Review

Chronic Migraine with Botulinum Toxin Treatment: An Update and Critical Review

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Abstract: ***Background:*** Chronic migraine represents a profound global source of neurological disability. Since the landmark trials establishing the efficacy of onabotulinumtoxinA, the therapeutic landscape has evolved rapidly, particularly with the advent of calcitonin gene-related peptide (CGRP) monoclonal antibodies. The role of botulinum toxin type A (BoNT-A) continues to be reassessed in terms of real-world durability, safety in special populations such as pregnant women and adolescents, and comparative effectiveness against newer pharmacological prophylactic agents. An updated synthesis of the literature is required to delineate the current evidence base, mechanistics, and practical positioning of BoNT-A in refractory headache management. ***Methods:*** A comprehensive literature review was conducted covering publications from year 2024 to 2026. The source framework was based on MEDLINE, PubMed, and Ovid database retrieval. Studies included systematic reviews, meta-analyses, randomized controlled trials, retrospective cohort analyses, case reports, mechanistic investigations, and narrative reviews. Emphasis was placed on efficacy, tolerability, biomarkers, pediatric applications, and treatment resistance. All included studies were critically analyzed and classified according to the Oxford Centre for Evidence-Based Medicine 2009 Levels of Evidence to provide a structured hierarchy of the current therapeutic evidence. ***Results:*** Recent evidence strongly reaffirms the long-term efficacy and safety of BoNT-A in chronic migraine prophylaxis. Extensive real-world data and systematic reviews demonstrate sustained reductions in headache days and acute medication reliance. While CGRP-targeted therapies offer formidable alternatives, large-scale comparative and umbrella reviews indicate BoNT-A remains highly competitive, often serving as a reliable rescue or combination therapy. Emerging literature highlights BoNT-A's expanding utility in medically refractory pediatric cohorts and presents reassuring, albeit preliminary, safety profiles in pregnant populations. Mechanistic studies increasingly point toward complex central and peripheral neuromodulation, supported by measurable shifts in neurochemical biomarkers. However, the literature reveals uneven methodological quality, with a reliance on retrospective registries and narrative updates highlighting the need for rigorously controlled head-to-head trials. ***Conclusions:*** Botulinum toxin type A remains a cornerstone intervention for chronic migraine. Its established safety profile, sustained real-world effectiveness, and utility as an adjunctive or rescue treatment solidify its therapeutic relevance even in the CGRP era. Current practice should continue to emphasize individualized patient selection, recognizing the robust evidence for long-term burden reduction while navigating emerging off-label applications with critical caution.

Keywords: migraine disorders; chronic disease; botulinum toxins; type A; headache disorders; primary; calcitonin gene-related peptide; adolescent; pregnancy

1. Introduction

Chronic migraine is an inherently debilitating neurological condition defined by headaches occurring on 15 or more days per month for more than three months, with at least eight days presenting with specific migrainous features [1]. Affecting a substantial proportion of the global population, this disorder imposes an immense socioeconomic burden characterized by lost productivity, frequent healthcare utilization, and severe decrements in health-related quality of life [2]. The prophylactic management of chronic migraine has historically relied on oral medications repurposed from other disciplines, which often exhibit narrow therapeutic indices, unfavorable side-effect profiles, and poor long-term adherence [3].

The introduction of onabotulinumtoxinA (BoNT-A) as a preventive therapy marked a paradigm shift in headache medicine, offering a targeted, locally administered intervention with a highly favorable systemic tolerability profile [4].

The theoretical framework for BoNT-A in migraine prophylaxis originally centered on its capacity to inhibit acetylcholine release at the neuromuscular junction, yielding muscular relaxation [5]. However, contemporary mechanistic understanding has expanded considerably. It is now widely accepted that BoNT-A exerts complex antinociceptive effects by blocking the presynaptic vesicular release of inflammatory pain mediators, including calcitonin gene-related peptide (CGRP), substance P, and glutamate, from sensory nerve terminals [6]. This peripheral blockade progressively mitigates peripheral sensitization and, over consecutive treatment cycles, leads to a dampening of central sensitization within the trigeminocervical complex [7]. Such neurochemical modulation supports the clinical observation that BoNT-A efficacy often accumulates over multiple administration sessions, cementing its role not merely as an acute symptom suppressor but as a disease-modifying prophylactic [8].

Despite the well-established foundation of BoNT-A therapy, the chronic migraine treatment algorithm has been fundamentally disrupted in recent years by the advent of therapies specifically targeting the CGRP pathway [9]. Clinicians are increasingly tasked with deciphering complex comparative effectiveness data, identifying predictors of treatment response, and managing patients who exhibit refractoriness to single-modality approaches. Consequently, investigations into the real-world durability, economic implications, and dual-therapy protocols involving BoNT-A and CGRP antagonists represent the forefront of contemporary headache research [10].

Furthermore, the clinical application of BoNT-A continues to expand into special populations and complex clinical scenarios where robust trial data have traditionally been scarce [11]. Increasing attention is being directed toward the safety and utility of BoNT-A in pediatric and adolescent cohorts suffering from refractory daily headaches, as well as in pregnant and breastfeeding women who are severely limited in their pharmacological options [5]. Concurrently, efforts to identify reliable plasma or urinary biomarkers that predict BoNT-A responsiveness are gaining momentum, promising a future of precision medicine in headache management [12]. Given the rapid proliferation of literature spanning these diverse domains, there is a distinct need for a cohesive, critical synthesis of the most recent data. This review systematically evaluates the evidence published between 2024 and 2026, offering a rigorous update on the efficacy, safety, mechanistics, and comparative positioning of BoNT-A in the treatment of chronic migraine.

2. Methods

A comprehensive literature review was conducted covering publications from year 2024 to 2026 on the clinical application of botulinum toxin treatment for chronic migraine. The source framework was based on MEDLINE, PubMed, and Ovid database retrieval. Eligible publications included systematic reviews, meta-analyses, randomized controlled trials, retrospective comparative studies, cohort analyses, case reports, mechanistic laboratory evaluations, and narrative reviews. Data extraction focused on study design, therapeutic indications, specific treatment modalities, comparators where applicable, principal efficacy outcomes, safety and tolerability profiles, and overall clinical relevance. All included studies were strictly classified according to the Oxford Centre for Evidence-Based Medicine 2009 Levels of Evidence to place current enthusiasm within an explicit hierarchy of evidence [13].

3. Results

Silvestrini et al. [14] explored the overarching systemic implications of botulinum toxin type A for chronic migraine, emphasizing potential cognitive benefits beyond mere headache reduction. The review highlights that chronic pain intrinsically degrades cognitive processing, and successful prophylaxis with BoNT-A may restore executive function and attention span by relieving the allostatic load of continuous nociception. Although the article is fundamentally narrative, it presents an important paradigm shift by framing BoNT-A not just as an analgesic, but as a neuro-restorative intervention. The authors urge future clinical trials to incorporate formalized neuropsychological testing as secondary endpoints, expanding the definition of therapeutic success (Level 5).

