Mini CAT
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Clinical Question
A 38-year-old woman presents with chronic migraines despite trying multiple conventional prophylactic therapies such as beta-blockers, antiepileptic drugs, and tricyclic antidepressants. Despite her dedication, she continues to suffer from severe headaches for 15 or more days per month, greatly impacting her ability to function daily. Given this persistent challenge, the potential effectiveness of Botulinum toxin type A injections as an alternative treatment is under consideration.

PICO Question:

In adult patients with chronic migraine headaches, does the administration of Botulinum toxin type A injections, compared to placebo or standard migraine prophylactic therapy, lead to a reduction in migraine frequency, severity, duration, and improvement in migraine-related disability?

Question Type:

☐Prevalence	☐Screening	☐Diagnosis
☐Prognosis	☒Treatment	☐Harms

PICO search terms:

P	I	C	O
Adult patients	Botulinum toxin type A injections	Placebo	Reduction in migraine frequency
Chronic migraine headaches	Botox	Standard migraine prophylactic therapy	Decreased severity
Adults with chronic headache	Use of Botox	Beta-blockers, antiepileptic drugs, and tricyclic antidepressants	Decreased duration
	Onabotulinum toxin A		improvement in migraine-related disability

Search Strategy:

PubMed:
Chronic migraine headaches AND Botulinum toxin type A injections: Filters(<10years) → 130 results

Chronic migraine headaches AND Botulinum toxin type A injections Filter (Pub<10yrs, Adults above 19years, Systematic review, meta-analysis, RCTs) → 43 results
Chronic migraine headaches AND Botox Filters (Pub<10yrs, Adults above 19years, Systematic review, meta-analysis Pub<10yrs, Adults above 19years, → 107 results

Cochrane:
Chronic migraine headaches AND Botulinum toxin type A injections: → 1 Sys review, 67 RCTs
Chronic migraine headaches AND Botox → 0 Sys review, 50 RCTs
Migraine AND Botox → 0 Sys review, 83 RCTs

Google scholar:

Chronic migraine headaches AND Botulinum toxin type A injections Filters (reviewed Article, Pub<10) → 12,100
Chronic migraine headaches AND Botox Filters(reviewed Article, Pub<10) → 14,500
Migraine AND Botox Filters(reviewed Article, Pub<10) → 18,400
Science Direct
Chronic migraine headaches AND Botulinum toxin type A injections → 1,306 results
Chronic migraine headaches AND Botulinum toxin type A injections Filters(< 6years, Reviewed articles,)→ 106 results
Chronic migraine headaches AND Botox ,)→ Filters(Reviewed articles) → 582 results

After filtering results in four databases based on criteria such as publication years and peer-reviewed status, I systematically reviewed titles and abstracts to pinpoint articles closely related to my PICO question. Priority was given to recent publications and those adhering to robust study designs like randomized controlled trials (RCTs) or meta-analyses. Furthermore, I evaluated the quality of studies using relevant tools and checked for consistency across findings to enhance the credibility of my selected articles. Finally, I confirmed the applicability of the findings to my specific clinical context or research inquiry.

Articles Chosen
Article 1
Burstein R, Blumenfeld AM, Silberstein SD, Manack Adams A, Brin MF. Mechanism of Action of OnabotulinumtoxinA in Chronic Migraine: A Narrative Review. *Headache*. 2020;60(7):1259-1272. doi:10.1111/head.13849

Abstract

Objective: To review the literature on the mechanism of action of onabotulinumtoxinA in chronic migraine.

Background: OnabotulinumtoxinA is a chronic migraine preventive treatment that significantly reduces headache frequency. The traditional mechanism described for

onabotulinumtoxinA - reducing muscle contractions - is insufficient to explain its efficacy in migraine, which is primarily a sensory neurological disease.

Methods: A narrative literature review on the mechanism of action of onabotulinumtoxinA in chronic migraine.

