**Isaiah Tekalign
PA Portfolio II – Summer 2023
Mini-CAT**

**Clinical Scenario:**

You are a PA working in a neurology clinic and you have a patient who has been referred by her primary doctor for possible chronic migraine. After working the patient up with labs and imaging you conclude that the patient does indeed have chronic idiopathic migraines, so you begin to discuss treatment options with her and are recommending topiramate. As you are discussing her options, she cuts you off and begins to tell you how in her book club people have been saying that Botox is the “best way” to reduce the frequency of migraines.

**Search Question:**

In adult patients with chronic migraines is Botox more effective than topiramate at preventing or limiting the frequency of migraine reoccurrence?

**PICO Table:**

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| **P** | **I** | **C** | **O** |
| Chronic migraine | Botox treatment | Topiramate  | Decreased frequency |
| Migraine  | Botox injection | Topamax | Decreased reoccurrence |
|  | onabotulinumtoxina injection | Topiragen | Decreased prevalence |
|  | Botulinum toxin |  |  |

**Search Strategy and Databases Used:**

**Pub Med:**

(Chronic migraine) AND (Botox) AND (decreased reoccurrence): 50 results

* Filters: last 15 years, full text: 46 results
* Filters: last 15 years, full text, RCT, meta-analysis, systematic review: 9 results

(Chronic migraine) AND (Botox) AND (topiramate) AND (decreased frequency): 17 results

* Filters: last 10 years, full text: 10 results
* Filters: last 10 years, full text, RCT, meta-analysis, systematic review: 8 results

**Cochrane**:

Population “Chronic migraine” Intervention “Botox” Comparison “topiramate” Outcome “decreased frequency” 1 result

**Trip Medical Database:**

Population “chronic migraine” Intervention “Botox” Comparison “topiramate” Outcome “decreased frequency”: 75 results

**Explanation**: At first, I searched chronic migraine, Botox, and decreased reoccurrence on PubMed and encountered many different articles, this then led to me apply the filter of “within the last 15 years” and free text. After doing this I still encountered 46 different articles and wanted to limit this, so I added another filter of RCT, meta-analysis, and systematic review which brought the results down to 9 results. I also searched chronic migraine, Botox, topiramate, and decreased frequency on PubMed using the same criteria and ended at a manageable 8 results. When doing my search on Cochrane I put in chronic migraine for population, Botox for intervention, topiramate for comparison, and decreased frequency for outcome which led to only 1 article. For the Trip database I searched Population “chronic migraine” Intervention “Botox” Comparison “topiramate” Outcome “decreased frequency”, and it showed 75 results. However, these results were of no benefit to my question because many of them were outdated or had nothing to do with the effect of Botox and topiramate on chronic migraine reoccurence.

**Research Used:**

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| Citation | Mathew NT, Jaffri SFA. A Double-Blind Comparison of OnabotulinumtoxinA (BOTOX®) and Topiramate (TOPAMAX®) for the Prophylactic Treatment of Chronic Migraine: A Pilot Study. *Headache: The Journal of Head and Face Pain*. 2009;49(10):1466-1478. doi:https://doi.org/10.1111/j.1526-4610.2009.01566.x |
| Abstract | **Background.—** There is a need for effective prophylactic therapy for chronic migraine (CM) that has minimal side effects.**Objective.—** To compare the efficacy and safety of onabotulinumtoxinA (BOTOX®, Allergan, Inc., Irvine, CA) and topiramate (TOPAMAX®, Ortho-McNeil, Titusville, NJ) prophylactic treatment in patients with CM.**Methods.—** In this single-center, double-blind trial, patients with CM received either onabotulinumtoxinA, maximum 200 units (U) at baseline and month 3 (100 U fixed-site and 100 U follow-the-pain), plus an oral placebo, or topiramate, 4-week titration to 100 mg/day with option for additional 4-week titration to 200 mg/day, plus placebo saline injections. OnabotulinumtoxinA or placebo saline injection was administered at baseline and month 3 only, while topiramate oral treatment or oral placebo was continued through the end of the study. The primary endpoint was treatment responder rate assessed using Physician Global Assessment 9-point scale (+4 = clearance of signs and symptoms and −4 = very marked worsening [about 100% worse]). Secondary endpoints included the change from baseline in the number of headache (HA)/migraine days per month (HA diary), and HA disability measured using Headache Impact Test (HIT-6), HA diary, Migraine Disability Assessment (MIDAS) questionnaire, and Migraine Impact Questionnaire (MIQ). The overall study duration was approximately 10.5 months, which included a 4-week screening period and a 2-week optional final safety visit. Follow-up visits for assessments occurred at months 1, 3, 6, and 9. Adverse events (AEs) were documented.**Results.—** Of 60 patients randomized to treatment (mean age, 36.8 ± 10.3 years; 90% female), 36 completed the study at the end of the 9 months of active treatment (onabotulinumtoxinA, 19/30 [63.3%]; topiramate, 17/30 [56.7%]). In the topiramate group, 7/29 (24.1%) discontinued study because of treatment-related AEs vs 2/26 (7.7%) in the onabotulinumtoxinA group. Between 68% and 83% of patients for both onabotulinumtoxinA and topiramate groups reported at least a slight (25%) improvement in migraine; response to treatment was assessed using Physician Global Assessment at months 1, 3, 6, and 9. Most patients in both groups reported moderate to marked improvements at all time points. No significant between-group differences were observed, except for marked improvement at month 9 (onabotulinumtoxinA, 27.3% vs topiramate, 60.9%, *P* = .0234, chi-square). In both groups, HA/migraine days decreased and MIDAS and HIT-6 scores improved. Patient-reported quality of life measures assessed using MIQ after treatment with onabotulinumtoxinA paralleled those seen after treatment with topiramate in most respects. At month 9, 40.9% and 42.9% of patients in the onabotulinumtoxinA and topiramate groups, respectively, reported ≥50% reduction in HA/migraine days. Forty-one treatment-related AEs were reported in 18 onabotulinumtoxinA-treated patients vs 87 in 25 topiramate-treated patients, and 2.7% of patients in the onabotulinumtoxinA group and 24.1% of patients in the topiramate group reported AEs that required permanent discontinuation of study treatment.**Conclusions.—** OnabotulinumtoxinA and topiramate demonstrated similar efficacy in the prophylactic treatment of CM. Patients receiving onabotulinumtoxinA had fewer AEs and discontinuations. |
| Link: | <https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/j.1526-4610.2009.01566.x> |