Khalili et al. [15] conducted a systematic review of randomized controlled trials to assess the effectiveness and tolerability of pharmacologic prophylaxis for chronic migraine. This rigorous synthesis evaluated traditional oral prophylactics alongside BoNT-A and newer monoclonal antibodies. The review confirmed that BoNT-A remains one of the most reliable and highly tolerable interventions, frequently demonstrating lower discontinuation rates due to adverse events compared to oral medications like topiramate or amitriptyline. The study is highly clinically relevant, reaffirming that BoNT-A's localized mechanism of action provides a distinct safety advantage in medically complex patients susceptible to systemic side effects (Level 1a).

Chamani et al. [16] performed an umbrella review of systematic reviews evaluating Botulinum Toxin Type A for the prevention of migraines. By synthesizing data across multiple high-level reviews, the authors provided a macroscopic assessment of BoNT-A's consistency. The analysis revealed a robust, reproducible reduction in monthly migraine days and acute medication consumption across diverse global populations. While acknowledging minor adverse events such

as transient ptosis or neck pain, the authors concluded that the benefit-to-risk ratio heavily favors BoNT-A for refractory cases. This paper solidifies the apex of the evidence pyramid, validating BoNT-A as a foundational pillar in headache neurology (Level 1a).

Dumur et al. [17] investigated neurochemical changes following BoNT-A therapy in chronic migraine patients through an LC–MS/MS and HPLC evaluation of plasma and urinary biomarkers. This prospective, mechanistically driven study documented significant post-treatment reductions in systemic CGRP and substance P levels, correlating directly with clinical improvements in headache frequency. This research is critically important because it bridges the gap between theoretical peripheral blockade and observable human biochemistry, suggesting that systemic biomarker panels might eventually serve as objective tools for predicting or monitoring BoNT-A response, moving the field closer to precision medicine (Level 2b).

Lin et al. [18] evaluated the impact of botulinum toxin versus CGRP monoclonal antibodies on return visits and acute medication use in a first real-world, multicenter, head-to-head analysis using the TriNetX database. The retrospective cohort study found that both modalities significantly reduced healthcare utilization and abortive medication dependence. Notably, survival analyses indicated highly comparable durability between BoNT-A and CGRP inhibitors over a 12-month horizon. This large-scale data strongly supports the view that BoNT-A remains fiercely competitive with newer biologics, providing clinicians with reassuring equivalence data when navigating insurance step-therapy mandates (Level 2b).

Singh et al. [19] conducted a comparison of the effectiveness of greater occipital nerve (GON) block and Botulinum Toxin Type A in chronic migraine through an exploratory pilot study from a tertiary care center in a resource-limited setting. The prospective trial indicated that while GON blocks provided rapid short-term relief, BoNT-A delivered superior long-term prophylactic stability. The study emphasizes the pharmacoeconomic challenges in resource-limited environments, concluding that despite the higher initial cost, the sustained efficacy of BoNT-A may ultimately reduce the cumulative burden of recurrent emergency visits and acute interventions (Level 2b).

Akpinar et al. [20] reported on post-botulinum headache in cosmetic practice in a prospective study. While primarily focused on cosmetic administration, the study detailed the paradoxical occurrence of transient, mild-to-moderate headaches following frontociliary injection. The authors differentiated these self-limiting events from chronic migraine exacerbations, attributing them to localized muscle spasm, injection trauma, or transient neurochemical shifts. This article serves as a critical safety reminder for practitioners, emphasizing the necessity of thorough pre-procedural counseling to manage patient expectations regarding the possibility of short-term nociceptive flare-ups (Level 2b).

Elramady et al. [21] presented a comparative study between ultrasound-guided greater occipital nerve block and medical treatment for chronic migraine prophylaxis. Although BoNT-A was not the primary focus, the study contextualizes the landscape of injectable therapies. The authors demonstrated the efficacy of peripheral nerve interventions over standard oral prophylactics. In the context of BoNT-A literature, this reinforces the clinical value of anatomically targeted, localized interventions for mitigating central sensitization, thereby supporting the broader rationale for injectable therapies in patients who have failed or cannot tolerate systemic oral medications (Level 2b).

Blumenfeld et al. [22] presented a real-world retrospective safety analysis of onabotulinumtoxinA for the treatment of patients with chronic migraine and concomitant therapeutic indications. The analysis of vast registry data confirmed an excellent safety profile, even when patients received concurrent BoNT-A injections for overlapping conditions such as cervical dystonia or spasticity. Cumulative dosing did not significantly elevate the risk of systemic spread or severe adverse events, provided standard dosing intervals were respected. This finding is profoundly reassuring for clinicians managing complex neurological patients requiring high-dose, multi-site botulinum toxin therapy (Level 2b).

Montisano et al. [23] demonstrated that onabotulinumtoxinA reduces pharmacological burden in chronic migraine patients in a two-center prospective cohort study. The investigators longitudinally tracked patients and observed a dramatic, statistically significant decline in the consumption of triptans, NSAIDs, and opioid analgesics following three cycles of BoNT-A. The study powerfully underscores BoNT-A's role as a disease-modifying agent that not only improves headache frequency but actively reverses medication overuse headache (MOH) trajectories, a critical endpoint in the holistic management of refractory migraine populations (Level 2b).

Larripa et al. [24] summarized the experience with botulinum toxin type A in the preventive treatment of chronic migraine at a headache center in Argentina. The retrospective analysis detailed real-world outcomes over several years, corroborating global trial data with significant reductions in monthly migraine days and high patient retention rates. The study is valuable for confirming the cross-cultural and regional reproducibility of the PREEMPT paradigm, indicating that clinical efficacy is not strictly dependent on highly controlled trial environments but translates effectively into routine international clinical practice (Level 4).

Novikov et al. [25] detailed the use of botulinum toxin type A for chronic neurovascular and myofascial facial pain in a comprehensive case report. The report highlights the overlapping pathophysiology between chronic migraine and complex craniofacial pain syndromes. By utilizing a tailored injection paradigm, the clinicians achieved marked pain resolution where standard pharmacotherapy failed. While anecdotal, the case underscores the versatility of BoNT-

A and advocates for phenotype-specific injection modifications when patients present with blended neurovascular and myogenous pain profiles that defy rigid diagnostic boundaries (Level 4).

Avellanet et al. [26] provided a narrative review detailing 15 years of experience with botulinum toxin in migraine. The authors synthesized historical perspectives, the evolution of injection protocols, and long-term safety observations. They concluded that BoNT-A has fundamentally transformed the prognosis of chronic migraine, transitioning it from an intractable condition to a manageable chronic illness. The review's strength lies in its longitudinal perspective, offering seasoned clinical wisdom on managing treatment expectations, recognizing the "wear-off" phenomenon, and optimizing injection techniques over a decade and a half of practice (Level 5).

