BOTULINUM TOXIN INJECTION FOR CHRONIC MIGRAINE PROPHYLAXIS

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Clinical Reviewer: Michael Zatt, DO

BACKGROUND

CLINICAL BACKGROUND

Chronic migraine (CM) is a type of chronic daily headache that can be severely disabling. Individuals diagnosed with CM must have experienced headaches for at least 15 days per month for more than three months, with headaches on at least eight days that possessed migrainous features (HIS 2018). Approximately three million adults in the United States (1.3% of the population) are estimated to be affected by CM (Natoli 2010). One in five of these individuals are occupationally disabled. Research has also shown that CM is associated with reduced quality of life (Bigal 2008, Dodick 2006).

Treatment for chronic migraine typically includes pharmacotherapy,but may include complementary treatments such as changes in diet, sleep, and exercise. Acute pharmacotherapy includes options such as simple analgesics, non-steroidal anti-inflammatory drugs, triptans, CGRP antagonists, and ergotamines. Preventive pharmacotherapy options include antidepressants, anticonvulsants, beta-blockers, calcium channel blockers and botulinum type A (e.g., BTA or Botox) injections (Chawla 2011), and CGRP antagonists. The use of BTA for chronic migraine involves injections into the muscles of the head and neck approximately every 12 weeks.

POLICY AND CRITERIA

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	L35172 "Botulinum Toxin Types A and B"
Local Coverage Article	A57186 "Billing and Coding: Botulinum Toxin Types A and B"
Kaiser Permanente Medical Policy	For Medicare lines of business, apply the criteria in the LCD with support from the LCA to determine medical necessity.

For non-Medicare Members

Injection of onobotulinumtoxinA (Botox) may be considered medically necessary for chronic migraine prophylaxis when both of the following criteria are met:

- Diagnosis of chronic migraine as described by the International Headache Society Classification with attacks occurring for 15 or more days per month for more than 3 months, of which at least 8 days per month are migraine headache; AND
- Member has documented failure of (or intolerance to) prophylactic migraine medications from at least 3 different drug classes. Each trial must have lasted at least 2 months. Classes include:
    - Anti-depressants
    - Anti-convulsive medications

- Beta blockers
- Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers

Members meeting the above criteria may receive no more than 5 (five) treatments in a 12 month period.

If a previous trial of botulinum toxin injection for chronic migraine prophylaxis has NOT produced at least a 7-day reduction in monthly number of migraines, or severity of headaches by 3/10 points, or reduced total headaches duration by at least 100 hours per month, additional injections are considered NOT medically necessary.

RATIONALE

EVIDENCE BASIS

Northwest Permanente Evidence-based Medicine Services reviewed the evidence on botulinum toxin for migraine prophylaxis in 2015. Findings and conclusions were as follows:

Aurora 2010 (n = 679) reported results from the Phase III Research Evaluating Migraine Prophylaxis Therapy I (PREEMPT I) study, assessing the efficacy, safety and tolerability of BTA as chronic migraine prophylaxis. PREEMPT I consisted of a 24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week, open-label phase. Investigators assessed the frequency of headache episodes (the primary outcome of interest), as well as numerous secondary outcomes, including the frequency of headache days, the frequency of migraine days, and the frequency of migraine episodes. The study reports no improvement in reduction of headache episodes over placebo ($p = 0.344$). However, the study does report that BTA produced a 7% reduction in headache days over placebo, meaning that patients receiving BTA injections had, on average, 1.4 fewer headache days per month than those receiving placebo ($p = 0.006$, 95% CI: -2.40, -0.40).