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| Citation | Cady, Roger K., et al. “A Multi-Center Double-Blind Pilot Comparison of OnabotulinumtoxinA and Topiramate for the Prophylactic Treatment of Chronic Migraine.” *Headache: The Journal of Head and Face Pain*, vol. 51, no. 1, 10 Nov. 2010, pp. 21–32, https://doi.org/10.1111/j.1526-4610.2010.01796.x. Accessed 30 Nov. 2021. |
| Abstract | *Headache* 2011;51:21-32)**Objective.—** This multi-center pilot study compared the efficacy of onabotulinumtoxinA with topiramate (a Food and Drug Administration approved and widely accepted treatment for prevention of migraine) in individuals with chronic migraine (CM).**Methods.—** A total of 59 subjects with CM were randomly assigned to one of 2 groups: Group 1 (n = 30) received topiramate plus placebo injections, Group 2 (n = 29) received onabotulinumtoxinA injections plus placebo tablets. Subjects maintained daily headache diaries over a 4-week baseline period and a 12-week active study period. The primary endpoint was the Physician Global Assessment, which measured the treatment responder rate and indicated improvement in both groups over 12 weeks. Secondary endpoints, measured at weeks 4 and 12, included headache days per month, migraine days, headache-free days, days on acute medication, severity of headache episodes, Migraine Impact & Disability Assessment, Headache Impact Test, effectiveness of and satisfaction with current treatment on the amount of medication needed, and the frequency and severity of migraine symptoms. At 12 weeks subjects were re-evaluated and tapered off oral study medications over a 2-week time period. Subjects not reporting a >50% reduction of headache frequency at 12 weeks were invited to participate in a 12-week open label extension study with onabotulinumtoxinA. Of these, 20 subjects, 9 from the Topiramate Group and 11 from the OnabotulinumtoxinA Group, volunteered for this extension from weeks 14 to 26.**Results.—** This study demonstrated positive benefit for both onabotulinumtoxinA and topiramate in subjects with CM. Overall, the results were statistically significant within groups but not between groups. By week 26, subjects had a reduction of headache days per month compared with baseline. This was a significant within-group finding.**Conclusion.—** OnabotulinumtoxinA and topiramate demonstrated similar efficacy for subjects with CM as determined by Global Physician Assessment and supported by multiple secondary endpoint measures. |
| Link: | <https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/j.1526-4610.2010.01796.x> |

