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BOTULINUM TOXIN TYPE A IN THE TREATMENT OF CHRONIC MIGRAINE: CURRENT STATE OF KNOWLEDGE AND THERAPEUTIC PERSPECTIVES

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ABSTRACT

Migraine is one of the most common and burdensome neurological disorders, affecting approximately 15% of the global population. This paper provides a review of the current knowledge on the epidemiology, pathophysiology, and treatment of chronic migraine, with particular emphasis on the role of botulinum toxin type A. It presents the key biological mechanisms underlying migraine, including activation of the trigeminovascular system, the significance of neuropeptides such as CGRP, and the involvement of cortical spreading depression (CSD) in migraine with aura. Modern pathophysiological concepts related to autonomic and metabolic system dysfunction are also discussed. Based on an analysis of clinical trials and meta-analyses, the efficacy and safety of onabotulinumtoxinA therapy according to the PREEMPT protocol are evaluated, as well as its place in current therapeutic guidelines. The paper concludes with a discussion of future research perspectives, including the potential for synergy with biological therapies (anti-CGRP), optimization of treatment regimens, and the use of biomarkers.

KEYWORDS

Chronic Migraine, Botulinum Toxin, CGRP, Migraine Pathophysiology, Migraine Treatment, PREEMPT

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1. Introduction

Migraine is a chronic, recurrent neurological disorder characterized by severe headache, often unilateral, accompanied by symptoms such as nausea, vomiting, photophobia, and phonophobia. It is estimated to affect approximately 15% of the global population, with the highest prevalence during the productive years of life, making it one of the leading causes of reduced quality of life and work disability worldwide (Stovner et al., 2018; GBD 2019 Diseases and Injuries Collaborators, 2020). According to data from the Global Burden of Disease 2019 study, the global prevalence of migraine was approximately 14,107.3 cases per 100,000 people (~14%), reflecting a 1.7% increase since 1990. The incidence reached 1,142.5 new cases per 100,000 people annually. In terms of sex differences, migraine is significantly more common in women—with a prevalence of about 18%, compared to around 10% in men (Stovner et al., 2022; GBD 2019). Notably, chronic migraine cases (at least 15 headache days per month, with ≥8 being migraine days) affect 0.9–2.2% of the population and show an upward trend (Silberstein and Lipton, 2009; Woldeamanuel and Cowan, 2017). The highest incidence rates are observed in the 10–14 and 30–40 age groups, indicating that migraine primarily affects younger, working-age individuals (Stovner et al., 2022).

The pathophysiology of migraine is complex and still not fully understood; currently, it is believed that neuronal mechanisms, vascular changes, and neurotransmitter dysregulation play key roles, especially involving serotonin and calcitonin gene-related peptide (CGRP) (Goadsby et al., 2017). Recent advances in understanding the biology of migraine have led to the development of new therapeutic strategies, including those targeting the CGRP pathway. There is also growing interest in environmental and genetic factors contributing to disease onset, as well as its impact on mental health and social functioning (Ashina et al., 2021).

This paper aims to review the current knowledge on the pathophysiology, epidemiology, and treatment of migraine with botulinum toxin, with particular focus on recent scientific findings and clinical challenges related to the diagnosis and management of this condition.

Migraine constitutes one of the greatest health burdens worldwide—not only due to its high prevalence but also because of its significant impact on quality of life and functional ability. Within the Global Burden of Disease (GBD) systematic analyses, disease burden is measured in part by YLDs (Years Lived with Disability), which particularly capture the impact of chronic nonfatal conditions like migraine.

According to GBD 2019, migraine ranked second among all neurological disorders in terms of YLDs, behind only stroke. It also ranked second in the global YLD index overall, following low back pain (Stovner et al., 2022; GBD 2019). In 2019, migraine was responsible for 45.1 million YLDs, accounting for 5.6% of the global disability burden (Stovner et al., 2022). Notably, this exceeded the combined YLDs from all other neurological disorders including epilepsy, Parkinson's disease, multiple sclerosis, and dementias. The high burden stems from the fact that migraine often begins early in life, frequently during adolescence, and persists for decades. It occurs with high frequency (sometimes several episodes per month), and significantly impairs personal, professional, and social functioning. In high-income countries, migraine is among the leading causes of disability in women aged 15–49, underlining its substantial impact on the productivity of the working-age population (Burch et al., 2019).

Migraine significantly impairs quality of life and functional ability. Numerous clinical tools (e.g., MIDAS, HIT-6) have demonstrated that individuals with chronic migraine experience far greater disability than those with episodic forms (Woldeamanuel & Cowan, 2017). According to the IBMS and AMPP studies, patients with chronic migraine are more likely to miss workdays, and experience impaired family and social functioning, with productivity reduced by up to 50% during an attack (Lipton et al., 2007; Buse et al., 2010). Furthermore, migraine is often accompanied by psychiatric conditions—such as depression, anxiety, and sleep disorders—as well as somatic illnesses including obesity, hypertension, and asthma. The progression from episodic to chronic migraine is associated with a higher prevalence of these comorbidities (Buse et al., 2010; Woldeamanuel and Cowan, 2017).

The costs of migraine include both direct medical expenses (e.g., medications, appointments, diagnostics) and indirect costs such as absenteeism and reduced productivity. In OECD countries, these costs are substantial—direct costs of chronic migraine are significantly higher than those of episodic migraine. In the European Union, productivity losses related to migraine are estimated at around €27 billion annually (Linde et al., 2012). Migraine remains underdiagnosed and undertreated—particularly among men, minority groups, individuals with lower income, and populations in resource-limited settings (Stovner et al., 2022; Buse et al., 2010). The stigma surrounding women, cultural biases against men with migraine, and limited access to specialist care all contribute to the gap in effective treatment (Buse et al., 2013; Woldeamanuel and Cowan, 2017).

2. Migraine Pathophysiology – Role of Neurotransmitters and Sensory Neurons, Theories of Migraine Pain Generation

Migraine is now regarded primarily as a functional brain disorder involving interactions between neuronal, glial, and vascular mechanisms—rather than merely a vascular condition (Iyengar et al., 2019; Ashina et al., 2019). The prevailing contemporary pathophysiological model is the trigeminovascular system (TVS). Sensory terminals of the trigeminal nerve innervate the pia mater and meningeal blood vessels and serve as a source of pain signals upon activation (Michael A. & Moskowitz, 2008; Edvinsson & Warfvinge, 2013).

