to it [16].

5. Safety and Adverse Effects

BoNT-A is generally safe when administered according to the protocol [13,16]. Common adverse events include: pain at injection sites, neck pain or stiffness, mild ptosis (temporary), localized muscle weakness. Severe complications are rare [13,16]. According to the Chronic Migraine OnabotulinumtoxinA Prolonged Efficacy open Label (COMPEL) study the frequency of side effects decreased from cycle to cycle with repeated onabotulinumtoxinA treatment:: first cycle, 24.2%; fourth cycle, 18.4%; ninth cycle, 12.2%. [19]

Table 3. Frequency of side effects of botox in migraine after first cycle [19]

Adverse effect	Frequency [%]
Neck pain	2,7
Eyelid ptosis	1,8
Musculoskeletal stiffness	1,4
Injection-site pain	1,3
Headache	1,3

6. BoNT-A immunogenicity and the problem of neutralizing antibodies

The immunogenicity of BoNT-A has become an increasingly relevant topic in recent literature, particularly in the context of chronic therapeutic use such as in chronic migraine, dystonia, spasticity, and aesthetic indications. Although BoNT-A is generally considered a medication with low antigenic potential, there are factors that can be divided into two groups that play role in the immunogenicity of BoNT-A:

6.1 Manufacturing process

Even minor modifications in the manufacturing process can affect the three-dimensional configuration of therapeutic proteins, potentially influencing their clinical behavior and immunogenicity. Isolation technique, the way the product is finished during drying, the type or quantity of excipients used, or accidental exposure to unprotected surfaces may introduce variations in the final product's composition or structure and change its immunogenicity [20].

6.2 The antigenic protein load

The immunogenicity of botulinum neurotoxin (BoNT) formulations is primarily determined by the 150-kDa core neurotoxin, which is the only component capable of eliciting neutralizing antibodies [21, 22, 23]. Consequently, the "antigenic protein load" - the mass of the 150-kDa BoNT - provides a more accurate measure of immunogenic potential than total protein content, which includes non-toxic accessory proteins (NAPs) [24]. For instance, onabotulinumtoxinA contains only ~1/6 of its total protein as 150-kDa BoNT, whereas incobotulinumtoxinA consists solely of the core neurotoxin, resulting in a higher antigenic protein load per total protein [21].

6.3 Presence of accessory proteins

Comparative preclinical studies indicate that abobotulinumtoxinA may produce higher rates of neutralizing antibodies than onabotulinumtoxinA or incobotulinumtoxinA, despite having less NAPs [20. It suggests that NAPs are probably not the main drivers of antibody formation, while additional factors may play a role, such as the presence of flagellin, which is a a bacterial protein with immunostimulatory properties could contribute to immunogenicity [25].

Table 4. [20] Factors

Product-related factors	Treatment-related factors
Manufacturing process	The overall toxin dose
The antigenic protein load	Injections frequency
Presence of accessory proteins	Prior vaccination or exposure

6.4 The overall toxin dose

Published studies suggest a positive association between cumulative BoNT exposure and the risk of neutralizing antibody formation. In a retrospective study, patients with neutralizing antibodies to pre-1997 poznabotulinumtoxinA were found to have received a higher total cumulative dose than patients without neutralizing antibodies [26].

The other research has also shown that lower rates of neutralizing antibodies against BoNT have been reported in patients with conditions requiring lower botulinum toxin type A doses such as cosmetic use or blepharospasm compared to applications requiring higher doses like spasticity [27].

6.5 Injections frequency

Frequency of injections is one of the factors that contributes to immunogenicity of botox. Two studies reported that patients who developed secondary non-response to onabotulinumtoxinA tended to receive injections at shorter intervals and underwent more booster treatments compared with those who maintained responsiveness [28, 29]. Moreover, a recent analysis of serum from secondary non-responders to abobotulinumtoxinA and to pre-1997 onabotulinumtoxinA showed that neutralizing antibodies were detected more often in patients treated at 1–2-month intervals than in those whose injection intervals ranged from 4 to 13 months [27]. These and many other studies confirm that when the intervals between botox injection are shorter, the risk of neutralizing antibodies and weak treatment-effect to the botox is higher [30,31].

6.6 The correlation between previous exposure

When there was a previous exposure to BoNT-A, there is a higher risk of immunization to this substance. The proof to this are the results of the research in 2004, in which it was proved that recombinant bivalent vaccine rBV A/B (Pichia pastoris) stimulated serotype-specific neutralizing antibodies among the majority of vaccine recipients [32].

7. Economics of Botox Treatment

The economic efficiency of BoNT-A treatment is an important factor for both the individual and the community. Cost-effectiveness analyses indicate that BoNT-A is economically favorable for chronic migraine due to reductions in headaches frequency [33]. While the upfront cost of therapy is higher than traditional oral agents, calculations of the National Institute for Health and Care Excellence (NICE) show that long-term clinical improvements translate into substantial economic savings for patients, healthcare systems, and employers [34].

8. Comparison with CGRP Monoclonal Antibodies

CGRP-targeting monoclonal antibodies are an emerging class of migraine preventives. Both BoNT-A and anti-CGRP therapies demonstrate efficacy in chronic migraine [35]. Currently, monotherapy remains the standard first-line approach in migraine prevention. However, advances in the understanding of migraine pathophysiology support the development of well-justified combination treatment strategies, particularly for chronic migraine. Using two agents together may produce a synergistic effect due to their distinct pharmacological mechanisms [36]. Early studies suggest combination or sequential therapy may benefit non-responders, although more research is needed [35].

9. Limitations and Future Directions

- BoNT-A is effective only in chronic migraine, not episodic migraine [14].
- Predictors of response (clinical or biomarker-based) require further investigation [13].
- Combination therapy with CGRP inhibitors is a promising area of research [16].

10. Conclusions

OnabotulinumtoxinA is a well-established, effective, and safe preventive treatment for chronic migraine. Standardized injection protocols, choosing an experienced practitioner, maintaining a minimum interval between injections and careful patient selection maximize benefit. The side effects are rare and side effects are rare and the effect of this medicine outweighs its risks. It is also an economic option of treatment, thanks to reducing the frequency of chronic migraine attacks. Emerging therapies such as CGRP-targeting may complement BoNT-A, and future research will clarify optimal combinations.

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