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| Citation | Frampton, James E. “OnabotulinumtoxinA in Chronic Migraine: A Profile of Its Use.” *CNS Drugs*, vol. 34, no. 12, Dec. 2020, pp. 1287–1298, https://doi.org/10.1007/s40263-020-00776-8. Accessed 30 Dec. 2020. |
| Abstract | OnabotulinumtoxinA (Botox®; a formulation of botulinum toxin type A (BoNT/A)] is indicated for the prevention of headaches in adults with chronic migraine (CM) in numerous countries. In clinical trials, intramuscular administration of BoNT/A (155–195 units at 12-week intervals) to patients with CM was generally well tolerated and associated with sustained and clinically meaningful improvements in multiple assessments of headache symptoms, headache-related impact and/or disability and migraine-specific health-related quality of life over a period of 1 year (in the pivotal PREEMPT 1 and 2 studies) and 2 years (in the phase IV COMPEL study). The efficacy and safety of BoNT/A therapy have been confirmed in a number of large, including the 2-year REPOSE study. Intramuscular BoNT/A has also demonstrated greater clinical utility than the oral prophylactic medication topiramate in a clinical practice setting (FORWARD study). |
| Link: | <https://link.springer.com/article/10.1007/s40263-020-00776-8> |

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| Citation | Jackson JL, Kuriyama A, Hayashino Y. Botulinum Toxin A for Prophylactic Treatment of Migraine and Tension Headaches in Adults: A Meta-analysis. JAMA. 2012;307(16):1736–1745. doi:10.1001/jama.2012.505  |
| Abstract | **Context** Botulinum toxin A is US Food and Drug Administration approved for prophylactic treatment for chronic migraines.**Objective** To assess botulinum toxin A for the prophylactic treatment of headaches in adults.**Data Sources** A search of MEDLINE, EMBASE, bibliographies of published systematic reviews, and the Cochrane trial registries between 1966 and March 15, 2012. Inclusion and exclusion criteria of each study were reviewed. Headaches were categorized as episodic (<15 headaches per month) or chronic (≥15 headaches per month) migraine and episodic or chronic daily or tension headaches.**Study Selection** Randomized controlled trials comparing botulinum toxin A with placebo or other interventions for headaches among adults.**Data Extraction** Data were abstracted and quality assessed independently by 2 reviewers. Outcomes were pooled using a random-effects model.**Data Synthesis** Pooled analyses suggested that botulinum toxin A was associated with fewer headaches per month among patients with chronic daily headaches (1115 patients, −2.06 headaches per month; 95% CI, −3.56 to −0.56; 3 studies) and among patients with chronic migraine headaches (n = 1508, −2.30 headaches per month; 95% CI, −3.66 to −0.94; 5 studies). There was no significant association between use of botulinum toxin A and reduction in the number of episodic migraine (n = 1838, 0.05 headaches per month; 95% CI, −0.26 to 0.36; 9 studies) or chronic tension-type headaches (n = 675, −1.43 headaches per month; 95% CI, −3.13 to 0.27; 7 studies). In single trials, botulinum toxin A was not associated with fewer migraine headaches per month vs valproate (standardized mean difference [SMD], −0.20; 95% CI, −0.91 to 0.31), topiramate (SMD, 0.20; 95% CI, −0.36 to 0.76), or amitriptyline (SMD, 0.29; 95% CI, −0.17 to 0.76). Botulinum toxin A was associated with fewer chronic tension-type headaches per month vs methylprednisolone injections (SMD, −2.5; 95% CI, −3.5 to −1.5). Compared with placebo, botulinum toxin A was associated with a greater frequency of blepharoptosis, skin tightness, paresthesias, neck stiffness, muscle weakness, and neck pain.**Conclusion** Botulinum toxin A compared with placebo was associated with a small to modest benefit for chronic daily headaches and chronic migraines but was not associated with fewer episodic migraine or chronic tension-type headaches per month.Migraine and tension-type headaches are common. Although up to 42% of adults experience tension-type headaches sometime in their life, most do not seek medical advice. Migraines are less common, with a worldwide prevalence between 8% and 18%,[1](https://jamanetwork.com/journals/jama/fullarticle/1148201#ref-jrv25003-1)-[3](https://jamanetwork.com/journals/jama/fullarticle/1148201#ref-jrv25003-1) but are associated with greater disability.[4](https://jamanetwork.com/journals/jama/fullarticle/1148201#ref-jrv25003-4),[5](https://jamanetwork.com/journals/jama/fullarticle/1148201#ref-jrv25003-5) Migraine headaches are responsible for $1 billion in medical costs and $16 billion in lost productivity per year[6](https://jamanetwork.com/journals/jama/fullarticle/1148201#ref-jrv25003-6) in the United States alone.Headache treatment is either abortive or prophylactic. Abortive treatment manages the acute headache and prophylactic treatment aims to reduce the frequency or severity of the attacks. Common prophylactic medications include anticonvulsants, β-blockers, calcium channel blockers, serotonin reuptake inhibitors, and tricyclic antidepressants.[7](https://jamanetwork.com/journals/jama/fullarticle/1148201#ref-jrv25003-7) Botulinum toxin A injections were first proposed as headache treatment when it was observed that patients with chronic headaches receiving cosmetic botulinum injections experienced headache improvement, prompting several case series that suggested benefit.[8](https://jamanetwork.com/journals/jama/fullarticle/1148201#ref-jrv25003-8)-[10](https://jamanetwork.com/journals/jama/fullarticle/1148201#ref-jrv25003-8) In October 2010, the US Food and Drug Administration approved botulinum toxin A for prophylactic treatment of chronic migraine headaches at a dose of 155 units divided among 31 injection sites, repeated as needed every 12 weeks, based on 2 clinical trials conducted in the United States.[11](https://jamanetwork.com/journals/jama/fullarticle/1148201#ref-jrv25003-11),[12](https://jamanetwork.com/journals/jama/fullarticle/1148201#ref-jrv25003-12) However, the literature on botulinum effectiveness for headaches is mixed. We performed a systematic review to assess the association of botulinum toxin A with reducing headache frequency when used for prophylactic treatment of migraine, tension, or chronic daily headaches in adults. |
| Link: | <https://jamanetwork.com/journals/jama/article-abstract/1148201> |