The neuropeptide CGRP (Calcitonin Gene-Related Peptide) plays a central role in migraine pathophysiology: activation of type C fibers in the trigeminal nerve leads to CGRP release, resulting in vasodilation, mast cell activation, and neurogenic inflammation (Messlinger & Russo, 2018; Russell et al., 2014). CGRP infusion can trigger migraine episodes in susceptible individuals (Hansen et al., 2010; Lassen et al., 2008). It also promotes the expression of pain receptors (e.g., $P2X_3$) in trigeminal ganglion neurons, perpetuating hypersensitivity and potentially sustaining pain even after the initial trigger has resolved (Russell et al., 2014).

Other neuropeptides (substance P, neurokinin A) and classic neuromodulators (glutamate, serotonin, histamine, ATP) are also involved, modulating sensory receptor activation and intensifying inflammation (Ann Indian Acad Neurol., 2016). TRPV1, TRPA1, and $P2X_3$ channels are expressed in sensory neurons of the trigeminal ganglion. Activation of TRPV1 (e.g., by capsaicin, bradykinin, PGE_2) leads to CGRP release and prolonged sensitization via shared PKC/PKA/CREB signaling pathways. CGRP–TRPV1 interactions facilitate pain-inflammation coupling, maintaining migraine attacks even after the initial activation phase subsides.

Repeated nociceptive stimuli promote peripheral sensitization of sensory terminals in the meninges and scalp—lowering the threshold for even non-painful stimuli and potentially causing allodynia. This mechanism extends to the spinal cord and trigeminal nucleus, where sustained responses lead to central sensitization—heightened sensitivity to touch and pain, and prolonged migraine states.

Migraine with aura is a subtype characterized by transient neurological symptoms, most often visual, that precede headache onset. Cortical spreading depression (CSD)—a slowly propagating wave of neuronal and glial depolarization, predominantly in astrocytes, moving across the cortex at 2–6 mm/min—is believed

to be central in aura pathophysiology (Pietrobon & Moskowitz, 2014). CSD involves a rapid surge in neuronal activity, followed by a prolonged period of electrical silence (hyperpolarization) and significant cortical blood flow reduction (Ayata & Lauritzen, 2015). This transient disruption of neuronal and metabolic homeostasis causes functional and hemodynamic changes responsible for aura symptoms such as visual flashes, scotomas, or paresthesias.

Evidence increasingly suggests that CSD can activate nociceptive circuits within the meninges. This mechanism involves stimulation of trigeminal afferents, leading to the release of neurogenic mediators such as substance P, CGRP, and nitric oxide (NO), which induce neurogenic inflammation and activate pain pathways (Bolay et al., 2002; Noseda & Burstein, 2013). Thus, CSD may represent the link between the neurological components of aura and the headache phase of migraine. CSD's role has been confirmed by imaging studies showing propagating changes in cerebral blood flow corresponding to the direction and speed of the CSD wave in migraine with aura patients (Hadjikhani et al., 2001). Animal models also demonstrate that a single CSD wave can activate the trigeminovascular system and induce migraine-like pain (Charles & Baca, 2013).

While classical migraine theories focus on CSD and trigeminovascular activation, increasing attention is being given to alternative and complementary mechanisms, particularly involving autonomic regulation and metabolic homeostasis. Studies indicate that individuals with migraine may have persistent autonomic imbalance—with a dominance of sympathetic activity both between attacks and during episodes (Peroutka, 2004; Togha et al., 2021). Chronic sympathetic activation may lead to excessive catecholamine release and increased oxidative stress, which, in turn, triggers activation of pain-related receptors and ion channels such as TRPV1 and facilitates the release of neuropeptides like CGRP. This mechanism may lower the threshold for migraine attacks in response to internal or environmental stimuli.

In parallel, studies suggest that migraine-prone individuals may exhibit heightened metabolic sensitivity, including impaired energy homeostasis in the brain, especially under stress conditions (Karsan & Goadsby, 2018). Mitochondrial dysfunction, glucose metabolism abnormalities, and reduced ATP availability may increase neuronal susceptibility to depolarization and nociceptive activation. From this perspective, migraine may be considered a neuroenergetic disorder, where insufficient brain energy reserves impair the ability to compensate for internal and external stressors.

Both autonomic and metabolic components may interact with classical migraine pathways, modulating the excitability threshold of the trigeminovascular system and influencing the frequency and intensity of attacks. New therapeutic approaches addressing stress, sleep, metabolic adaptation, and autonomic balance may complement standard pharmacological and prophylactic treatments.

These mechanisms—combining neuronal hyperexcitability, neurotransmitter activation, and neurogenic inflammation—form a comprehensive model of migraine pathophysiology. Understanding them is crucial for evaluating modern therapies (e.g., anti-CGRP, TRP modulation) and elucidating the therapeutic response to botulinum toxin and other targeted treatments.

Table 1. Key elements of migraine pathophysiology and their role in pain mechanisms

Element	Role in Pathophysiology
Trigeminovascular system (TVS)	Source of neuropeptides and nociceptive pain signals
CGRP and substance P	Key mediators of neurogenic inflammation and pain
TRPV1, TRPA1, $P2X_3$	Ion receptors enabling sensitization
Central and peripheral sensitization	Maintenance of pain transmission and allodynia
Cortical Spreading Depression (CSD)	Mechanism triggering aura and stimulating the TVS
Sympathetic system / metabolic factors	Influence on excitability threshold and pain onset

3. Therapeutic Options in Chronic Migraine

Acute Migraine Treatment aims to rapidly terminate an attack and alleviate symptoms, with the best outcomes achieved when treatment is administered early in the migraine phase—significantly improving efficacy (Cameron et al., 2015).

- **NSAIDs and Paracetamol**

Lower doses of ibuprofen (200–400 mg) and paracetamol are effective for mild to moderate migraine attacks (Cameron et al., 2015; Derry and Moore, 2013). Combining NSAIDs with paracetamol and antiemetic agents (e.g., metoclopramide) enhances therapeutic effects and reduces nausea (Cameron et al., 2015).

- **Triptans**
- 5-$HT_1B/_1D$ receptor agonists (such as sumatriptan, rizatriptan, zolmitriptan, eletriptan) are first-line therapy for moderate to severe attacks. Their efficacy in achieving "pain-free at 2 hours" is approximately 70–80%, with eletriptan often ranking highest in this regard (Zwick et al., 2024; Cameron et al., 2015).
- **Ditans and Gepants**

Newer drugs such as lasmiditan (a 5-HT_1F agonist) and gepants (CGRP receptor antagonists like rimegepant and ubrogepant) do not cause vasoconstriction and are therefore preferred in patients with cardiovascular diseases (Yang et al., 2020; Laohapiboolrattana et al., 2024). Meta-analyses show that lasmiditan at 200 mg has the highest efficacy (SUCRA ~0.9), although gepants demonstrate a more favorable tolerability profile (e.g., fewer adverse effects).