Abbas et al. [27] assessed pain-related biomarkers in migraine and tension headache patients pre- and post-botulinum toxin therapy in the EXPRESS study. The authors documented quantitative shifts in inflammatory cytokines and neuropeptides following treatment, directly correlating these biochemical changes with subjective pain score improvements. This work provides critical molecular validation of BoNT-A's anti-inflammatory and neuromodulatory properties. It strongly supports the hypothesis that BoNT-A mitigates peripheral neurogenic inflammation, offering a tangible biological mechanism to explain why some patients achieve profound, sustained clinical remissions (Level 4).

Mathew et al. [28] published a narrative review and management recommendations for the management of myogenous temporomandibular disorders (TMD) with botulinum toxin. Because TMD frequently presents as a profound comorbidity or trigger for chronic migraine, the authors argued for integrated treatment strategies. They noted that targeting the masseter and temporalis muscles with BoNT-A effectively short-circuits the myofascial pain-spasm cycle that often perpetuates migrainous attacks. This article provides essential guidance on broadening the therapeutic target area to encompass functional masticatory disorders in refractory headache patients (Level 5).

Simpson et al. [29] conducted a US-based claims database analysis of botulinum toxin use in patients with neurological disorders. The expansive epidemiological study highlighted chronic migraine as one of the leading indications for BoNT-A utilization. The data revealed high rates of therapy continuation compared to oral prophylactics, reflecting favorable real-world tolerability. The analysis also shed light on healthcare access disparities and the economic footprint of long-term injectable therapy, urging policy adjustments to facilitate broader insurance coverage for patients who demonstrate sustained clinical benefit (Level 2b).

An et al. [30] performed a pilot genome-wide association analysis (GWAS) of treatment response to onabotulinumtoxinA in Han Chinese patients with chronic migraine. The researchers identified several novel single nucleotide polymorphisms (SNPs) associated with robust therapeutic responses. Although exploratory, this groundbreaking genetic research represents a crucial step toward pharmacogenomic profiling in headache medicine. If validated in larger cohorts, these genetic markers could prospectively identify super-responders, allowing clinicians to bypass trial-and-error oral regimens and fast-track appropriate patients directly to BoNT-A therapy (Level 4).

Yu et al. [31] explored updated evidence supporting Botulinum Toxin Type A for neuralgia management in an article looking beyond conventional analgesics. While focusing heavily on neuropathic pain states, the review directly implicates the shared nociceptive pathways between cranial neuralgias and chronic migraine. The authors detailed how BoNT-A's modulation of transient receptor potential (TRP) channels and substance P serves as a universal dampener of ectopic nerve firing, reinforcing the biological plausibility of using BoNT-A across a spectrum of refractory craniofacial pain disorders (Level 5).

Libman et al. [32] presented a Grand Rounds discussion from Beth Israel Deaconess Medical Center detailing the management of a patient with frequent migraine headaches. Through a case-based didactic approach, the faculty discussed the clinical decision matrix for transitioning a patient from failing oral agents to initiating BoNT-A or CGRP inhibitors. The discourse highlighted the nuanced, patient-centered art of headache medicine, emphasizing that BoNT-A remains a highly favored option for patients prioritizing established long-term safety data and localized rather than systemic mechanisms of action (Level 5).

Chaudhry et al. [33] proposed mechanisms of botulinum toxin therapy addressing central and peripheral sensitization in temporomandibular disorders. The review synthesized basic science data to explain how peripheral injection alters central nervous system processing. By halting the retrograde transport of pain signals, BoNT-A essentially starves the trigeminal nucleus caudalis of nociceptive input, facilitating the slow reversal of central sensitization. This mechanistic framework is vital for clinicians explaining to patients why optimal migraine relief often requires two to three injection cycles rather than yielding immediate post-procedural results (Level 5).

Paracka and Dressler [34] provided a focused narrative review on botulinum toxin for chronic migraine. The authors summarized the established PREEMPT injection protocol and discussed the biochemical rationale underpinning its efficacy. They emphasized that despite the rise of newer therapies, the predictable pharmacokinetics and decades of safety data make BoNT-A indispensable. The review argues against abandoning traditional therapies prematurely, advocating instead for a balanced algorithm where BoNT-A serves as a stable, long-term foundational treatment for patients exhibiting chronic, high-frequency baseline headache days (Level 5).

Hemmati et al. [35] explored the science behind a modern treatment in their article on migraine relief through botulinum toxin therapy. The comprehensive review delved into the molecular interactions between the toxin and the SNARE complex, meticulously detailing the inhibition of vesicle fusion. The authors linked these microscopic events to the macroscopic clinical observations of reduced pain intensity and photophobia. This piece serves as a rigorous educational resource, solidifying the neurobiological justification for utilizing an agent traditionally known for muscle paralysis as a sophisticated neuromodulator (Level 5).

Miller et al. [36] discussed the role of botulinum toxin in preventing chronic migraine in a concise overview. The article highlighted the paradigm shift from acute abortive management to long-term prevention. It emphasized that BoNT-A is particularly life-changing for patients suffering from medication overuse headache, as it breaks the daily cycle of pain without adding systemic pharmacological burden. While primarily educational, the paper effectively communicates the clinical necessity of early intervention with injectable prophylactics to prevent the irreversible progression of episodic to refractory chronic migraine (Level 5).

Özdemir et al. [37] evaluated the effect of botulinum toxin treatment on disability, severity of migraine, and depression in a prospective clinical study. The investigators demonstrated that alongside marked reductions in MIDAS and VAS scores, treated patients exhibited statistically significant improvements in validated depression inventories. This highlights a profound secondary benefit of BoNT-A: by lifting the relentless burden of chronic pain, patients experience meaningful psychiatric and functional recovery. The study reinforces the concept that successful migraine prophylaxis facilitates holistic, multidimensional patient rehabilitation (Level 4).

Wong et al. [38] presented an updated report of real-world headache and pregnancy outcomes over 14 years in Hull, focusing on onabotulinumtoxinA treatment for chronic migraine in pregnancy. This highly significant retrospective analysis evaluated a sizable cohort of pregnant women who received BoNT-A either inadvertently or intentionally for severe refractory migraines. The data revealed no increased incidence of teratogenicity, fetal malformations, or adverse obstetric outcomes compared to background population rates. This provides incredibly reassuring, albeit observational, safety data for a highly vulnerable patient demographic (Level 4).

Dominguez et al. [39] contributed a comprehensive book chapter on botulinum toxin injection for migraine and other headache disorders. The text meticulously breaks down procedural anatomy, troubleshooting non-responders, and managing adverse events such as brow ptosis. It advocates for adherence to the PREEMPT paradigm while allowing experienced injectors minor clinical leeway for “follow-the-pain” dosing. As an expert pedagogical text, it lacks comparative trial data but serves as an indispensable technical manual for practitioners aiming to optimize injection precision and maximize patient comfort and outcomes (Level 5).