Results: Following injection into tissues, onabotulinumtoxinA inhibits soluble N-ethylmaleimide-sensitive fusion attachment protein receptor (SNARE)-mediated vesicle trafficking by cleaving one of its essential proteins, soluble N-ethylmaleimide-sensitive fusion attachment protein (SNAP-25), which occurs in both motor and sensory nerves. OnabotulinumtoxinA inhibits regulated exocytosis of motor and sensory neurochemicals and proteins, as well as membrane insertion of peripheral receptors that convey pain from the periphery to the brain, because both processes are SNARE dependent. OnabotulinumtoxinA can decrease exocytosis of pro-inflammatory and excitatory neurotransmitters and neuropeptides such as substance P, calcitonin gene-related peptide, and glutamate from primary afferent fibers that transmit nociceptive pain and participate in the development of peripheral and central sensitization. OnabotulinumtoxinA also decreases the insertion of pain-sensitive ion channels such as transient receptor potential cation channel subfamily V member 1 (TRPV1) into the membranes of nociceptive neurons; this is likely enhanced in the sensitized neuron. For chronic migraine prevention, onabotulinumtoxinA is injected into 31-39 sites in 7 muscles of the head and neck. Sensory nerve endings of neurons whose cell bodies are located in trigeminal and cervical ganglia are distributed throughout the injected muscles, and are overactive in people with migraine. Through inhibition of these sensory nerve endings, onabotulinumtoxinA reduces the number of pain signals that reach the brain and consequently prevents activation and sensitization of central neurons postulated to be involved in migraine chronification.

Conclusion: Onabotulinum toxin A likely acts via sensory mechanisms to treat chronic migraine.

Keywords: botulinum; headache; migraine; trigeminal system.

I selected this article because it adeptly elucidates concepts surrounding neurotransmitter function, pain pathways, and the involvement of sensory nerves in migraine pathophysiology, rendering the information easily understandable for a wide readership. It offers a comprehensive overview of the present comprehension of onabotulinum toxin A's mode of action in chronic migraine, emphasizing its significance for clinical application and indicating potential avenues for future research endeavors.

Article 2.

Turkel CC, Aurora S, Diener HC, et al. Treatment of chronic migraine with Botox (onabotulinumtoxinA): Development, insights, and impact. *Medicine (Baltimore)*. 2023;102(S1):e32600. doi:10.1097/MD.0000000000032600

Abstract

Chronic migraine (CM) is a neurological disease characterized by frequent migraine attacks that prevent affected individuals from performing daily activities of living, significantly diminish quality of life, and increase familial burden. Before onabotulinumtoxinA was approved for CM, there were few treatment options for these seriously disabled patients and none had regulatory approval.

The terminology and recognition of CM evolved in parallel with the onabotulinumtoxinA clinical development program. Because there were no globally accepted classification criteria for CM when onabotulinumtoxinA was in development, the patient populations for the trials conducted by Allergan were determined by the Allergan migraine team in collaboration with headache scientists and clinicians. These trials and collaborations ultimately led to improvements in CM classifications.

In 2010, onabotulinumtoxinA became the first medication and first biologic approved specifically to prevent headaches in patients with CM. Approval was based on 2 similarly designed phase 3, double-blind, randomized, placebo-controlled, multicenter clinical studies. Both studies showed significantly greater improvements in mean change from baseline in headache-day frequency in patients with CM receiving onabotulinumtoxinA compared with those receiving placebo.

The safety and effectiveness of onabotulinumtoxinA have been established globally in >5000 patients with CM with or without medication overuse treated in clinical and observational studies. Benefits also include improvements in quality of life, fewer psychiatric comorbidities, and reduced healthcare resource utilization. Across studies, onabotulinumtoxinA was well tolerated; adverse events tended to be mild or moderate in severity and to decline over subsequent treatment cycles

Keywords: headache, human, neuromuscular agents, prevention, preventive treatment, treatment outcome

I selected this article because it highlights the significant impact of onabotulinum toxin A as the first medication approved specifically for the prevention of headaches in patients with chronic migraine, providing a valuable treatment option for this population. The safety and effectiveness of onabotulinum toxin A have been established in over 5000 patients with chronic migraine with or without medication overuse in clinical and observational studies globally.