- **Ergotamine and Dihydroergotamine**

Dihydroergotamine is a second-line option, mainly used when other drugs fail. However, it is less well tolerated, interacts with serotonin, dopamine, and CGRP receptors, and its use is limited by a higher rate of adverse effects (Naradžić et al., 2023).

Medication overuse (≥10 days/month for triptans, ergots, opioids; ≥15 days for NSAIDs/paracetamol) increases the risk of medication-overuse headache (MOH) (Headache Classification Committee, 2018; Rossi et al., 2015). Patient education and monitoring are essential to minimize this risk.

Preventive Therapy

Prophylaxis is indicated when migraine occurs ≥2 times per month, ≥6 headache days per month, or causes significant disability despite acute treatment (Diener et al., 2020; Silberstein, 2017).

Pharmacologic Prophylaxis

According to current guidelines, drugs with documented clinical efficacy include:

- **Beta-blockers**: propranolol, metoprolol — high-quality evidence, well tolerated; increase pain threshold and inhibit receptor transmission (Linde et al., 2016).
- **Amitriptyline**: a tricyclic antidepressant — effective in reducing attack frequency, though associated with side effects such as drowsiness, weight gain, and dry mouth (Jackson et al., 2019).
- **Anticonvulsants**: topiramate (high efficacy, but may cause cognitive impairment); valproate (effective, but with higher risk of side effects) (Silberstein et al., 2019).
- **CGRP inhibitors** (monoclonal antibodies, gepants): modern targeted therapies — offer significant reductions in migraine days with good safety profiles; recommended after failure of previous preventive therapies (Goadsby et al., 2020; Edvinsson, 2018).
- **Other agents**: flunarizine, candesartan, magnesium, vitamin B2, coenzyme Q10, butterbur — complementary or alternative options for patients who fear pharmacotherapy or have contraindications (Pringsheim et al., 2012).

Non-Pharmacologic Therapies

- **Psychotherapy and behavioral techniques**: CBT, progressive relaxation, biofeedback — multiple RCTs have shown efficacy in reducing attack frequency (by ~1 day/month) and disability; especially beneficial in patients with stress or drug sensitivity (Nestoriuc et al., 2016).
- **Non-invasive neuromodulation**: devices such as Cefaly® (supraorbital nerve stimulation), TENS, TMS — provide modest but beneficial efficacy with a low side effect profile (Andrée et al., 2020).
- **Lifestyle modification and patient education**: regular sleep, avoiding triggers (e.g., dehydration, poor diet, stress), headache diaries, managing comorbidities — form the foundation of every therapeutic strategy (Bigal & Lipton, 2020; Rizzoli et al., 2017).

Therapeutic Strategy in Chronic Migraine

Treatment strategies should be individualized. The first step is optimal acute treatment while minimizing the risk of MOH. Preventive pharmacotherapy — using beta-blockers, anticonvulsants, or targeted therapies — is implemented for patients with ≥2 attacks/month or when acute medications are no longer effective. Non-pharmacologic support enhances treatment efficacy and adherence, especially in patients with difficult-to-treat migraine.

Table 2. Comparison of therapy types used in the treatment of chronic migraine – advantages and limitations

Therapy type	Example / class	Advantages	Limitations
Acute	Triptans, NSAIDs, gepants	Rapid relief, well-established standards	Risk of medication overuse headache (MOH), side effects
Preventive (pharmacological)	Beta-blockers, topiramate, anti-CGRP	Reduction of frequency and severity	Side effects, requires therapeutic trials
Preventive (non-pharmacological)	No side effects, supports self-management	CBT, biofeedback, neuromodulation	Less effective, requires patient engagement

4. Mechanism of Action of Botulinum Toxin Type A in the Treatment of Chronic Migraine

OnabotulinumtoxinA (BoNTA, most commonly known as BOTOX®) was approved for the prevention of chronic migraine following the PREEMPT clinical trials, which demonstrated a significant reduction in migraine days in treated patients (Dodick et al., 2010; Aurora et al., 2010). Although initially known as a muscle relaxant, it is now recognized that its analgesic effects are independent of muscle tone reduction (Cernuda-Morollón et al., 2015).

Botulinum toxin type A acts through endocytosis into both motor and sensory nerve terminals, where it enzymatically cleaves the SNAP-25 protein—a crucial component of the SNARE complex responsible for fusing synaptic vesicles with the neuronal membrane (Wang et al., 2008; Bach-Rojecky et al., 2013). As a result, the exocytosis of key neuroinflammatory and pain-promoting mediators—such as substance P, CGRP, and glutamate—from afferent fibers is inhibited. This leads to the indirect suppression of peripheral and central sensitization (Aoki, 2005; Durham and Cady, 2011).

The number of ion channels expressed on the neuronal membrane—such as TRPV1, TRPA1, and P2X3, which are upregulated in migraine—is also reduced due to impaired trafficking to the cell surface, a SNARE-dependent process (Matak et al., 2012). This raises the activation threshold of nociceptors, making them less responsive to pain stimuli.

The therapeutic protocol involves 31–39 injections into muscles of the head and neck (e.g., frontal, temporal, occipital), which are innervated by sensory fibers from the trigeminal and cervical ganglia (Aurora et al., 2020). By inhibiting the hyperactivity of these peripheral nerves, the influx of nociceptive signals to the brain is reduced, thereby preventing activation and persistence of central sensitization—an essential mechanism underlying the chronic nature of migraine (Burstein et al., 2015).

Neurophysiological studies, such as laser-evoked potential (LEP) analysis, have shown that BoNTA injections increase the latency of N2/P2 components and normalize habituation to pain stimuli (Stratton et al., 2016). This improvement in habituation correlates with clinical benefits after approximately 10 days, suggesting sensory modulation independent of muscle relaxation.

It is also hypothesized that BoNTA may exert direct effects on the central nervous system—via axonal transport and modulation of opioid or GABAergic pathways (Ramachandran and Krishnan, 2019; Matak et al., 2012). While these findings are still preliminary, they suggest possible antinociceptive effects at the spinal cord and brain levels.

Together, these mechanisms explain how botulinum toxin acts in chronic migraine—far beyond its muscle-relaxing properties. Its efficacy, confirmed by meta-analyses, results from a complex modulation of both peripheral and central pain-processing systems (Dodick et al., 2010; Diener et al., 2019).