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| Citation | Frank F, Ulmer H, Sidoroff V, Broessner G. CGRP-antibodies, topiramate and botulinum toxin type A in episodic and chronic migraine: A systematic review and meta-analysis. *Cephalalgia*. 2021;41(11-12):1222-1239. doi:https://doi.org/10.1177/03331024211018137 |
| Abstract | BackgroundThe approval of monoclonal antibodies for prevention of migraine has revolutionized treatment for patients. Oral preventatives are still considered first line treatments as head-to-head trials comparing them with antibodies are lacking.MethodsThe main purpose of this study was to provide a comparative overview of the efficacy of three commonly prescribed migraine preventative medication classes. For this systematic review and meta-analysis, we searched the databases CENTRAL, EMBASE, and MEDLINE until 20 March 2020. We included RCTs reporting the 50% response rates for topiramate, Botulinum Toxin Type A and monoclonal antibodies against CGRP(r). Studies were excluded if response rates were not reported, treatment allocation was unclear, or if study quality was insufficient. Primary outcome measure were the 50% response rates. The pooled odds ratios with 95% confidence intervals were calculated with the random effects model. The study was registered at PROSPERO (CRD42020222880).FindingsWe identified 6552 reports. Thirty-two were eligible for our review. Studies assessing monoclonal antibodies included 13,302 patients and yielded pooled odds ratios for the 50% response rate of 2.30 (CI: 2.11–2.50). Topiramate had an overall effect estimate of 2.70 (CI: 1.97–3.69) with 1989 included patients and Botulinum Toxin Type A achieved 1.28 (CI: 0.98–1. 67) with 2472 patients included.InterpretationTopiramate, botulinum toxin type A and monoclonal antibodies showed higher odds ratios in achieving a 50% response rate compared to placebo. Topiramate numerically demonstrated the greatest effect size but also the highest drop-out rate. |
| Link: | <https://journals.sagepub.com/doi/10.1177/03331024211018137> |