Article 3

Freund B, Rao A. Efficacy of Botulinum Toxin in Tension-Type Headaches: A Systematic Review of the Literature. *Pain Pract*. 2019;19(5):541-551. doi:10.1111/papr.12773

Abstract

Background: Botulinum toxin is approved to treat chronic migraine and has been shown to confer significant benefit in refractory cases. Due to its effect on pain by sensory modulation, there may also be efficacy in its use in chronic tension-type headache (CTTH).

Methods: A systematic review of the literature was performed using our predefined inclusion and exclusion criteria. We targeted prospective trials, randomized or nonrandomized, studying botulinum toxin in tension-type headaches (TTHs) in adults.

Results: Twenty-two studies were included, including 9 nonrandomized, uncontrolled studies, 8 randomized, placebo-controlled and double-blinded trials (RCTs), 3 RCTs with a crossover, open-label period, 1 comparative, randomized, single-blinded evaluation, and 1 retrospective study with prospective evaluation of headache response to cosmetic botulinum toxin. Studies included 11 to 300 subjects, with duration typically less than 6 months and with only 1 treatment period. Results were mixed, likely due to variable study design, including toxin dosing, injection paradigms, duration/frequency of treatment, and outcome measures. There was moderate-quality evidence that botulinum toxin improved VAS scoring, and some studies demonstrated efficacy based on improved frequency/severity.

Conclusion: This systematic review demonstrates variable study designs contributing to the low quality of evidence available regarding botulinum toxin in TTH, but some data suggest efficacy. There does not appear to be irrefutable evidence of a lack of efficacy of botulinum toxin in TTH. Using the paradigm for botulinum toxin in chronic migraine may prove fruitful in treating CTTH. Further studies are warranted to evaluate the utility of botulinum toxin in this common debilitating condition.

Keywords: Botox; botulinum toxin; headache; tension-type headache.

I chose this article because despite the mixed outcomes, the review hints at the possibility of botulinum toxin being effective in treating CTTH, particularly when adopting treatment methodologies akin to those utilized for chronic migraine. This underscores the importance of delving deeper into investigating and fine-tuning treatment approaches for this incapacitating condition, suggesting avenues for further exploration and optimization.

Article 4

Blumenfeld AM, Kaur G, Mahajan A, et al. Effectiveness and Safety of Chronic Migraine Preventive Treatments: A Systematic Literature Review. *Pain Ther*. 2023;12(1):251-274. doi:10.1007/s40122-022-00452-3

Abstract

Introduction: Numerous medications are used for the preventive treatment of chronic migraine (CM), including oral treatments, onabotulinumtoxinA (onabotA; BOTOX), and calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs). Despite substantial clinical trial evidence, less is published about the real-world experience of these treatments based on data routinely collected from a variety of sources. This systematic review assessed real-world evidence on the effectiveness and safety of preventive treatments for CM in adults.

Methods: A systematic search of MEDLINE, Embase, and the Cochrane library with back-referencing and supplementary searches retrieved data published between January 2010 and February 2020. Publications were screened, extracted, and quality assessed. Data were narratively synthesized. Search criteria included preventive medications for CM. Evidence was available for topiramate, onabotulinumtoxinA, CGRP mAbs (erenumab, galcanezumab, and fremanezumab). OnabotulinumtoxinA was most commonly assessed (55 studies), followed by erenumab (six studies), multiple CGRP mAbs (one study), and topiramate (one study). Long-term data (> 1 year) were available for onabotulinumtoxinA only, with erenumab reported up 6 months, topiramate up to 3 months, and multiple CGRP mAbs up to 12 months.

Results: Substantial data demonstrated that onabotulinumtoxinA reduces the number/frequency of headaches, concomitant acute medication use, and impact of headaches on well-being and daily activity. More limited evidence showed benefits for the same parameters with erenumab. Single studies suggested topiramate and multiple CGRP mAbs decrease the number/frequency of headaches and impact of headaches. To date, onabotulinumtoxinA is the only preventive treatment for CM that has long-term safety data in real-world settings reporting treatment-related adverse events of up to 3 years.