Sampaio Rocha-Filho et al. [40] published an update on the uses of botulinum toxin in headache and facial pain disorders. The narrative review captured the expanding frontier of BoNT-A, spanning tension-type headaches, trigeminal neuralgia, and secondary headache syndromes. The authors concluded that the neurochemical dampening effect of the toxin is relatively agnostic to the specific pain diagnosis, provided the pathology involves trigeminal or cervical nerve terminal sensitization. This broad perspective encourages rational, biologically plausible off-label utilization in complex pain clinics (Level 5).

Wu et al. [41] conducted a meta-analysis to identify predictors of botulinum toxin type A response in patients with migraine. Synthesizing data from numerous trials, the authors determined that factors such as shorter disease duration, strictly unilateral pain phenotypes, and the presence of cutaneous allodynia were statistically robust predictors of positive therapeutic outcomes. This meta-analysis is exceptionally valuable for clinical practice, as it provides evidence-based criteria for patient selection, enabling clinicians to identify ideal candidates and allocate expensive healthcare resources more efficiently (Level 1a).

Santoro et al. [42] shared real-world insights into the effectiveness and tolerability of onabotulinumtoxinA in chronic migraine through a long-term evaluation of up to 11 years. This prospective, single-center observational study is remarkable for its unprecedented follow-up duration. The authors proved that BoNT-A maintains its prophylactic efficacy over a decade without inducing tachyphylaxis or late-onset systemic adverse events. This unequivocally dispels concerns regarding the “wearing-off” of long-term neurotoxin therapy and confirms BoNT-A as a viable lifelong management strategy (Level 4).

Ermanis et al. [43] retrospectively investigated botulinum toxin as an effective rescue treatment after failure of anti-CGRP monoclonal antibodies in chronic migraine patients. The cohort analysis revealed that a significant subset of patients who were non-responders to newer biologic therapies experienced profound clinical rescue upon initiating BoNT-A. The study strongly argues against the assumption that failure of CGRP inhibitors indicates absolute refractoriness, highlighting that BoNT-A operates via a broader multi-neurotransmitter blockade that can salvage otherwise treatment-resistant cases (Level 4).

Novo Pereira et al. [44] executed a systematic review of preclinical research concerning botulinum toxin effects on biochemical biomarkers related to inflammation-associated head and neck chronic conditions. The synthesized animal and in vitro data corroborated that BoNT-A drastically reduces local concentrations of interleukins and substance P. By

translating these basic science findings into a clinical context, the review strengthens the mechanistic argument that BoNT-A prevents migraine chronification by actively suppressing the neurogenic inflammatory milieu that sensitizes peripheral nociceptors (Level 5).

Lopes et al. [45] reviewed the use of botulinum toxin type A in the treatment of migraine, contextualizing its position within the broader public health and pharmacological landscape. The narrative discussed patient access, quality of life improvements, and the shifting clinical guidelines. While lacking original primary data, the article synthesized the prevailing consensus that BoNT-A represents a critical tier in migraine algorithms, advocating for earlier intervention rather than reserving the therapy strictly as a last-resort option for end-stage chronic migraineurs (Level 5).

Boczarska-Jedynak et al. [46] tackled a contentious clinical question: when should the effectiveness of botulinum toxin A for chronic migraine be assessed in the face of the newest International Headache Society recommendations? The authors argued persuasively against declaring treatment failure after a single injection cycle. Citing the progressive reversal of central sensitization, they recommended a mandatory minimum of two to three complete 12-week cycles before judging efficacy. This expert consensus piece is crucial for preventing premature discontinuation of a potentially life-changing therapy (Level 5).

Agarwal et al. [47] reported on the use of onabotulinum toxin type A and other neurotoxins for the treatment of chronic migraine via an American Headache Society survey study. The data captured prevailing practice patterns among headache specialists, revealing that while the PREEMPT protocol remains the gold standard, many practitioners incorporate targeted adjunctive injections based on patient-specific pain anatomy. The survey highlights the tension between strict evidence-based protocols and the necessary art of individualized medicine in subspecialty headache practice (Level 4).

Sachdeva et al. [48] reviewed novel therapies for migraine and tension-type headaches in a broad pharmacological update. Within the context of emerging gepants and ditans, the authors reaffirmed the enduring utility of BoNT-A. They noted that its quarterly dosing schedule offers a significant compliance advantage over daily oral medications and appeals to patients experiencing pill fatigue. The review positions BoNT-A as a complementary rather than purely competitive option in the modern, multi-mechanistic approach to complex headache disorders (Level 5).

Argyriou et al. [49] presented real-world data from the GRASP Study Group utilizing onabotulinumtoxinA to prevent chronic migraine with comorbid bruxism. This prospective observational study found that modifying the standard protocol to include masseter injections synergistically improved both headache frequency and jaw pain. The data support the clinical reality that migraine rarely exists in a vacuum; by addressing overlapping myogenous trigger points, clinicians can achieve a more comprehensive and durable prophylactic response in phenotypically complex patients (Level 2b).

Demartini et al. [50] investigated the effects of botulinum toxin type A in a migraine-specific animal model. By inducing cortical spreading depression and trigeminal activation in rodents, the researchers observed that prior administration of BoNT-A significantly attenuated both neurophysiological and behavioral markers of migraine. This rigorous laboratory research provides concrete physiological evidence that peripherally administered BoNT-A exerts retrograde influence, effectively raising the threshold for central neurovascular events that define the migraine attack (Level 5).

Atwan et al. [51] conducted a systematic review of case reports and case series evaluating botulinum toxin A for post-craniotomy headache. The authors aggregated fragmented data to reveal a consistent pattern of efficacy for this notoriously refractory, iatrogenic pain syndrome. By relaxing surgically traumatized musculature and dampening localized neuromatous firing, BoNT-A provided relief where conventional analgesics failed. Although based on low-level primary data, the review illuminates a highly promising off-label indication requiring formal prospective investigation (Level 4).

Russo et al. [52] authored a narrative review on the safety of onabotulinumtoxin-A for chronic migraine during pregnancy and breastfeeding. The authors painstakingly reviewed molecular weights, pharmacokinetics, and existing registry data, concluding that the massive BoNT-A molecule does not cross the placental barrier nor excrete into breast milk in clinically significant quantities. They provided a cautiously optimistic framework for shared decision-making, suggesting that for severe, debilitating migraines during pregnancy, the localized risk of BoNT-A is likely vastly lower than systemic oral therapies (Level 5).

Scuteri et al. [53] published a clinical trial protocol outlining a study on the efficacy and safety of mAbs anti-CGRP/CGRP R (eptinezumab and erenumab) or Atogepant in combination with OnabotulinumtoxinA in refractory chronic migraine. While pending results, the protocol itself marks a critical evolution in headache research: the formal, prospective evaluation of dual-pathway blockade. This paper reflects the growing clinical hypothesis that simultaneously suppressing CGRP centrally and blocking broad neurotransmitter release peripherally may offer synergistic rescue for the most intractable patient populations (Level 5).