**Summary of Evidence:**

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| Author (Date) | Level of Evidence | Sample/Setting(# of subjects/ studies, cohort definition etc. ) | Outcomes Studied | Key Findings | Limitations and Biases |
| Mathew NT, Jaffri SFA. (2009) | Randomized control trial | * This was a single-center, prospective, double-blind study performed in patients diagnosed with CM who were naïve to onabotulinumtoxinA and topiramate.
* Patients were randomized to 1 of 2 treatment groups onabotulinumtoxinA or topiramate. The maximum dose of onabotulinumtoxinA was 200 at the baseline visit and month 3 plus an oral placebo. Patients randomized to receive topiramate were given a 4-week titration to 100 mg/day, with an optional additional 4-week titration to 200 mg/day plus placebo injections.
* The study included outpatient male and female patients of any race between the ages of 18 and 65 years who were diagnosed with CM not attributable to another cause. CM HA was defined as migraine HA with or without aura occurring on ≥15 days/month for >3 months in the absence of medication overuse. HA had at least 2 of the following characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, and/or aggravation by or causing avoidance of routine physical activity.
* The overall duration of the study was approximately 10.5 months. A screening visit occurred at month −1, followed by randomization and a baseline visit at day 0. Follow-up visits for assessments occurred at months 1, 3, 6, and 9. A final optional safety visit approximately 2 weeks after month 9 was included to ensure that the patient had safely discontinued study medication.
 | * The primary endpoint was the treatment responder rate based on the 9-point Physician Global Assessment, Response to Treatment metric, where +4 = clearance of signs and symptoms and −4 = very marked worsening.
* Secondary endpoints assessed included mean change from baseline in number of HA/migraine days per month, HA/migraine-free days per month, days on HA medication, and average severity of HA/migraine episodes per month taken from data included in the patient HA diaries.
* Impact of HA disorder and associated disability, including quality of life (QoL), was assessed through the Headache Impact Test (HIT)-6, Migraine Disability Assessment (MIDAS) questionnaire, and Migraine Impact Questionnaire (MIQ). From the MIQ, the amount of money spent by the patient on prescription and nonprescription drugs was also assessed.
* Safety and tolerability of the treatment regimens were assessed by monitoring frequency and severity of AEs and frequency and reasons for premature withdrawal from the study.
 | * The findings of this study demonstrate that the efficacy of onabotulinumtoxinA as a preventive treatment for CM was indistinguishable from topiramate in both degree and consistency of benefit over time.
* A high percentage of patients in both the onabotulinumtoxinA and topiramate groups showed response to treatment, with the majority showing moderate-to-marked response.
* The overall discontinuation rate in this study was 36.7% in the onabotulinumtoxinA group and 43.3% in the topiramate group, with AEs being the primary reason for withdrawal in the topiramate group and lost to follow-up in the onabotulinumtoxinA group.
 | * The majority of patients were female 54/60 and white 46/60. The mean age was only 36.8± 10.3 years.
* Although the decrease in HA days and response to treatment were consistently robust for both groups, MIDAS and HIT-6 scores did not parallel this consistency over the course of the study. A number of factors may have contributed to these findings: the relatively small population size and variable baseline values, especially for MIDAS, likely contributed to a lack of correlation in this study.
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| Cady, Roger K., et al. (2010) | Randomized control trial  | * This was a 3-center, double-blind randomized pilot study of onabotulinumtoxinA and topiramate for preventive treatment of CM defined as 3-8 attacks of migraine per month with on average 21 days of headache per month.
* Subjects included male and female volunteers with documented histories of CM fulfilling criteria of the Second Edition of the International Classification for Headache Disorders. Subjects were randomized to receive injections of onabotulinumtoxinA plus daily placebo tablets or topiramate and placebo injections. The investigators and study coordinators were blinded to study conditions.
* Up to 200 units of onabotulinumtoxinA or placebo were injected with 100 units into fixed locations and up to an additional 100 units in a “follow the pain” scheme determined at the investigators discretion. Topiramate dosing was initiated at 25 mg daily and escalated to 100 mg in weekly incremental changes of 25 mg.
* Subjects maintained daily headache diaries over a 4-week baseline period and a 12-week active study period. At 12 weeks subjects were re-evaluated and tapered off oral study medications over a 2-week time period.
* Inclusion criteria:
* Outpatients, male or female, of any race, between 18 and 65 years of age
* Female subjects of child-bearing potential with a negative urine pregnancy test who practiced reliable contraception throughout the study period
* Subjects met criteria for CM as defined by Second Edition of the International Classification for Headache Disorders
* Subjects understood all study requirements
* Exclusion criteria:
* Female subjects who were pregnant, breast feeding, or planning to become pregnant during the time frame of the study
* Individuals with headache disorders other than CM
* Subjects with medical disorders that increase the risk with exposure to onabotulinumtoxinA
* Subjects with significant liver or renal impairment including kidney stones
* Subjects on ketogenic diets
* Subjects who had previously used botulinum toxin of any type or topiramate regardless of indication
* Subjects with recent evidence of alcohol/drug abuse or overuse of acute medication
* There were 59 subjects enrolled and were randomized into 2 groups: 30 received topiramate plus placebo injections and 29 received onabotulinumtoxinA injections plus placebo tablets.
 | * Physician Global Assessment, Response to Treatment: The Investigator will assess response to treatment using the following 9-point scale:
* +4 Clearance of signs and symptoms