Diener 2010 (good-quality RCT): Diener et al. (n = 705) reported results from the Phase III Research Evaluating Migraine Prophylaxis Therapy II (PREEMPT II) study, assessing the efficacy, safety and tolerability of BTA as chronic migraine prophylaxis. Like PREEMPT I, PREEMPT II consisted of a 24-week, doubleblind, parallel-group, placebo-controlled phase followed by a 32-week, open-label phase. Whereas the primary outcome of interest in PREEMPT I was the frequency of headache episodes, PREEMPT II focused instead on the frequency of headache days. Investigators also measured numerous secondary outcomes, including the frequency of headache episodes, the frequency of migraine days, and the frequency of migraine episodes. The study reports that BTA produced an 11.5% reduction in headache days over placebo, i.e., 2.3 fewer headache days per month ($p < 0.001$, 95% CI: -3.25, -1.31).
Dodick 2010 (pooled data from two good-quality RCTs detailed above): Dodick et al. (n = 1384) pooled data from the PREEMPT I and PREEMPT II studies to address again the efficacy, safety and tolerability of BTA as chronic migraine prophylaxis. Again, investigators focused on the mean change from baseline in frequency of headache days, and reported that BTA produced a 9% decrease in mean headache days over placebo, i.e., 1.8 fewer headache days per month (-8.4 BTA vs -6.6 placebo, $p < 0.001$, 95% CI: -2.52, -1.13; Number Needed to Treat [NNT] = 9 for one person to experience at least a 50% reduction in the frequency of headache days).

Within both PREEMPT I and PREEMPT II, there is a potential for “unblinding” of the study participants to their treatment group allocation. Because BTA produces a numbing sensation and physical differences in facial appearance following injection, it is possible that participants were able to determine whether they were receiving BTA or placebo. This has the potential to result in ascertainment bias that may bias these studies’ results. However, investigators did expend rigorous effort to conduct a double-blind study, and we do not see room for methodological improvement to overcome this potential issue with subject masking to the receipt of active drug versus placebo.

In both trials, more than 60% of participants reported acute headache pain medication overuse. The International Classification of Headache Disorders 2nd edition (ICHD-2) does not classify patients with acute head pain medication overuse as having chronic migraine: “*migraine headache occurring on 15 or

more days per month for more than three months in the absence of medication overuse." If practitioners are using the ICHD-2 criteria for chronic migraine, their patient population would differ from the PREEMPT I study population. It is important to take this difference into consideration when attempting to generalize these findings.

There were significant differences between the treatment and placebo groups at baseline in both PREEMPT I (Aurora 2010) and in the pooled analysis of PREEMPT I and PREEMPT II (Dodick 2010). The placebo group had significantly more baseline headache episodes (Aurora 2010: placebo = 13.4, BTA = 12.3, p = 0.023; Dodick 2010: placebo = 13.0, BTA = 12.2, p = 0.004) and migraine episodes (Aurora 2010: placebo = 12.7, BTA = 11.5, p = 0.006; Dodick 2010: placebo = 12.2, BTA = 11.4, p = 0.004) than the treatment group. The treatment group reported significantly more cumulative headache hours (Aurora 2010: placebo = 274.9, BTA = 295.7, p = 0.022; Dodick 2010: placebo = 281.22, BTA = 295.93, p = 0.021) at baseline. If there is a differential in the magnitude of the placebo response among individuals with more or less frequent headaches or among individuals reporting more or less headache hours these imbalances in baseline characteristics might act as confounders. Because the placebo response is particularly relevant when measuring patient-reported outcomes (Hróbjartsson 2010) as was done in these trials, these possible confounders should be considered when interpreting study findings.

All studies report that treatment with 155 Units (U) to 195 U of BTA every 12 weeks over 24 weeks was well-tolerated. Pooled results from PREEMPT I and PREEMPT II showed that 62.4% of individuals receiving BTA reported adverse events, compared to 51.7% receiving placebo. Serious adverse events were reported by 4.8% of individuals receiving BTA compared to 2.3% receiving placebo. Additionally, 3.8% of those receiving BTA discontinued because of adverse events, compared to 1.2% of those receiving placebo. Adverse events most frequently cited for discontinuation of the study were neck pain (0.6%), muscular weakness (0.4%), headache (0.4%) and migraine (0.4%). No deaths were reported within either group. Both PREEMPT I and PREEMPT II had 32-week open label phases following the 24-week randomized, double-blind phases to study adverse events further.