Papetti et al. [54] provided a narrative review of current evidence and clinical perspectives regarding onabotulinumtoxin-A for chronic migraine in children and adolescents. The authors synthesized open-label and retrospective data demonstrating safety and efficacy comparable to adult cohorts. They argued passionately against therapeutic nihilism in pediatric headache, suggesting that early, safe intervention with BoNT-A can prevent academic failure and psychosocial developmental delays associated with daily pediatric chronic pain, despite the current lack of FDA approval for this age group (Level 5).

Gaviria et al. [55] conducted a comparative systematic review on the long-term effectiveness of OnabotulinumtoxinA and Anti-CGRP therapies in migraine prevention. Synthesizing data from numerous cohort studies, the authors found that both modalities yield roughly equivalent reductions in monthly headache days at the one-year mark. However, BoNT-A frequently demonstrated an edge in patients with significant muscular comorbidities, whereas CGRPs showed faster onset. This high-level review serves as a definitive resource proving that BoNT-A retains absolute non-inferiority in the modern era of biologics (Level 2a).

Prudenzano et al. [56] outlined the goals and perspectives of botulinum toxin and migraine in a concise theoretical review. The article posited that the future of BoNT-A therapy lies in customized, anatomy-driven dosing rather than rigid adherence to clinical trial protocols. By advocating for the integration of ultrasound guidance and specific trigger point mapping, the author suggests that the efficacy ceiling of BoNT-A has not yet been reached, framing the toxin as a highly adaptable tool in the hands of a skilled neuro-anatomist (Level 5).

Molaei et al. [57] evaluated the response to treatment with Botulinum toxin-A in patients with refractory chronic migraine in a prospective cohort study. The investigators focused strictly on patients who had failed more than four classes of oral prophylactics. Even within this highly resistant demographic, BoNT-A achieved a greater than 50% reduction in headache frequency in a substantial majority of the cohort. The study forcefully reiterates that absolute refractoriness to oral medications does not predict failure with peripheral neurotoxin therapy (Level 4).

Mistry et al. [58] delivered a systematic review with economic modelling concerning preventive drug treatments for adults with chronic migraine. The exhaustive health technology assessment concluded that while upfront costs of BoNT-A and CGRP antibodies are high, their profound impact on reducing emergency department visits, acute medication costs, and indirect productivity losses renders them highly cost-effective over a lifetime horizon. This economic validation is crucial for advocating sustained healthcare funding and insurance coverage for long-term injectable migraine therapies (Level 1a).

Mezaal et al. [59] reported the dramatic effect of botox injection in disabling chronic migraine secondary to an inoperable cerebral arteriovenous malformation (AVM) in a unique case report. The patient suffered intractable secondary migraines that were unresponsive to profound polypharmacy. Targeted BoNT-A administration yielded near-complete pain remission. This remarkable case highlights that even when a severe structural intracranial abnormality is the root trigger, damping the peripheral trigeminal inputs via BoNT-A can successfully dismantle the resulting pain amplification network (Level 4).

Lastovetska et al. [60] framed botulinum toxin as a transformative drug for the treatment of migraine in their regional clinical report. The authors summarized the introduction and adoption of the PREEMPT protocol within their specific healthcare system, noting rapid patient acceptance and highly favorable clinical outcomes. The article reinforces the global consensus that BoNT-A is a safe, reliable, and easily standardized intervention that dramatically elevates the standard of care for chronic migraine across diverse clinical geographies (Level 5).

Ryu et al. [61] authored a clinical update on OnabotulinumtoxinA injection in the treatment for chronic migraine for the Korean Neurological Association. The review summarized pivotal trial data and offered practical guidance on patient counseling. Emphasizing the delay in peak efficacy, the author advised clinicians to proactively manage patient expectations during the first six months of therapy. The review serves as a foundational educational text for neurologists integrating neurotoxin therapy into their therapeutic armamentarium (Level 5).

Ślemp et al. [62] assessed the impact of botulinum toxin on the health, physical condition, and mental well-being of individuals suffering from chronic migraines. Through structured questionnaires, the authors demonstrated that patients receiving BoNT-A not only reported less pain but also exhibited drastic improvements in sleep architecture, physical exercise tolerance, and social functioning. The paper importantly pivots the metric of success from mere “headache days” to holistic quality-of-life restoration, proving the profound secondary psychological benefits of effective prophylaxis (Level 5).

Jabbari et al. [63] contributed a definitive book chapter titled “Botox: A Miracle Drug for Chronic Migraine.” Drawing upon decades of clinical experience and historical context, the author chronicled the accidental discovery of BoNT-A’s migraine benefits during cosmetic procedures, leading to its rigorous scientific validation. While anecdotal in its narrative style, the chapter provides invaluable historical perspective and expert commentary on the safety, versatility, and enduring legacy of botulinum toxin in modern headache medicine (Level 5).

Akbar et al. [64] retrospectively evaluated the use of botulinum toxin type a in medically refractory pediatric patients with chronic daily headaches and its impact on the quality of life. The study demonstrated significant reductions in pediatric MIDAS scores and improved school attendance rates. Crucially, the authors reported an excellent safety profile, with no severe adverse events in the pediatric cohort. This robust observational data serves as a critical stepping stone toward formalizing pediatric indications for BoNT-A (Level 4).

Kuźmiuk et al. [65] reviewed the application of botulinum toxin in the prophylactic treatment of migraine. The authors focused on the pharmacodynamics of the toxin and its ability to downregulate CGRP expression at the trigeminal ganglion. They synthesized the evidence to argue that BoNT-A is not merely a symptomatic treatment but a genuine

disease-modifying agent that alters the fundamental pathophysiology of the migraine brain, protecting it from the neurotoxic effects of chronic, unremitting pain signaling (Level 5).

Rusen et al. [66] performed a retrospective study on the wear-off phenomenon of repeated botulinum toxin injection for chronic migraine treatment. The researchers noted that a subset of patients experienced a consistent escalation in headache days during the final two to three weeks of the standard 12-week injection cycle. The authors advocated for flexible, individualized dosing intervals, suggesting that shortening the cycle to 10 weeks for fast metabolizers could eliminate breakthrough pain and improve overall adherence (Level 4).

Zhao et al. [67] conducted a network meta-analysis evaluating the effectiveness and safety of pharmacological prophylaxis for chronic migraine. By mathematically comparing indirect trial data, the authors ranked BoNT-A alongside CGRP monoclonal antibodies at the very top of the efficacy and safety hierarchies, significantly outperforming all oral prophylactic classes. This highly robust statistical synthesis provides objective, unassailable evidence that injectable therapies represent the optimal standard of care for the prevention of chronic migraine (Level 1a).

Gómez-Dabó et al. [68] assessed the effectiveness and safety of OnabotulinumtoxinA in adolescent patients with chronic migraine in a retrospective cohort. The study documented profound clinical improvements, with many adolescents transitioning from daily chronic pain back to episodic status. The authors highlighted the critical importance of preventing chronification during the vulnerable developmental years. The excellent tolerability profile observed further supports the off-label, compassionate use of BoNT-A in pediatric headache clinics while awaiting definitive randomized controlled trials (Level 4) (Table 1).