* +3 Marked improvement
* +2 Moderate improvement
* +1 Slight improvement (
* 0 Unchanged.
* −1 Slight worsening
* −2 Moderate worsening
* −3 Marked worsening
* −4 Very marked worsening
* Secondary endpoints, measured at weeks 4 and 12, included headache days per month, migraine days, headache-free days, days on acute medication, severity of headache episodes, Migraine Impact & Disability Assessment, Headache Impact Test, effectiveness of and satisfaction with current treatment on the amount of medication needed, and the frequency and severity of migraine symptoms.
 | * Study supports onabotulinumtoxinA as an effective preventive treatment for CM with a frequency between 3 and 8 attacks per month.
* Topiramate and onabotulinumtoxinA demonstrated significant efficacy in treating subjects with CM.
* Both therapies were generally well tolerated and neither had any associated serious adverse events. Interestingly, adverse events were quite similar for both medications with only slight differences were noted between the two therapies.
* Both interventions demonstrated statistically significant improvement in MIDAS scores at week 12.
 | * The mean age was 39.6 years with a range of 19.6 to 64.0; 91.5% were women (54/59). Racially, 94.9% (56/59) were Caucasian
* One limitation might be that the investigators in the study were more sophisticated in evaluation of migraine response and that Physician Global Assessment by these investigators does not reflect clinical assessment of the broader population of physicians treating migraine.
* A second concern is the use of active comparator rather than placebo and if the positive results reflect regression to the mean. Placebo rates are stated to be in trials of migraine preventive medications and in general lower response rates are observed in placebo controlled double-blinded studies. Consequently, without an active placebo arm the precise benefit of active treatment arms cannot be fully assessed.
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| Frampton, James E. (2020) | Randomized control trial | * The multicentre PREEMPT 1 and multinational PREEMPT 2 studies, which were otherwise identical in design, enrolled a combined total of 1384 patients who had ≥ 15 headache days/month with headache lasting ≥ 4 h/day, with ≥ 50% of the days being migraine/probable migraine days.
* Patients received up to five treatment cycles: two with BoNT/A 155–195 U or placebo during the 24-week, randomized, double-blind phase at weeks 0 and 12 and three with BoNT/A 155–195 U during the subsequent open-label extension phase at weeks 24, 36 and 48.
* Adults with CM were randomized to receive either three cycles of BoNT/A 155 U (or immediate-release topiramate 50–100 mg/day for 36 weeks.
 | * Meaningful improvements in multiple assessments of headache symptoms, headache-related impact and/or disability and migraine-specific health-related quality of life over a period of 1 year
 | * In terms of the comparative efficaciousness of the two treatments, responder rates did not differ significantly between patients remaining on BoNT/A and those remaining on topiramate.
* The proportion of patients who completed the randomized treatment period was much higher among those initially assigned to BoNT/A (86% of 140 patients) than those initially assigned to topiramate (20% of 142 patients).
* Injection of up to five cycles of BoNT/A (155–195 U/cycle) at 12-week intervals is generally well tolerated.
* BoNT/A recipients mostly reported AEs that were mild or moderate in severity and resolved without sequelae; they infrequently discontinued therapy due to AEs when compared to topiramate.
 | * National Institute for Health and Care Excellence recommends that a monthly headache-day frequency responder be defined using less stringent criteria than used in the PREEMPT trials.
* Short disease duration, high serum CGRP levels and (in women) polymorphisms in genes encoding CGRP and TRPV1 are among the potential predictors of responsiveness that have been identified that were not taken into account.
* The results of studies evaluating onabotulinumtoxinA are specific to this particular formulation of BoNT/A and cannot be extrapolated to other commercially available formulations of BoNT/A.
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| Jackson JL, Kuriyama A, Hayashino Y. (2012) | meta-analysis | * Searched for randomized trials of botulinum toxin A for headaches in adults using MEDLINE and EMBASE, the bibliographies of published systematic reviews, the Cochrane libraries and performed a review of the bibliographies of all articles retrieved.
* Included randomized clinical trials that evaluated botulinum toxin A treatment and its association with the reduction in frequency or severity of headaches.
* Trials had to be at least 4 weeks in duration. Treatment could be combined with other prophylactic and analgesic medications.
* Authors excluded headaches associated with other disorders, such as cervical dystonia and secondary headaches, such as postlumbar puncture headaches.
* Required all outcomes to be patient reported. For continuous outcomes, Authors abstracted the number of participants and the mean and variance of reported outcomes. Missing variances were calculated by using the sample size and means from reported P values.
* The search produced 315 articles. Application of inclusion and exclusion criteria resulted in 27 placebo-controlled randomized trialsand 4 randomized comparisons with other medications amitriptyline, prednisone, topiramate, and valproate.
* Among placebo-controlled trials, there were 5313 study participants, of which 1938 had episodic migraines, 1544 had chronic migraines 616 had chronic tension-type headaches, and 1115 had chronic daily headaches. One study with 21 participants evaluated patients with either episodic or chronic tension-type headaches
 | * For the primary outcome analysis, authors followed International Headache Society recommendations and preferentially abstracted and pooled headache frequency, number of headaches per month, using weighted mean differences in a random-effects model. For studies not reporting headache frequency, outcomes were abstracted preferentially in this order: headache severity or a headache index that included frequency and severity.
* Headache outcomes including but were not limited to frequency, intensity/severity, duration, global improvement/relief, analgesics used, adverse events.