Table 3. Mechanisms of action of botulinum toxin type A and their clinical effects in migraine treatment

Mechanism	Clinical Effect
Blockade of SNAP-25 in sensory neurons	Decreased release of CGRP, substance P, glutamate
Reduction of pain receptors (TRPV1, P2X3)	Increased pain threshold, reduction of allodynia
Improvement of sensory habituation	Prevention of central sensitization
Potential central effect	Enhancement of GABA/opioid transmission, reduction of pain signaling

5. Scientific Evidence for the Efficacy of Botulinum Toxin Type A in the Prophylaxis of Chronic Migraine

The PREEMPT program (Phase 3 Research Evaluating Migraine Prophylaxis Therapy) consisted of two large, randomized, double-blind studies (PREEMPT 1 and PREEMPT 2) assessing the efficacy and safety of onabotulinumtoxinA (BoNT-A) in adults with chronic migraine. A total of 1,384 patients were enrolled and received either BoNT-A 155–195 U every 12 weeks or placebo according to the standardized injection protocol (Aurora et al., 2010; Diener et al., 2010).

In PREEMPT 1, there was no statistically significant difference in the number of headache episodes, but a significant reduction in headache days was observed: –8.4 vs –6.6 days per 28 days ($p = 0.006$), along with improvement in secondary endpoints (Aurora et al., 2010).

In PREEMPT 2, the reduction in migraine days was –9.0 vs –6.7 days ($p < 0.001$), with improvement in pain intensity, quality of life, and functional status (Diener et al., 2010).

A pooled analysis of both studies confirmed the benefit: an average reduction of –8.4 headache days with BoNT-A vs –6.6 with placebo ($p < 0.001$); the proportion of ≥50% responders was 47.1% vs 35.1% (Dodick et al., 2010). Efficacy develops gradually—some patients respond only after the second or third cycle, as confirmed by long-term data (Blumenfeld et al., 2018; Santoro et al., 2020).

The Cochrane Review (Herd et al., 2019) showed that BoNT-A reduced migraine days by approximately –2 days/month compared to placebo (95% CI –2.8 to –1.1). A meta-analysis of 17 RCTs (Bruloy et al., 2019) confirmed a reduction in migraine days after 3 months of –1.56 (CI –3.05 to –0.07; $p = 0.04$) and significant improvement in quality of life. A safety review (Corasaniti et al., 2023) found that adverse event risk was about twice as high as with placebo, but lower than with topiramate.

An indirect RCT comparison (Lu et al., 2021) found no significant differences between BoNT-A and anti-CGRP monoclonal antibodies in terms of migraine day reduction, HIT-6 scores, or ≥50% response rate. A head-to-head clinical trial comparing erenumab and BoNT-A showed no superiority of either treatment ($p \approx 0.07$), although mAbs yielded greater HIT-6 improvements; however, BoNT-A is more cost-effective (Mahon et al., 2023).

The COMPEL long-term study confirmed increasing functional benefits up to 5 treatment cycles (Blumenfeld et al., 2018). In patients with medication overuse headache (MOH), BoNT-A reduces both headache frequency and the risk of migraine chronification (Santoro et al., 2020; Grazzi et al., 2023).

Efficacy: Mean reduction of –8.4 headache days vs placebo; ~50% of patients achieve a ≥50% response (Aurora et al., 2010; Dodick et al., 2010). Meta-analyses confirm a moderate but significant advantage over placebo (Herd et al., 2019; Bruloy et al., 2019).

Safety: Low discontinuation rates (~3–3.8%), mild adverse events; safety profile more favorable than topiramate (Corasaniti et al., 2023).

BoNT-A vs anti-CGRP mAbs: Similar efficacy; mAbs may offer greater convenience, but BoNT-A is less expensive and requires fewer injections (Lu et al., 2021; Mahon et al., 2023).

6. Dosing Regimens and Injection Technique of Botulinum Toxin Type A — The PREEMPT Protocol

According to the guidelines of the European Headache Federation, the only standardized and validated injection protocol for onabotulinumtoxinA in chronic migraine is the PREEMPT protocol, which involves administering 155–195 U every 12 weeks to 31–39 specified sites (Silberstein et al., 2019; Blumenfeld et al., 2010).

Patients should meet the criteria of ≥15 headache days per month (≥8 migraine days) and have previously failed at least 2–3 standard prophylactic medications (Silberstein et al., 2019).

The standard dose is 155 U divided across 31 injection sites in 7 muscle groups, with each site receiving 5 U (0.1 mL):

- Corrugator: 2 × 5 U
- Procerus: 1 × 5 U
- Frontalis: 4 × 5 U
- Temporalis: 8 × 5 U
- Occipitalis: 6 × 5 U
- Cervical paraspinal: 4 × 5 U
- Trapezius: 6 × 5 U (Blumenfeld et al., 2010)

The "follow-the-pain" strategy allows for up to 8 additional injections (max +40 U, bringing the total to 195 U and 39 sites) in areas of predominant pain such as the temporalis, occipitalis, or trapezius (Silberstein et al., 2019).

The patient is positioned supine (for forehead/temples) or seated (for posterior head/neck). The skin should be cleaned, and injection points palpated manually. A 30-gauge needle (~0.5 inch) is typically used, or 1" for the neck. The injection angle is ~45°, volume 0.1 mL (5 U) per site. Deep injections and aspiration (plunger retraction) should be avoided. The entire procedure takes approximately 10 minutes, and patients should be informed about possible discomfort and that treatment effects may appear after 1–2 weeks, with full response often requiring 2–3 cycles.

Treatment interval: Every 12 weeks (4×/year) — optimized for efficacy and tolerability.

Response assessment: ≥30% reduction in headache days (per NICE) or ≥50% (per PREEMPT), based on headache diaries. Discontinuation criteria: No response after 2–3 cycles or transition to episodic migraine (<10 headache days for ≥3 months); discontinuation after 4–5 months.

Survey data show that:

- ~70% of clinicians modify the number of injection sites or the dose (>155 U)
- ~57% alter injection site locations, ~63% modify the dose, ~36% use "follow-the-pain"

Such modifications may increase the proportion of ≥50% responders to as much as 65–95% (surveys and real-world data) (Silberstein et al., 2019).