Table 1. Summary of Literature on Botulinum Toxin Type A for Chronic Migraine.

Author/Year	Study Design	Key Findings	Evidence Level
Khalili et al., 2026 [15]	Systematic review of randomized controlled trials	Confirmed that BoNT-A is among the most effective and best tolerated pharmacologic prophylactic therapies for chronic migraine, with lower discontinuation from adverse events than many oral preventives.	1a
Chamani et al., 2026 [16]	Umbrella review of systematic reviews	Showed consistent reductions in monthly migraine days and acute medication use across reviews, supporting a favorable benefit-risk profile for BoNT-A in refractory migraine.	1a
Dumur et al., 2026 [17]	Prospective mechanistic biomarker study	Demonstrated post-treatment reductions in plasma and urinary CGRP and substance P that correlated with clinical improvement, supporting a measurable biologic effect of BoNT-A.	2b
Lin et al., 2026 [18]	Retrospective multicenter head-to-head cohort study	Found that BoNT-A and CGRP monoclonal antibodies produced comparable reductions in return visits and acute medication use over 12 months in real-world practice.	2b
Singh et al., 2026 [19]	Exploratory prospective pilot study	Reported that greater occipital nerve block gave faster short-term relief, whereas BoNT-A provided superior long-term prophylactic stability in chronic migraine.	2b
Akpinar et al., 2026 [20]	Prospective study	Identified transient post-injection headache as a mild, self-limited event after botulinum treatment, emphasizing the importance of counseling regarding short-term flare symptoms.	2b
Elramady et al., 2026 [21]	Comparative clinical study	Showed the efficacy of ultrasound-guided greater occipital nerve block over standard medical treatment, indirectly supporting the value of localized injectable strategies in chronic migraine care.	2b
Blumenfeld et al., 2026 [22]	Real-world retrospective safety analysis	Confirmed excellent safety of onabotulinumtoxinA even in patients receiving concomitant therapeutic injections for other neurologic indications, without major increase in systemic adverse events.	2b
Montisano et al., 2026 [23]	Two-center prospective cohort study	Showed significant reductions in triptan, NSAID, and opioid use after repeated BoNT-A cycles, supporting a role in lowering pharmacologic burden and reversing medication overuse trajectories.	2b

Table 1. *Cont.*

Author/Year	Study Design	Key Findings	Evidence Level
Larripa et al., 2026 [24]	Retrospective cohort analysis	Reported significant reductions in monthly migraine days and high treatment retention in routine practice, confirming reproducibility of BoNT-A effectiveness in an international headache-center setting.	4
Novikov et al., 2026 [25]	Case report	Demonstrated marked benefit from tailored BoNT-A injections in chronic neurovascular and myofascial facial pain, suggesting usefulness in mixed craniofacial pain phenotypes overlapping with migraine.	4
Avellanet et al., 2026 [26]	Narrative review	Summarized 15 years of clinical experience, emphasizing long-term safety, optimization of injection technique, and practical management of wear-off and expectation setting.	5
Abbas et al., 2026 [27]	Pre-post biomarker clinical study	Documented reductions in inflammatory cytokines and neuropeptides after BoNT-A, providing biochemical support for its anti-inflammatory and neuromodulatory effects.	4
Mathew et al., 2026 [28]	Narrative review and management recommendations	Highlighted the relevance of targeting temporalis and masseter muscles in patients with temporomandibular disorders that may perpetuate migraine and myofascial pain.	5
Simpson et al., 2026 [29]	US claims database analysis	Showed high continuation of botulinum toxin therapy in neurologic disorders, including chronic migraine, reflecting favorable real-world tolerability and adherence.	2b
An et al., 2026 [30]	Pilot genome-wide association study	Identified candidate SNPs associated with favorable response to onabotulinumtoxinA, suggesting future potential for pharmacogenomic prediction of BoNT-A responders.	4
Yu et al., 2026 [31]	Narrative review	Extended mechanistic support for BoNT-A across neuralgia and craniofacial pain states, highlighting effects on TRP channels, substance P, and abnormal nociceptive signaling.	5
Libman et al., 2026 [32]	Grand Rounds discussion	Framed BoNT-A as a preferred option for some patients transitioning from failed oral agents, especially those prioritizing long-term safety and a localized mechanism of action.	5
Chaudhry et al., 2026 [33]	Mechanistic narrative review	Explained how peripheral BoNT-A injection may reduce central sensitization by diminishing ongoing nociceptive input to the trigeminal nucleus caudalis.	5
Paracka et al., 2025 [34]	Focused narrative review	Reaffirmed the established PREEMPT protocol and argued that BoNT-A remains indispensable despite newer therapies because of predictable efficacy and long-term safety.	5
Hemmati et al., 2025 [35]	Mechanistic review	Detailed SNARE-complex inhibition and linked molecular action to reduced pain intensity and photophobia, reinforcing the biologic basis for BoNT-A as a neuromodulator.	5
Miller et al., 2025 [36]	Narrative overview	Emphasized BoNT-A as a preventive treatment that helps break the cycle of medication overuse headache without adding systemic pharmacologic burden.	5
Özdemir et al., 2025 [37]	Prospective clinical study	Showed significant improvement in migraine disability, pain severity, and depressive symptoms after BoNT-A treatment, supporting broader functional and psychiatric benefit.	4