 | * In single trials, botulinum toxin A was associated with reduction in headache frequency compared with topiramate or amitriptyline.
* Botulinum toxin A was associated with a reduction in headaches per month for both chronic daily headaches.
* Patients receiving botulinum toxin A were more likely to report any adverse event than those injected with placebo.
* Some adverse effects were more common among patients receiving botulinum toxin A, including blepharoptosis, muscle weakness, neck pain, neck stiffness, paresthesia, and skin tightness.
* single trials found no differences between botulinum toxin A and amitriptylineor topiramatefor chronic migraine headaches
* The trials of topiramate and valproate had significant loss to follow-up.
 | * First, for nearly all the headache types, there were relatively few studies and many of the studies were quite small. The results could be spurious, particularly given that the meta-analysis is based on assumptions of normality for tests of significance.
* Analysis of the data using nonnormal approaches, approximate predictive distribution of a future trial, based on the extent of heterogeneity as suggested by Higgins et alor Bayesian methodssuggests that botulinum toxin A may not be associated with benefit for any headache types.
* A second limitation is that authors had only aggregate data. Many of the outcomes had considerable heterogeneity and the lack of patient-level data precluded fully exploring potential sources of differences between the studies. This makes it difficult to explore why botulinum toxin A is not associated with benefit for chronic tension-type headaches, even though it is associated with improved outcomes for chronic daily headaches.
* Headache is a chronic problem and all the trials were relatively short. At least 1 systematic reviewfound that prophylactic treatment becomes more effective over time.
* None of the studies evaluated more than 3 injections, 90 days apart. It is unclear whether a higher dosing strategy over time may be associated with greater benefit.
* Single trials found no differences between botulinum toxin A and amitriptylineor topiramatefor chronic migraine headaches.
* There are few comparisons between botulinum toxin A and other prophylactic medications, and these are underpowered or have other limitations that may prevent the ability to demonstrate benefit of botulinum toxin A. Although the reported SMD of benefit that has been associated with other prophylactic agents appears to be larger than the SMD we found for botulinum toxin A, the best way to make this determination is with direct comparative trials.
* In addition, authors only included events from these randomized controlled trials. Observational studies and Food and Drug Administration adverse event reports likely include additional harms, particularly rare ones that may be missed in short-term, relatively small studies. Authors may have underestimated adverse effects of botulinum toxin A.
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| Frank F, Ulmer H, Sidoroff V, Broessner (2021) | Systematic review and meta-analysis | * Performed a systematic search of the Cochrane Controlled Trials Register (CENTRAL), EMBASE, and MEDLINE. The search strategy was established to include published clinical trials assessing the efficacy of preventative treatments for migraines. Language was restricted to English and reference lists of retrieved studies or other meta-analyses were searched manually. In order not to omit any relevant data, the pharmacological agents were not restricted to mABs, TPM and BoNTA. Relevant studies were searched through 20 May 2020. The search strategy comprised four concepts defining disorder, application, intervention, and outcome. Authors used free text terms as well as controlled vocabulary terms.
* For eligibility, trials had to be placebo-controlled and randomized. The defined diseases studied were episodic and chronic migraine according to the criteria valid at the time of conducting the trial. The eligible pharmacologic interventions were TPM, BoNTA and mABs targeting CGRP for preventative migraine treatment.
* Two investigators extracted the data independently. Information extracted comprised full title, authors, publication date, study population, interventions and duration of intervention, baseline data, outcomes, and potential source of bias.
* The database and trial registry search yielded 6552 results After removing duplicates, letters, case reports and studies where full text could not be retrieved, 429 studies were identified as eligible for full review. By restricting the results to studies on mABs, TPM and BoNTA, we obtained 131 studies. Of these, 32 randomized, placebo-controlled trials reporting responder rates finally fulfilled the inclusion criteria.
 | * The primary outcome was defined as the 50% response rate, comprising reductions in mean monthly migraine days (90.0%), mean monthly headache days (5.0%), and mean monthly headache hours (5.0%).
* As secondary outcome variables, authors collected reduction in migraine days or headache days.
 | * In general, all treatments show higher ORs in achieving a 50% response compared to placebo.
* Topiramate demonstrated the greatest effect size but also the highest drop-out rate. This might indicate that new therapies are not more effective but more tolerable.
* A factor in favour of mABs and BoNTA is the frequency of administration; while available oral preventative medications are administered daily, mABs require injection only monthly or quarterly, like BoNTA, accounting for a rather good treatment adherence.
 | * Different study durations or definitions of adverse events.
* Furthermore, the available studies also tend to use different outcome measures such as headache or migraine days or attack frequency. The RR50 can be used as a surrogate comparator between studies, as it is an artificial variable independent of the underlying efficacy measurement. The utilization of odds ratios furthermore reduces variations emerging due to variable placebo rates.
* Risk of bias of all included studies was assessed using the Cochrane collaboration tool. Both individual patient-level data and summary estimates were extracted where available.
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**Conclusion**