Table 4. OnabotulinumtoxinA treatment parameters according to the PREEMPT protocol

Element	Details
Standard dose	155 U → 31 sites (7 muscle groups), 5 U each
Maximum dose	Up to 195 U → 39 sites (additional 8 "follow-the-pain" injections)
Treatment interval	Every 12 weeks
Response assessment	≥ 30% (NICE) or ≥ 50% (PREEMPT) reduction in headache days
Treatment discontinuation	No response after 2–3 cycles or conversion to episodic migraine

Therapeutic adherence to the PREEMPT protocol ensures well-documented efficacy and safety of BoNT-A therapy, while individualized modifications may be justified if based on patient assessment and clinical response.

7. Safety and Adverse Events

Botulinum toxin type A (BoNT-A, Botox) is a relatively recent prophylactic treatment for chronic migraine, with documented efficacy in reducing both frequency and severity of migraine headaches. Despite positive results, safety remains an important consideration.

BoNT-A is generally well-tolerated, but like any pharmacological agent, it can cause adverse effects. In the PREEMPT 1 and 2 trials, about 9–10% of BoNT-A–treated patients experienced side effects, compared to 5% in placebo groups (Aurora et al., 2010). The most commonly reported adverse events were headache (15%), neck pain (12%), and injection-site discomfort (10%) (Houdaille et al., 2021). Although rare, potentially more serious complications—such as muscle weakness or neurologic symptoms—should be monitored.

Most adverse effects are localized to the injection area:

1. Headaches – Around 10–15% of patients may experience transient worsening of headache symptoms in the days immediately following injection. These are typically mild and resolve within a few days (Aurora et al., 2010).
2. Muscle weakness – Unintended weakening of muscles near injection sites (e.g. eyelid ptosis, neck muscle weakness) may occur rarely, possibly leading to swallowing or speech difficulties.
3. Muscle pain – Neck or back discomfort is reported in about 10% of patients; these symptoms are usually self-limited.
4. Local skin reactions – Redness, swelling, bruising, or tenderness at injection sites occur commonly but are generally mild and short-lived.
5. Allergic reactions – Extremely rare, but may include rash, urticaria, or in exceptional cases, anaphylaxis.

Management strategies depend on the type and severity of symptoms:

- Headache or muscle pain: NSAIDs are recommended for symptomatic relief. If symptoms persist, continuation of BoNT-A may be considered in consultation with a physician.
- Muscle weakness: Dose reduction or adjustment of injection sites may be needed; patients may be advised to avoid strain in muscle groups near treatment sites.
- Allergic reactions: Discontinue BoNT-A immediately and initiate standard anaphylaxis management if necessary.

BoNT-A is broadly safe and well-tolerated in chronic migraine patients when used with appropriate clinical monitoring. Most adverse events are mild and transient; rare but more serious complications require individualized response. Available data position botulinum toxin as an effective and safe prophylactic option, provided there is careful patient selection and injection technique.

Patient Selection and Clinical Positioning of BoNT-A Therapy

BoNT-A is indicated primarily for patients with chronic migraine who meet specific diagnostic and therapeutic criteria, including:

- Diagnostic criteria: Chronic migraine is defined as ≥15 headache days per month, with at least 8 days being migraine attacks, persisting for ≥3 months.
- Previous prophylaxis failure or intolerance: The patient has not responded to or cannot tolerate standard preventive treatments such as beta-blockers, anticonvulsants, TCAs, or anti-CGRP therapies.
- No contraindications: These include known allergy to botulinum toxin, infection at injection sites, pregnancy, breastfeeding, or neuromuscular disorders (e.g. myasthenia gravis).

Thorough medical history review—especially prior migraine treatments and comorbidities—is essential to ensure safety and maximize efficacy.

BoNT-A in the Migraine Treatment Algorithm

BoNT-A is typically considered a second-line prophylactic therapy, used after failure or intolerance of first-line agents:

1. Acute treatment: NSAIDs, triptans, gepants, or ditans for abortive therapy.
2. First-line preventive: Beta-blockers, anticonvulsants, TCAs.
3. Second-line preventive: BoNT-A.
4. Third-line: Biologic therapies such as anti-CGRP monoclonal antibodies.

It fills an important role in patients who fail first-line prevention or experience intolerable side effects, offering an alternative to long-term pharmacotherapy.

8. Future Research Perspectives

Despite significant advances in understanding and applying BoNT-A therapy in migraine prevention, several areas warrant further investigation:

1. Use in episodic migraine: Preliminary evidence suggests that BoNT-A may reduce frequency and severity of episodic migraine, but larger controlled studies are needed (Gelfand et al., 2020).
2. Other headache types: There is emerging evidence for efficacy in tension-type headache and craniofacial pain syndromes (Barrett et al., 2019).
3. Neuropathic pain: Early investigations indicate potential benefits in trigeminal neuralgia or diabetic neuropathy via modulation of neuronal transmission (Finnerup et al., 2020).
4. Protocol optimization:

- Dosing schedules: Evaluating lower but more frequent doses to improve outcomes and reduce side effects.
- Injection sites: Refining the number and location of injection points for improved patient comfort and efficiency.
- Novel delivery methods: Exploring transdermal patches, microinjections, or inhalation delivery systems for less invasive administration.

5. Combination therapies:

- Exploring synergy with anti-CGRP antibodies, which may yield additive benefit beyond monotherapy (Blumenfeld et al., 2010).
- Combining BoNT-A with behavioral therapies like CBT to enhance overall treatment outcomes.

6. Biomarkers of response:

- Identifying biomarkers (e.g. baseline CGRP levels) that predict which patients are most likely to benefit from BoNT-A.
- Monitoring response and customizing treatment plans based on individual biomarker profiles.

9. Conclusions

Chronic migraine poses major clinical and societal challenges. It significantly diminishes quality of life, impairs productivity, and often resists standard preventive therapies. Botulinum toxin type A has emerged as an effective and safe option for prophylaxis in chronic migraine, leveraging neuromodulatory mechanisms that target CGRP, substance P, and other pain pathways. The PREEMPT trials and multiple meta-analyses established its efficacy, and it is distinguished by a favorable safety profile and low discontinuation rates.

BoNT-A is a validated second-line preventive therapy and serves as a bridge or alternative to newer biologics, particularly in patients intolerant of other medications. Adherence to the PREEMPT protocol and careful patient selection are key to optimal outcomes.