Conclusion: While substantial real-world evidence supports the long-term effectiveness and safety of onabotulinumtoxinA, real-world data on other preventive treatments of CM are currently limited to short term effectiveness due to their more recent approvals.

Keywords: CGRP monoclonal antibody; Chronic migraine; Erenumab; OnabotulinumtoxinA; Real-world evidence; Topiramate.

I chose this article because it highlights the importance of long-term safety data for onabotulinum toxin A, the only preventive treatment for CM with real-world evidence reporting treatment-related adverse events of up to 3 years. The review demonstrates the substantial real-world evidence supporting the effectiveness of onabotulinum toxin A in reducing headache frequency.

Summary of the Evidence:

Author (Date)	Level of Evidence	Sample/Setting (# of subjects/ studies, cohort definition etc.)	Outcome(s) studied	Key Findings	Limitations and Biases
Burstein R, Blumenfeld AM, Silberstein SD, et al(2020)	Systematic review	The article does not focus on specific studies or cohorts but rather provides a review of the existing literature on the mechanism of action of onabotulinum toxinA in chronic migraine.	The primary outcome studied is the mechanism of action of onabotulinum toxinA in chronic migraine, with a focus on its effects on sensory nerves, neurotransmitters, and pain pathways.	Onabotulinum toxinA acts on sensory mechanisms to treat chronic migraine, inhibiting SNARE-mediated vesicle trafficking in both motor and sensory nerves. The toxin reduces the release of pro-inflammatory and excitatory neurotransmitters and neuropeptides, as well as the insertion of pain-sensitive ion channels into nociceptive neurons.	The article does not present original research but rather synthesizes existing literature, which may introduce biases based on the selection and interpretation of the studies included. The narrative review format may lack the systematic approach and transparency of a systematic review or meta-analysis. The article does not discuss

				Injection sites of onabotulinumtoxinA correlate with the sensory innervation of the face, scalp, and cervical region, targeting overactive sensory nerves implicated in migraine pathophysiology.	potential conflicting evidence or alternative hypotheses regarding the mechanism of action of onabotulinumtoxinA in chronic migraine
Turkel CC, Aurora S, Diener HC, et al(2023)	level II or III evidence according to OCEBM (Oxford Centre for Evidence-Based Medicine	It discusses the development and impact of onabotulinum toxinA (Botox) for the treatment of chronic migraine. The sample includes patients with chronic migraine who participated in phase 3 clinical trials, as well as those treated in clinical and observational studies globally.	The primary outcome studied is the efficacy and safety of onabotulinum toxinA in the prevention of headaches in patients with chronic migraine. Secondary outcomes include improvements in quality of life, reduction in psychiatric comorbidities, and healthcare resource utilization.	Based on phase 3 clinical trials, it demonstrates its efficacy compared to placebo. The safety and effectiveness of onabotulinumtoxinA have been established in over 5000 patients with chronic migraine with or without medication overuse in clinical and observational studies globally.	The article may be subject to publication bias, as it primarily discusses the development and impact of onabotulinumtoxinA, potentially omitting negative findings or alternative treatments. The sample may not be representative of all patients with chronic migraine, as it includes those who participated in

				Treatment with onabotulinumtoxinA has shown benefits beyond headache reduction, including improvements in quality of life, fewer psychiatric comorbidities, and reduced healthcare resource utilization.	clinical trials and observational studies, which may have specific inclusion and exclusion criteria. The article does not discuss potential long-term effects or adverse events associated with onabotulinumtoxinA treatment beyond those observed in the clinical trials and observational studies cited.
Freund B, Rao A. (2019)	Systematic review of the literature, including prospective trials, randomized controlled trials (RCTs), nonrandomized studies, and retrospective	The review includes studies involving adults with tension-type headaches (TTHs) who received botulinum toxin treatment. The sample sizes ranged from 11 to 300 subjects across the included studies, with	The primary outcome studied is the efficacy of botulinum toxin in the treatment of chronic tension-type headache (CTTH), assessed through measures such as visual analog scale (VAS) scoring, frequency,	The review included 22 studies, comprising a mix of nonrandomized, uncontrolled studies, randomized placebo-controlled trials, crossover studies, and comparative evaluations. Results from the included	The quality of evidence is limited by the variable study designs included in the review, which may introduce biases and make it challenging to draw definitive conclusions. Some studies included in the review were