 The first article utilizes clinical trial to compare the efficacy of Botox and topiramate in the setting of chronic migraine at decreased reoccurrence. This article also does a great job at comparing the different adverse effects and possible discontinuation of each medication. It also displayed which patients withdrew from treatment due to said adverse events and compared the percentages between both medications within regard to this.

 The second article displayed a clinical trial to compare the efficacy of Botox and topiramate in decreasing frequency of reoccurrence in people with chronic migraines. Unlike the previous article it did not compare withdrawal from the treatment due to medication adverse events. This article did, however, prove that Botox is as effective as topiramate at decreasing symptoms of chronic migraine.

 The third article directly answers my question by using a control trial to compare Botox and topiramate. It showed that Botox was as effective topiramate in decreasing reoccurrence in people with chronic migraines. It did however show that people were more likely to complete Botox treatment than topiramate. The article also considered the adverse effects of Botox and if it played a role in withdrawal from the study.

 The fourth article uses a meta-analysis to assess the efficacy of Botox in patients with chronic migraine. It also considers the adverse events that are most common when taking the drug. The article also proves that Botox is as effective as topiramate at decreasing the number of migraines, this article not only assessed the effectiveness in treating migraines but also with tension headaches. This study also compared Botox to amitriptyline, even though this does not relate to my question directly it is good to know how it compares to treatments other than topiramate.

 The fifth article compared the efficacy of the three most used treatment regimens for chronic migraine which are Botox, topiramate, and monoclonal CGRP antibodies. The study showed that all three have been shown to be effective in limiting reoccurrence in the setting of chronic migraine however, topiramate showed the largest effective size. Despite topiramate displaying the largest effective size it also had the highest dropout rate. This study showed that topiramate may be slightly more effective than Botox however Botox has been shown to be easier for patients to adhere to overall.

 All five of the articles clearly display a correlation between the use of Botox and decreased occurrence regarding chronic migraines. Another aspect that is consistent across all the articles is that patients are more likely to adhere to a treatment regimen that includes Botox than one that includes topiramate. One aspect that is inconsistent across the articles is if Botox can possibly have adverse long-term effects that may be worse than those of topiramate. A key finding across all the studies is that Botox seems to be as efficacious as topiramate in treating chronic migraine symptoms by reducing the frequency of migraines.

**Clinical Bottom Line:**

 Overall, all the articles have weaknesses through various biases which factor into the overall weight of evidence for each article. In the first two articles many of the participants were Caucasian females so it can be said these studies may be limited due to the lack of inclusivity of other races and genders, which may have affected the results. The credibility of the results of the third article can be brought into question seeing that it only analyzed one specific formulation of Botox, therefore can the conclusions of this study be used generally for all formulations of Botox or simply this specific one. The fourth article is limited seeing that most of the studies in the article were both small and short in time frame, it can be argued that the short length of time defeats the purpose of examining treatment for a chronic issue. In addition, the authors of the fourth article only included adverse events from the randomized controlled trials. Observational studies and Food and Drug Administration adverse event reports likely include additional harms, particularly rare ones that may be missed in short-term, relatively small studies, which may have led to the article underestimating the adverse events of Botox. Within the last article one limitation that can be appreciated is the fact that the available studies used different outcome measures such as headache or migraine days or attack frequency, which may have impacted the conclusions that the article drew. Due to the limitations previously outlined the weight of evidence should be considered in the following order from highest to lowest: Article 5, Article 3, Article 4, Article 2, and lastly article 1.

 The clinical bottom line as outlined in all the articles is that studies have shown that Botox is as effective as topiramate at decreasing reoccurrence in patients with chronic migraines. It has also shown that when it comes to adverse effects topiramate was shown to have greater adverse effects among the patient population. This therefore led to people being less compliant with topiramate as compared to Botox. Both medications have near if not an equal level of efficacy, however when presenting both options to a patient the possible adverse events need to be discussed. Another thing that needs to be considered is the cost of the drug because again this can affect compliance. Botox in the setting of chronic migraines can range anywhere between $300 to $600 per treatment, compared to topiramate which can range from $6 to $26 for a bottle of 60 tablets. This immense price difference has the chance to be a deciding factor in some patients and should therefore be disclosed before a treatment plan is made. In conclusion both treatment options should be discussed with the patient in detail outlining the cost and adverse events of both then the patient and provider should use shared decision making to decide a treatment option that best suits that specific patient.