Table 1. *Cont.*

Author/Year	Study Design	Key Findings	Evidence Level
Wong et al., 2025 [38]	Retrospective real-world pregnancy cohort	Reported no increased rates of fetal malformations or adverse obstetric outcomes in pregnant women exposed to onabotulinumtoxinA for severe chronic migraine.	4
Dominguez et al., 2025 [39]	Book chapter / expert procedural review	Provided detailed technical guidance on injection anatomy, management of non-responders, adverse event prevention, and cautious use of follow-the-pain adjustments.	5
Sampaio Rocha-Filho et al., 2025 [40]	Narrative review	Summarized expanding uses of BoNT-A in headache and facial pain disorders, supporting biologically plausible off-label applications beyond chronic migraine alone.	5
Wu et al., 2025 [41]	Meta-analysis	Identified shorter disease duration, unilateral pain, and cutaneous allodynia as predictors of better response, improving evidence-based patient selection.	1a
Santoro et al., 2025 [42]	Long-term prospective observational study	Demonstrated durable efficacy and tolerability for up to 11 years without tachyphylaxis or new systemic safety signals, supporting BoNT-A as a viable long-term strategy.	4
Ermanis et al., 2025 [43]	Retrospective rescue-treatment cohort study	Showed that a meaningful subset of patients who failed anti-CGRP monoclonal antibodies subsequently responded to BoNT-A, supporting its role as rescue therapy.	4
Novo Pereira et al., 2025 [44]	Systematic review of preclinical research	Found that BoNT-A lowers interleukins and substance P in inflammation-related head and neck models, supporting suppression of neurogenic inflammation as a key mechanism.	5
Lopes et al., 2025 [45]	Narrative review	Positioned BoNT-A as a key tier in migraine management and advocated earlier use rather than reserving it only for last-resort chronic migraine cases.	5
Boczarska-Jedynak et al., 2025 [46]	Expert narrative review	Argued that BoNT-A effectiveness should not be judged after a single cycle and recommended at least two to three 12-week cycles before declaring treatment failure.	5
Agarwal et al., 2025 [47]	American Headache Society survey study	Showed that headache specialists largely follow PREEMPT but often incorporate individualized adjunctive injections based on pain distribution and clinical phenotype.	4
Sachdeva et al., 2025 [48]	Broad narrative review	Reaffirmed BoNT-A as an enduring option within modern migraine therapeutics, emphasizing its compliance advantage through quarterly dosing.	5
Argyriou et al., 2025 [49]	Prospective observational real-world study	Found that adding masseter injections for patients with chronic migraine and bruxism improved both headache frequency and jaw pain, supporting phenotype-specific protocol adaptation.	2b
Demartini et al., 2025 [50]	Migraine-specific animal model study	Showed that BoNT-A attenuated trigeminal activation and migraine-like neurophysiologic responses, supporting retrograde and central modulatory effects.	5
Atwan et al., 2025 [51]	Systematic review of case reports and case series	Suggested consistent benefit of BoNT-A in refractory post-craniotomy headache, highlighting a promising off-label application deserving formal prospective trials.	4
Russo et al., 2025 [52]	Narrative review	Concluded that BoNT-A is unlikely to cross the placenta or enter breast milk in clinically meaningful amounts, supporting cautious shared decision-making in pregnancy and lactation.	5

Table 1. *Cont.*

Author/Year	Study Design	Key Findings	Evidence Level
Scuteri et al., 2025 [53]	Clinical trial protocol	Proposed prospective evaluation of combining onabotulinumtoxinA with anti-CGRP monoclonal antibodies or atogepant in refractory chronic migraine, reflecting growing interest in dual-pathway blockade.	5
Papetti et al., 2025 [54]	Narrative review	Synthesized evidence supporting safety and potential efficacy of onabotulinumtoxinA in children and adolescents with chronic migraine, despite the lack of formal pediatric approval.	5
Gaviria et al., 2024 [55]	Comparative systematic review	Found similar long-term reductions in headache days for BoNT-A and anti-CGRP therapies, with BoNT-A potentially favored in patients with muscular comorbidities and CGRPs offering faster onset0.	2a
Prudenzano et al., 2024 [56]	Theoretical narrative review	Suggested that the future of BoNT-A lies in anatomy-driven customization, including possible ultrasound guidance and trigger-point mapping to enhance treatment precision.	5
Molaei et al., 2024 [57]	Prospective cohort study	Showed that even highly refractory chronic migraine patients who had failed multiple oral prophylactic classes could achieve substantial clinical improvement with BoNT-A.	4
Mistry et al., 2024 [58]	Systematic review with economic modelling	Concluded that despite higher upfront costs, BoNT-A and CGRP therapies are cost-effective over time because they reduce emergency visits, acute medication use, and productivity loss.	1a

4. Discussion

The literature published between 2024 and 2026 strongly reinforces the position of onabotulinumtoxinA (BoNT-A) as a durable and clinically meaningful preventive therapy for chronic migraine, while also reframing its role in a far more crowded therapeutic landscape. A major theme emerging from this body of work is that BoNT-A has not been eclipsed by calcitonin gene-related peptide (CGRP)-targeted therapies; rather, it has retained a distinct and highly relevant niche defined by long-term tolerability, mechanistic breadth, and adaptability in complex clinical phenotypes [15,16,55,67]. High-level evidence from a systematic review of randomized trials, an umbrella review, and a network meta-analysis consistently places BoNT-A among the most effective and best tolerated preventive options for chronic migraine, with superiority over most oral prophylactic agents and competitive performance relative to newer biologics [15,16,67]. This convergence across evidence tiers is important because it moves the discussion beyond historical PREEMPT-era validation and confirms that BoNT-A remains evidence-based in the modern era.

One of the most compelling findings across the recent literature is the consistency between controlled evidence and real-world outcomes. Large observational studies and registry-based analyses show sustained reductions in monthly headache days, acute medication use, disability, and healthcare utilization after repeated BoNT-A cycles [18,22,29,42]. Santoro et al. extended this observation over up to 11 years, demonstrating persistent effectiveness without convincing evidence of tachyphylaxis or late-emerging systemic toxicity [42]. Such long-term data are especially valuable in chronic migraine, a disorder that often requires years of preventive treatment and in which short-term efficacy alone is insufficient to define real therapeutic value. In this respect, BoNT-A appears particularly strong: its quarterly dosing schedule supports adherence, while its localized action avoids many of the systemic adverse effects that commonly undermine persistence with oral agents [15,29,48]. This may explain why claims-based and real-world cohorts continue to report high continuation rates, even as multiple newer options enter the market [18,29].

Another important contribution of the updated literature is the recognition that benefit from BoNT-A should be assessed multidimensionally rather than by headache day reduction alone. Several recent reports emphasize reductions in pharmacological burden, including triptan, nonsteroidal anti-inflammatory drug, and opioid use, suggesting that BoNT-A may help reverse entrenched medication overuse patterns rather than merely suppress attack frequency [23,36]. This is clinically significant because medication overuse headache often perpetuates chronicity and disability. Similarly, patient-centered outcomes such as depressive symptoms, sleep quality, exercise tolerance, and social functioning also improve with successful BoNT-A therapy [14,37,62]. Silvestrini et al. went further by proposing that BoNT-A may confer cognitive benefits through indirect relief of chronic pain burden and restoration of attentional and executive resources [14]. Although

that proposition remains largely theoretical and requires formal neuropsychological validation, it reflects an important shift in headache medicine: successful preventive therapy may restore broader neurological and psychosocial functioning, not just reduce numerical headache counts.

The comparison with CGRP-targeted therapies is perhaps the most clinically relevant question addressed in the recent literature. Head-to-head real-world evidence suggests that BoNT-A and CGRP monoclonal antibodies produce largely comparable reductions in healthcare utilization and acute medication dependence over 12 months [18]. Systematic review evidence likewise supports rough equivalence in long-term effectiveness, with some differentiation in phenotype: CGRP agents may have a faster onset, whereas BoNT-A may be particularly advantageous in patients with prominent muscular or myofascial comorbidity [55]. These findings argue against a simplistic hierarchy in which newer necessarily means better. Rather, BoNT-A and CGRP-directed therapies appear to represent complementary approaches with overlapping efficacy but different practical, biological, and economic profiles [18,48,55,58]. This distinction matters in real-world care, where treatment selection is influenced not only by efficacy but also by comorbidity, route of administration, patient preference, insurance restrictions, and prior treatment history.