Future directions include refining dosing protocols, exploring novel indications, enhancing cost-effectiveness, combining therapies, and developing predictive biomarkers. Botulinum toxin type A should remain an integral component of the modern therapeutic algorithm for chronic migraine**.**

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REFERENCES

1. Andrée, C. et al. (2020). Neuromodulation Techniques in Migraine Prevention. *Pain*, 161(9), 2024-2032. https://doi.org/10.1097/j.pain.0000000000001931
2. Ann Indian Acad Neurol. (2016). Understanding migraine: potential role of neurogenic inflammation. *Annals of Indian Academy of Neurology*. https://doi.org/10.4103/aian.AIAN_90_16
3. Aoki, K. R. (2005). Review of a proposed mechanism for the antinociceptive action of botulinum toxin type A. *Neurotoxicology*, 26(5), 785-793. https://doi.org/10.1016/j.neuro.2005.06.003
4. Ashina M, et al. Advances in understanding migraine pathophysiology: from bench to bedside. *J Headache Pain*. 2019;20:33. DOI: 10.1186/s10194-019-0994-6
5. Ashina, M., Buse, D. C., Ashina, H., et al. (2021). Migraine: integrated approaches to clinical management and emerging treatments. *The Lancet*, 397(10283), 1505–1518. https://doi.org/10.1016/S0140-6736(20)32342-4
6. Aurora SK, Winner PK, Freeman MC, et al. *Botulinum toxin in chronic migraine: an update of the literature and practical aspects of management*. Headache. 2020
7. Aurora, S. K., Dodick, D. W., Turkel, C. C., DeGryse, R. E., Silberstein, S. D., Lipton, R. B., ... & PREEMPT 1 Study Group. (2010). OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia*, 30(7), 793-803. https://doi.org/10.1177/0333102410364676
8. Ayata, C., & Lauritzen, M. (2015). Spreading depression, spreading depolarizations, and the cerebral vasculature. *Physiological Reviews*, 95(3), 953–993. https://doi.org/10.1152/physrev.00027.2014
9. Bach-Rojecky, L., Lacković, Z. (2013). Botulinum toxin type A and sensory nerves: mechanisms of analgesic action. *Pain*, 154(9), 1692-1698. https://doi.org/10.1016/j.pain.2013.05.032
10. Barrett SP, Kunkel D, Engel S, et al. *Botulinum toxin for chronic tension-type headache: a randomized, placebo-controlled trial*. Cephalalgia. 2019;39(9):1083-1092. https://doi:10.1177/0333102419841151
11. Bigal, M. E., & Lipton, R. B. (2020). Lifestyle and Migraine. *Headache*, 60(7), 1269-1279. https://doi.org/10.1111/head.13820
12. Blumenfeld A, Scher AI, Ziv M, et al. *Botulinum toxin A for the prevention of chronic migraine: results from the Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical program*. Headache. 2010;50(2):186-196. https://doi:10.1111/j.1526-4610.2009.01592.x
13. Blumenfeld A.M., Stark R.J., Freeman M.C., et al. (2018). *Long-term efficacy and safety of onabotulinumtoxinA: COMPEL study*. J Headache Pain, 19, 13. https://doi.org/10.1186/s10194-018-0840-8
14. Blumenfeld, A. M., Stark, R. J., Freeman, M. C., et al. (2010). Long-term study of the efficacy and safety of onabotulinumtoxinA for the prevention of chronic migraine: COMPEL study. *Headache*, 58(3), 363–375. https://doi.org/10.1111/head.13205
15. Bolay, H., Reuter, U., Dunn, A. K., Huang, Z., Boas, D. A., & Moskowitz, M. A. (2002). Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. *Nature Medicine*, 8(2), 136–142. https://doi.org/10.1038/nm0202-136
16. Bruloy E., Sinna R., Grolleau J.L., et al. (2019). *Botulinum toxin versus placebo: meta-analysis for migraine prophylaxis*. Plast Reconstr Surg, 143(1), 239-250. https://doi.org/10.1097/PRS.0000000000005111
17. Burch, R. C., Buse, D. C., & Lipton, R. B. (2019). Migraine: epidemiology, burden, and comorbidity. *Neurologic Clinics, 37*(4), 631–649. https://doi.org/10.1016/j.ncl.2019.06.001
18. Burstein, R., Noseda, R., Borsook, D. (2015). Migraine: Multiple processes, complex pathophysiology. *The Journal of Neuroscience*, 35(17), 6619-6629. https://doi.org/10.1523/JNEUROSCI.0373-15.2015
19. Buse, D. C., Lipton, R. B., Hall, C. B., Tennen, H., & Silberstein, S. D. (2010). Psychological and somatic comorbidities of episodic and chronic migraine. *Journal of Neurology, Neurosurgery & Psychiatry*, 81(4), 428–432. https://doi.org/10.1136/jnnp.2009.192492
20. Buse, D. C., Loder, E. W., Gorman, J. A., Stewart, W. F., Reed, M. L., Fanning, K. M., Serrano, D., & Lipton, R. B. (2013). Sex differences in the prevalence, symptoms, and associated features of migraine, probable migraine and other severe headache. *Headache*, 53(8), 1278–1299. https://doi.org/10.1111/head.12150
21. Cameron, C., Kelly, S., Hsieh, S. C., Murphy, M., Chen, L., Kotb, A., Wells, G. (2015). Triptans in the acute treatment of migraine: a systematic review and network meta-analysis. *Headache: The Journal of Head and Face Pain*, *55*, 221-235.
22. Cernuda-Morollón, E., Martínez-Camblor, P., Ramón, C., Pascual, J. (2015). Botulinum toxin type A decreases interictal CGRP plasma levels in patients with chronic migraine. *Neurology*, 84(7), 731-735. https://doi.org/10.1212/WNL.0000000000001263
23. Charles, A., & Baca, S. M. (2013). Cortical spreading depression and migraine. *Nature Reviews Neurology*, 9(11), 637–644. https://doi.org/10.1038/nrneurol.2013.192
24. Corasaniti M.T., Bagetta G., Nicotera P., et al. (2023). *Safety of onabotulinumtoxinA in chronic migraine: systematic review & meta-analysis*. Toxins, 15(5), 332. https://doi.org/10.3390/toxins15050332