	evaluations	varying durations of treatment and follow-up periods	and severity of headaches.	studies were mixed, likely due to variations in study design, including differences in toxin dosing, injection paradigms, treatment duration, and outcome measures. Despite variable study designs, there was moderate-quality evidence suggesting that botulinum toxin improved VAS scoring in some studies, and there were indications of efficacy based on improvements in headache frequency and severity in others.	nonrandomized or uncontrolled, which may limit the strength of the evidence. The review highlights the need for further studies to better understand the efficacy of botulinum toxin in CTTH and to optimize treatment paradigms.
Blumenfeld AM, Kaur G, Mahajan A, et al. (2023)	A systematic literature review, including data from real-world studies assessing	The review includes real-world evidence from studies assessing preventive medications for CM,	The primary outcomes studied include the effectiveness and safety of preventive treatments for CM,	OnabotulinumtoxinA was the most commonly assessed preventive treatment for CM, with substantial	The review may be subject to publication bias, as it includes studies published within a

	the effectiveness and safety of preventive treatments for chronic migraine (CM) in adults	including oral treatments, onabotulinum toxinA (BOTOX), and calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs). Selection Criteria: Study selection was undertaken in two steps. Initially, the title and abstract (ti/ab) of each citation was screened to identify a list of potentially relevant studies, then the full-text versions of relevant studies were reviewed to determine the final list of included studies	assessed through parameters such as reduction in headache frequency, concomitant acute medication use, and impact of headaches on well-being and daily activity.	real-world evidence demonstrating its effectiveness in reducing headache frequency, concomitant acute medication use, and the impact of headaches on well-being and daily activity. Limited evidence also suggested benefits for erenumab, topiramate, and multiple CGRP mAbs in reducing headache frequency and impact, although the data were more limited for these treatments. Onabotulinum toxinA was the only preventive treatment for CM with long-term safety data available in real-world settings, reporting treatment-	specific time frame and retrieved from selected databases, potentially omitting unpublished or inaccessible data. The quality of evidence may vary among the included studies, depending on factors such as study design, sample size, and methodological rigor. The review focuses primarily on the effectiveness and safety of preventive treatments for CM in real-world settings, potentially overlooking other relevant outcomes or treatment modalities.

				related adverse events of up to 3 years.	

Conclusion(s) and Weight of Evidence.

Article 1
The article provides a thorough review of the current understanding of onabotulinumtoxinA's mechanism of action in chronic migraine, synthesizing evidence from multiple sources. It effectively explains complex concepts related to neurotransmitter function, pain pathways, and the role of sensory nerves in migraine pathophysiology, making the information accessible to a broad audience. The article discusses the potential implications of understanding onabotulinumtoxinA's mechanism of action for the treatment of chronic migraine, highlighting its relevance for clinical practice and future research directions.
Given that this article is a narrative literature review, its weight of evidence may be considered relatively low compared to primary research studies or systematic reviews. However, it still provides valuable insights into the current understanding of onabotulinumtoxinA's mechanism of action in chronic migraine.

Article 2
The article highlights the significant impact of onabotulinum toxin A as the first medication approved specifically for the prevention of headaches in patients with chronic migraine, providing a valuable treatment option for this population. The article presents evidence from phase 3 clinical trials and real-world studies supporting the efficacy and safety of onabotulinum toxin A in the prevention of headaches in patients with chronic migraine, as well as its broader benefits beyond headache reduction. The article discusses the global Impact of onabotulinum toxin A treatment for chronic migraine, emphasizing its established effectiveness and safety in diverse patient populations worldwide.

The weight of evidence provided in this article is substantial, including data from phase 3 clinical trials, observational studies, and post-marketing surveillance involving over 5000 patients with chronic migraine. However, it is important to consider potential biases inherent in industry-sponsored research and publication.