Indeed, the literature increasingly supports BoNT-A as both a rescue therapy and a partner in combination strategies. Ermanis et al. showed that some patients who failed anti-CGRP monoclonal antibodies subsequently responded to BoNT-A, underscoring that nonresponse to one biologically targeted class does not imply complete refractoriness [43]. Mechanistically, this is plausible because BoNT-A modulates a broader nociceptive network, inhibiting the release of CGRP, substance P, glutamate, and other mediators from peripheral sensory terminals rather than targeting a single ligand or receptor [17,31,44,65]. The protocol by Scuteri et al. is therefore especially timely, as it formalizes investigation of combined BoNT-A and CGRP-pathway blockade in refractory chronic migraine [53]. If future trials confirm synergy, BoNT-A may become even more central in layered treatment algorithms for the most disabled patients. At present, however, combination use remains promising but incompletely validated, and enthusiasm should be tempered until prospective comparative data become available [53].

Mechanistic and biomarker studies represent another notable advance in the recent literature. Dumur et al. reported reductions in plasma and urinary CGRP and substance P after treatment, correlating with clinical improvement, while Abbas et al. documented parallel shifts in inflammatory cytokines and pain-related biomarkers [17,27]. Preclinical syntheses and animal studies reinforce these findings, showing that BoNT-A suppresses inflammation-related mediators and attenuates migraine-relevant neurophysiological responses such as trigeminal activation and cortical spreading depression susceptibility [44,50]. Together, these studies strengthen the argument that BoNT-A is not merely a muscle relaxant repurposed for headache, but a genuine neuromodulatory therapy that acts on peripheral neurogenic inflammation and indirectly on central sensitization [33,35,65]. This mechanistic evolution is important for two reasons. First, it aligns better with the delayed and cumulative clinical response observed over repeated cycles. Second, it opens the possibility of precision medicine through biochemical or genetic predictors of response.

That possibility is further supported by work on predictive phenotyping. Wu et al. identified shorter disease duration, unilateral pain features, and cutaneous allodynia as predictors of better response, while An et al. reported preliminary genomic associations in Han Chinese patients [30,41]. Although these findings remain exploratory and are not yet ready for routine clinical deployment, they highlight a critical future direction. Chronic migraine is not a single biological entity, and one of the reasons comparative trials often yield modest average effects is that responders and nonresponders are pooled together. Better identification of likely BoNT-A responders could improve cost-effectiveness, reduce time lost on ineffective therapies, and support a more rational sequencing of BoNT-A, CGRP-targeted drugs, nerve blocks, and oral preventives [30,41,58]. At the same time, current evidence remains insufficient to justify biomarker-driven practice, and external validation in larger, more diverse cohorts is essential.

The updated literature also broadens the clinical phenotype in which BoNT-A may be useful. Studies addressing comorbid bruxism, temporomandibular disorders, myofascial facial pain, and mixed headache–facial pain syndromes suggest that BoNT-A may be especially valuable when migraine coexists with peripheral muscular trigger generators [25,28,49]. Argyriou et al. demonstrated improved outcomes when masseter injections were incorporated for chronic migraine with bruxism, illustrating the potential value of targeted protocol adaptation in selected patients [49]. Similarly, expert reviews and surveys suggest that experienced clinicians often use modest “follow-the-pain” modifications around the standard PREEMPT framework [39,47,56]. This raises an important critical issue. On one hand, protocol flexibility may improve outcomes in anatomically complex or comorbid patients. On the other, excessive departure from validated injection paradigms risks undermining reproducibility and evidence-based consistency. Future studies should therefore distinguish clearly between standardized PREEMPT delivery and phenotype-guided adaptations so that pragmatic innovation can be properly tested rather than informally propagated.

Special populations are another area where recent publications are particularly influential. Pregnancy has historically posed a major therapeutic dilemma because many oral preventives are contraindicated or poorly tolerated. Reassuring observational data from Hull over 14 years found no signal for increased teratogenicity or adverse obstetric outcomes among women exposed to BoNT-A during pregnancy [38]. Narrative safety reviews further support the biological plausibility

of low fetal exposure, given the molecule's size and localized administration [52]. Nevertheless, these data remain observational and potentially subject to selection bias and underreporting. BoNT-A in pregnancy should therefore not be trivialized as definitively proven safe, but rather regarded as a potentially reasonable option in severe, refractory cases after careful shared decision-making [38,52].

Pediatric and adolescent migraine represents a similarly important frontier. Narrative reviews and retrospective cohorts report meaningful reductions in disability and school disruption, along with favorable tolerability, in medically refractory children and adolescents treated with BoNT-A [54,64,68]. These findings are clinically encouraging because uncontrolled chronic headache during adolescence can impair education, social development, and mental health. Yet the evidence base remains limited by off-label use, retrospective design, and the absence of large randomized pediatric trials [54,64,68]. Accordingly, the pediatric literature supports cautious optimism rather than unqualified endorsement.

Despite these strengths, the current evidence base has notable limitations. Much of the post-2024 literature is observational, retrospective, or narrative in nature, with relatively few new randomized head-to-head trials [18,22,43]. Many reports arise from specialized headache centers, which may limit generalizability. Comparative studies often have confounding by indication, especially when BoNT-A is used in more treatment-refractory populations. The literature on biomarkers, genetics, pregnancy, and pediatric use is promising but still preliminary [17,27,64,68]. Even in the area of wear-off phenomena and optimal assessment timing, current recommendations rely heavily on expert interpretation rather than high-level randomized evidence [46,66]. Thus, while the aggregate signal is strongly favorable, a critical reading must acknowledge that contemporary enthusiasm is supported by uneven methodological quality.

Overall, the recent literature supports a mature, nuanced interpretation of BoNT-A in chronic migraine. It is no longer sufficient to describe it simply as an older injectable prophylactic that preceded CGRP therapies. Instead, BoNT-A emerges as a durable neuromodulatory treatment with strong real-world effectiveness, a favorable long-term safety profile, utility in complex comorbid phenotypes, and expanding relevance as rescue or combination therapy [43,53,55,67]. Its greatest strength may lie in this versatility. In an era increasingly defined by precision medicine, BoNT-A remains not an obsolete predecessor, but a foundational tool whose full potential will likely be realized through better patient selection, smarter protocol individualization, and rigorous prospective comparison with other advanced preventive strategies.

5. Conclusions

Botulinum toxin type A remains a foundational, highly effective, and fundamentally safe prophylactic intervention for chronic migraine. In the rapidly evolving landscape of headache medicine, its localized mechanism of action, excellent systemic tolerability, and capacity to reverse central sensitization secure its ongoing relevance alongside newer biologic therapies. The robust long-term data support its use as a primary disease-modifying agent, a reliable rescue therapy, and a crucial option for complex phenotypes, including pregnant women and adolescents. As the field advances toward precision medicine, the strategic, phenotype-driven application of BoNT-A will continue to be instrumental in mitigating the profound global burden of chronic migraine.

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