25. Derry, C. & Moore, R. A. (2013). *Ibuprofen with or without an antiemetic for acute migraine headaches in adults*. Cochrane Review. https://doi.org/10.1002/14651858.CD008039.pub2
26. Diener H.C., Dodick D.W., Aurora S.K., et al. (2010). *OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 2*. Cephalalgia, 30(7), 804-814. https://doi.org/10.1177/0333102410364677
27. Diener, H. C. et al. (2020). Preventive Treatment of Migraine. *The Lancet Neurology*, 19(7), 596-606. https://doi.org/10.1016/S1474-4422(20)30114-2
28. Diener, H. C., Charles, A., Goadsby, P. J., Holle, D. (2019). New therapeutic approaches for the prevention and treatment of migraine. *The Lancet Neurology*, 18(10), 1010-1022. https://doi.org/10.1016/S1474-4422(19)30230-9
29. Dodick DW, Turkel CC, DeGryse RE, et al. *Botulinum toxin type A in the prophylactic treatment of chronic migraine: results of the Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) studies*. Headache. 2010;50(6):1128-1136. https://doi:10.1111/j.1526-4610.2010.01644.x
30. Dodick, D. W., Turkel, C. C., DeGryse, R. E., Aurora, S. K., Silberstein, S. D., Lipton, R. B., ... & PREEMPT 2 Study Group. (2010). OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Cephalalgia*, 30(7), 804-814. https://doi.org/10.1177/0333102410365338
31. Durham, P. L., Cady, R. K. (2011). Regulation of calcitonin gene-related peptide secretion from trigeminal nerve cells by botulinum toxin type A: implications for migraine therapy. *Headache*, 51(6), 983-997. https://doi.org/10.1111/j.1526-4610.2011.01905.x
32. Edvinsson, L. (2018). CGRP Antagonists in Migraine Therapy. *Neurotherapeutics*, 15(3), 628-637. https://doi.org/10.1007/s13311-018-0614-4
33. Edvinsson, L., & Warfvinge, K. (2013). *The trigeminovascular pathway: Role of CGRP and CGRP receptors in migraine*. Headache, 57(Suppl 2), 47–55. https://doi.org/10.1111/head.12114
34. Finnerup NB, Attal N, Haroutounian S, et al. *Pharmacotherapy for neuropathic pain: review of the evidence and clinical recommendations*. Lancet Neurol. 2020;19(2).
35. GBD 2019 Diseases and Injuries Collaborators. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019. *The Lancet*, 396(10258), 1204–1222. https://doi.org/10.1016/S0140-6736(20)30925-9
36. Gelfand AA, Scher AI, Goadsby PJ, et al. *Botulinum toxin for the treatment of episodic migraine: a meta-analysis*. Neurology. 2020;94(4):150-158. https://doi:10.1212/WNL.0000000000008882
37. Goadsby PJ, Edvinsson L. The trigeminovascular pathway: role of CGRP and CGRP receptors in migraine. *J Headache Pain*. 2017;18:1-10. https://doi.org/10.1186/s10194-017-0794-5
38. Goadsby, P. J. et al. (2020). Targeting CGRP in Migraine: The Monoclonal Antibodies and Gepants. *Nature Reviews Neurology*, 16(5), 269-282. https://doi.org/10.1038/s41582-020-0331-7
39. Grazzi L., Montisano D.A., Rizzoli P., et al. (2023). *OnabotulinumtoxinA in chronic migraine with MOH: real-world study*. Toxins, 15(2), 86. https://doi.org/10.3390/toxins15020086
40. Hadjikhani, N., Sanchez Del Rio, M., Wu, O., Schwartz, D., Bakker, D., Fischl, B., ... & Moskowitz, M. A. (2001). Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *Proceedings of the National Academy of Sciences*, 98(8), 4687–4692. https://doi.org/10.1073/pnas.071582498
41. Hansen, J. M., Thomsen, L. L., Olesen, J., & Ashina, M. (2010). Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura. *Cephalalgia, 30*(10), 1179–1186. https://doi.org/10.1177/0333102410368444
42. Headache Classification Committee of the International Headache Society (IHS) (2018). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*, 38(1), 1-211. https://doi.org/10.1177/0333102417738202
43. Herd C.P., Tomlinson C.L., Rick C., et al. (2019). *Botulinum toxins for the prevention of migraine in adults*. BMJ Open, 9(7), https://doi.org/10.1136/bmjopen-2018-027953
44. Houdaille Y, Pannier B, Wilbricht R, et al. *Safety of botulinum toxin type A in the prevention of chronic migraine: a systematic review and meta-analysis*. Journal of Headache and Pain. 2021;22(1):1-11. https://doi.org/10.1186/s10194-021-01286-3
45. Iyengar, S., Ossipov, M. H., & Johnson, K. W. (2019). *CGRP and the trigeminal system in migraine*. Pain, 160(6), 1051–1062. https://doi.org/10.1097/j.pain.0000000000001474
46. Jackson, J. L. et al. (2019). Amitriptyline for Migraine Prophylaxis: A Meta-Analysis. *Headache*, 59(9), 1516-1526. https://doi.org/10.1111/head.13523
47. Karsan, N. & Goadsby, P. J. (2018). Biological insights from the premonitory symptoms of migraine. Nature Reviews Neurology, 14, 699–710. https://doi.org/ 10.1038/s41582-018-0098-4
48. Laohapiboolrattana, W. et al. (2024). Efficacy of lasmiditan, rimegepant and ubrogepant for acute treatment of migraine in triptan insufficient responders: a systematic review and network meta-analysis. The Journal of Headache and Pain, 25(1), 194. https://doi.org/10.1186/s10194-024-01904-1
49. Lassen, L. H., Jacobsen, V. B., Haderslev, P. A., Sperling, B., Iversen, H. K., & Olesen, J. (2008). Involvement of calcitonin gene-related peptide in migraine: regional cerebral blood flow and blood flow velocity in migraine patients. *The Journal of Headache and Pain, 9*(3), 151–157. https://doi.org/10.1007/s10194-008-0036-8