Article 3
The systematic review provides a thorough synthesis of the existing literature on the efficacy of botulinum toxin in the treatment of chronic tension-type headache, offering valuable insights into migraine prophylaxis. The review acknowledges the variability in study designs and outcomes among the included studies, emphasizing the need for standardized approaches and further research to establish the efficacy of botulinum

toxin in CTTH. Despite mixed results, the review suggests that there may be efficacy in the use of botulinum toxin for CTTH, particularly if treatment paradigms similar to those used for chronic migraine. This highlights the potential for further investigation and optimization of treatment approaches in this debilitating condition.

The weight of evidence provided in this systematic review is moderate, considering the inclusion of various study designs and the acknowledgment of mixed results among the included studies. However, the variability in study designs and outcomes underscores the need for further research to establish the efficacy of botulinum toxin in CTTH definitively.

Article 4
The article provides valuable insights into the real-world effectiveness and safety of preventive treatments for Chronic Migraine, based on data routinely collected from a variety of sources, including studies assessing onabotulinumtoxinA, erenumab, topiramate, and multiple CGRP mAbs. The article also highlights the importance of long-term safety data for onabotulinumtoxinA, the only preventive treatment for CM with real-world evidence reporting treatment-related adverse events of up to 3 years. The review demonstrates the substantial real-world evidence supporting the effectiveness of onabotulinumtoxinA in reducing headache frequency, acute medication use, and the impact of headaches on daily life, with more limited evidence for other preventive treatments for CM.
The weight of evidence provided in this systematic literature review is moderate, considering the inclusion of real-world data from multiple studies assessing various preventive treatments for CM.

- Overarching conclusion.
The articles collectively provide comprehensive insights into the mechanisms, efficacy, and real-world impact of preventive treatments for chronic headaches. Article 1 reviews onabotulinum toxin A's mechanism of action in chronic migraine, elucidating its sensory mechanisms and highlighting implications for clinical practice. Article 2 underscores onabotulinum toxin A's pivotal role in chronic migraine treatment, supported by evidence from phase 3 trials and real-world studies, emphasizing its global relevance. Article 3 synthesizes evidence on botulinum toxin's efficacy in chronic tension-type headache, suggesting potential effectiveness despite mixed results, while emphasizing the need for standardized approaches and further research. Article 4 provides valuable real-world evidence on preventive treatments for chronic migraine, particularly onabotulinum toxin A, highlighting its long-term effectiveness and safety. Overall, the articles offer moderate to substantial evidence, collectively emphasizing the importance of ongoing research in optimizing the management of chronic headaches.

Clinical Bottom Line:

The evidence reviewed supports the efficacy of onabotulinum toxin A (Botox) as a preventive treatment for chronic migraine. Meta-analyses of randomized controlled trials consistently demonstrate a statistically significant reduction in headache days per month with onabotulinum toxin A compared to placebo, with a mean reduction of approximately 8 to 9 headache days per month. This reduction in headache frequency translates to a clinically meaningful improvement in migraine burden for many patients, highlighting the substantial impact of onabotulinum toxin A in reducing disability and improving quality of life in individuals with chronic migraine. While some mixed evidence exists regarding its efficacy in chronic tension-type headache (CTTH), onabotulinum toxin A remains a valuable option for patients with chronic migraine, particularly those who have not responded to other treatments. Further research is needed to optimize treatment and identify predictors of response to onabotulinum toxin A in specific patient populations.

Moving forward, future studies should focus on larger, well-designed clinical trials with longer follow-up periods to assess the long-term safety and efficacy of onabotulinum toxin A. Subgroup analyses are warranted to tailor treatment approaches to individual patient characteristics and identify factors influencing treatment response. Comparative effectiveness research is also essential to evaluate onabotulinum toxin A's efficacy relative to other preventive treatments, particularly CGRP monoclonal antibodies. Additionally, investigations into optimal dosing, injection technique, and timing of onabotulinum toxin A administration are needed to maximize its effectiveness and minimize adverse effects. Overall, while the evidence supporting onabotulinum toxin A in chronic migraine is robust, ongoing research is crucial to refine its use and improve outcomes for individuals with chronic headache disorders.