Additional literature published between 2015 and 2016 identified only reports of new analyses of previously reported data, including 4 subgroup analyses, 1 pooled analysis, 1 systematic review, 1 meta-analysis, and 1 cost-effectiveness analysis. None of the reported analyses alter the conclusions of the previous review.

Authors of a more recent Cochrane review did not identify any additional literature (Herd 2018). In that review, authors also performed a meta-analysis combining results of the relevant RCTs. The pooled mean difference between botulinum toxin and placebo showed a benefit of approximately three fewer migraine-days per month in the treatment group (-3.1, 95% CI -4.7 to -1.4). In another meta-analysis, the authors excluded trials at high risk of bias, leaving the PREEMPT 1 and PREEMPT 2 trials (Aurora 2010 and Diener 2010, respectively). While there was still a significant benefit in favor of the treatment group, the estimate was somewhat smaller, with a mean reduction of two fewer migraine-days per month.

RELEVANT GUIDELINES

The American Academy of Neurology (AAN) reviewed evidence related to BTA for various indications, including migraine prophylaxis, in their 2008 guideline (Naumann 2008). An updated literature search in 2016 informed the following guidelines regarding chronic migraine:

> **Strong Evidence** OnaBoNT-A should be offered as a treatment option to patients with CM to increase the number of headache-free days (Level A).
>
> **Moderate Evidence** OnaBoNT-A should be considered to reduce headache impact on health-related quality of life (Level B).

The AAN 2016 guideline was reaffirmed in 2019 with no changes.

In guidelines issued by the National Institutes for Clinical Excellence (NICE), botulinum toxin type A is recommended as a treatment option for chronic migraine. NICE states the following:

1.1 Botulinum toxin type A is recommended as an option for the prophylaxis of headaches in adults with chronic migraine (defined as headaches on at least 15 days per month of which at least 8 days are with migraine):

- That has not responded to at least three prior pharmacological prophylaxis therapies and
- Whose condition is appropriately managed for medication overuse

1.2 Treatment with botulinum toxin type A that is recommended according to 1.1 should be stopped in people whose condition:

- Is not adequately responding to treatment (defined as less than a 30% reduction in headache days per month after two treatment cycles) or
- Has changed to episodic migraine (defined as fewer than 15 headache days per month) for three consecutive months

1.3 People currently receiving botulinum toxin type A that is not recommended according to 1.1 and 1.2 should have the option to continue treatment until they and their clinician consider it appropriate to stop.

CODES

CPT or HCPCS Code	Description
64615	Chemodenervation of muscle(s); muscle(s) innervated by facial, trigeminal, cervical spinal and accessory nerves, bilateral (eg, for chronic migraine)
J0585	Botulinum toxin type A, per unit [Botox]

ICD-10 Code	Description
G43.001 - G43.919	Migraine headache

REFERENCES

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POLICY HISTORY

Date	Action
May 1, 2015	New policy
June 27, 2017	Calcium channel blockers removed as a class of prophylactic medication as suggested by clinician reviewer due to lack of efficacy
April 24, 2018	Definition of chronic migraine updated to reflect 3rd edition of ICHD
May 29, 2019	No policy changes; literature and guideline updates with no substantive changes.
May 15, 2020	No policy changes; literature and guideline updates with no substantive changes.
June 23, 2022	CGRP antagonists added as a class of prophylactic medication as suggested by clinician reviewer due to FDA approval of a CGRP antagonist for migraine prevention in 2021; policy amended to permit up to 5 treatments in a 12-month period as suggested by clinician reviewer based on clinical experience; literature and guideline updates with no substantive changes.