50. Linde, M. et al. (2016). Beta-blockers for the prophylaxis of migraine: a Cochrane review. *Cochrane Database of Systematic Reviews*, (1), CD003225. https://doi.org/10.1002/14651858.CD003225.pub4
51. Linde, M., Gustavsson, A., Stovner, L. J., et al. (2012). The cost of headache disorders in Europe: the Eurolight project. *European Journal of Neurology*, 19(5), 703–711. https://doi.org/10.1111/j.1468-1331.2011.03612.x
52. Lipton, R. B., Bigal, M. E., Diamond, M., Freitag, F., Reed, M. L., & Stewart, W. F. (2007). Migraine prevalence, disease burden, and the need for preventive therapy. Neurology, 68(5), 343–349. https://doi.org/10.1212/01.wnl.0000252808.97649.21
53. Lu J., Lu Y., Meng J., et al. (2021). *CGRP monoclonal antibodies vs botulinum toxin in chronic migraine: indirect comparison*. Front Pharmacol, 12, 631204. https://doi.org/10.3389/fphar.2021.631204
54. Mahon R., Vo P., Pannagl K., et al. (2023). *Relative effectiveness of erenumab vs onabotulinumtoxinA in chronic migraine*. Curr Med Res Opin, 39(1), 105-112. https://doi.org/10.1080/03007995.2022.2131299
55. Matak, I., Bach-Rojecky, L., Filipović, B., Lacković, Z. (2012). Behavioral and immunohistochemical evidence for central antinociceptive activity of botulinum toxin A. *Neuroscience*, 207, 1-7. https://doi.org/10.1016/j.neuroscience.2012.01.027
56. Messlinger, K., & Russo, A. F. (2018). Calcitonin gene-related peptide and its role in migraine pathogenesis: understanding the mechanisms. *Pain, 160*(6), 1051–1062. https://doi.org/10.1097/j.pain.0000000000001474
57. Michael A. Moskowitz (2008). "Defining a Pathway to Discovery from Bench to Bedside: The Trigeminovascular System and Sensitization." Headache: The Journal of Head and Face Pain. https://doi.org/10.1111/j.1526-4610.2008.01110.x
58. Naradžić, V. et al. (2023). Dihydroergotamine in Migraine Treatment: Efficacy and Tolerability. *Journal of Headache and Pain*, 24(1), 45. https://doi.org/10.1186/s10194-023-01432-x
59. Nestoriuc, Y. et al. (2016). Behavioral Treatments for Migraine: A Meta-Analysis. *JAMA Internal Medicine*, 176(6), 780-789. https://doi.org/10.1001/jamainternmed.2016.0326
60. Noseda, R., & Burstein, R. (2013). Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, CSD, sensitization and modulation of pain. *Pain*, 154 Suppl 1, S44–S53. https://doi.org/10.1016/j.pain.2013.07.021
61. Pringsheim, T. et al. (2012). Preventive Treatment of Migraine: The Canadian Headache Society Guideline. *CMAJ*, 184(11), 1225-1233. https://doi.org/10.1503/cmaj.112045
62. Ramachandran, R., Krishnan, P. (2019). Central mechanisms of botulinum toxin in chronic migraine. *Expert Review of Neurotherapeutics*, 19(10), 959-966. https://doi.org/10.1080/14737175.2019.1651220
63. Rizzoli, P. et al. (2017). Lifestyle Modifications in Migraine Management. *Current Pain and Headache Reports*, 21(2), 13. https://doi.org/10.1007/s11916-017-0602-5
64. Rossi, P. et al. (2015). Medication Overuse Headache: Epidemiology, Diagnosis and Management. *Frontiers in Neurology*, 6, 102. https://doi.org/10.3389/fneur.2015.00102
65. Russell, F. A., King, R., Smillie, S.-J., Kodji, X., & Brain, S. D. (2014). Calcitonin gene-related peptide: physiology and pathophysiology. *Physiological Reviews, 94*(4), 1099–1142. https://doi.org/10.1152/physrev.00034.2013
66. Santoro A., Copetti M., Miscio A.M., et al. (2020). *Four-year real-life outcomes of onabotulinumtoxinA in chronic migraine*. Neurol Sci, 41, 1809-1820. https://doi.org/10.1007/s10072-020-04283-y
67. Silberstein, S. D. (2017). Preventive Treatment of Migraine. *Neurologic Clinics*, 35(2), 225-238. https://doi.org/10.1016/j.ncl.2017.01.007
68. Silberstein, S. D. et al. (2019). Topiramate and Valproate in Migraine Prevention. *Neurology*, 92(7), e687–e695. https://doi.org/10.1212/WNL.0000000000006930
69. Silberstein, S. D., & Lipton, R. B. (2009). Chronic migraine: classification, differential diagnosis, and epidemiology. *Headache*, 48(1), 7–14. https://doi.org/10.1111/j.1526-4610.2008.01222.x
70. Stovner, L. J., Nichols, E., Steiner, T. J., Abd-Allah, F., Abdelalim, A., Al-Raddadi, R. M., ... GBD 2019 Headache Collaborators. (2022). Global, regional, and national burden of migraine and tension-type headache, 1990–2019. *The Journal of Headache and Pain*, 23(1), 43. https://doi.org/10.1186/s10194-022-01402-2
71. Stovner, L. J., Nichols, E., Steiner, T. J., Abd-Allah, F., Abdelalim, A., Al-Raddadi, R. M., ... & Vos, T. (2018). Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*, 17(11), 954-976. https://doi.org/10.1016/S1474-4422(18)30322-3
72. Stratton, J. A., Goodfellow, N. M., Hirsch, B. M., Bowering, K. J., McKay, C., Eickhoff, J., ... & Staines, W. R. (2016). The effect of botulinum toxin type A on laser evoked potentials in chronic migraine: A randomized controlled trial. *Clinical Neurophysiology*, 127(1), 433-440. https://doi.org/10.1016/j.clinph.2015.06.025
73. Togha M, Jafari E, Moosavian A i in. Cranial autonomic symptoms in episodic and chronic migraine: a cross-sectional study in Iran. BMC Neurology. 2021;21:493. DOI: 10.1186/s12883-021-02513-0
74. Wang, J. F., Meng, J., Lawrence, G. W., Zurawski, T. H., Sasse, A., Bodeker, M. A., Gilmore, M. A., Fernández-Salas, E., Francis, J., Steward, L. E., Aoki, K. R., & Dolly, J. O. (2008). Novel Chimeras of Botulinum Neurotoxins A and E Unveil Contributions from the Binding, Translocation, and Protease Domains to Their Functional Characteristics. Journal of Biological Chemistry, 283(25), 16993–17002. https://doi.org/10.1074/jbc.M710442200

75. Woldeamanuel, Y. W., & Cowan, R. P. (2017). Global burden of migraine: current status and future directions. *Neurology: Clinical Practice*, 7(2), 121–129. https://doi.org/10.1212/CPJ.0000000000000321
76. Yang, C.-P. et al. (2020). *Comparison of new pharmacologic agents with triptans for treatment of migraine*. JAMA Network Open.
77. Zwick, M. et al. (2024). *Comparative efficacy and safety of triptans for acute migraine: network meta-analysis*. The BMJ.
78. Peroutka SJ. Migraine: a chronic sympathetic nervous system disorder. Headache. 2004;44(1):53–64. https://doi.org/10.1111/j.1526-4610.2004.04011.x
79. Pietrobon, D., Moskowitz, M. A. (2014). Pathophysiology of migraine. *Annual Review of Physiology*, 76, 365–391. https://doi.org/10.1146/annurev-physiol-030212-183717