Onabotulinumtoxin A (BTX) is a neurotoxin that is used to treat many neurologic conditions, including dystonic disorders, spasticity, and pain. Clinicians have used BTX off-label as a treatment for headache prophylaxis for many years, and about one year ago it became the first medication to be approved by the US Food and Drug Administration (FDA) for chronic migraine (CM). The results of the two recent clinical trials have provided evidence of efficacy and prompted discussion and research into the mechanisms by which BTX exerts its effect.

ONABOTULINUIMTOXIN A: THE FIRST TREATMENT FDA-APPROVED FOR CHRONIC MIGRAINE
CM is a highly disabling form of chronic daily headache. To be classified as CM, headaches must occur on at least 15 days per month and meet criteria for migraine on at least eight of those days. BTX has been studied at length in various forms of migraine. Despite positive open-label studies and good tolerability, BTX did not appear more effective than placebo for the prophylaxis of episodic migraine in large part because the placebo response was so great—as much as other established migraine medications, such as topiramate. The approval for BTX in CM was based on two large, Phase III, multicenter studies, called placebo-controlled Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) 1 and 2 trials. These studies enrolled 1,384 subjects with CM in trials consisting of a 24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week open-label phase. BTX injections were performed in the frontalis, corrugator, procerus, occipitalis, temporalis, and trapezius muscles, with
a minimum dose of 155 units of BTX administered at 31 injection sites across seven head and neck muscles, using a fixed-site, fixed-dose injection paradigm and up to 40 extra units. Compared with patients receiving placebo, BTX-treated patients had significantly fewer migraine and headache days, less disability due to migraine, and were less likely to use triptans for acute pain.

**MEDICATION OVERUSE AND OTHER CONTROVERSIES**

One area of controversy in the PREEMPT trials was the inclusion of patients with acute medication overuse. Medication overuse headache (MOH) is defined by the 2nd edition of the International Classification of Headache Disorders as a headache that begins in association with acute medication overuse, such as simple analgesics more than 15 days a month or combination analgesics, triptans, opioids, or barbiturate-containing medications more than 10 days a month. About two-thirds of the PREEMPT subjects overused analgesics, although only a small minority (less than two percent) regularly used opioids. Detoxification was not required before entry in the study. Since the mean duration of CM of subjects in the PREEMPT trials was about 19 years, MOH’s causative contribution to CM is unclear. Also, the entrance criteria allowed aura, which cannot occur in CM according to the ICHD. The study authors point out that MOH is extremely common and aura can occur in CM, meaning that the study population better reflects the real world population that would receive BTX than rigid ICHD guidelines do. Given that migraine is generally very painful, and that CM means headache is present more often than not, enrolling only subjects who do not take frequent acute medication can be unrealistic.

**ONABOTULINOUMTOXIN A PATHOPHYSIOLOGY IN PAIN**

The effectiveness of BTX in CM is almost certainly due to more than the best-described mechanism, which is blocking the release of the neurotransmitter acetylcholine from motor neurons at neuromuscular junctions by cleaving the 25 kDa synaptosomal-associated protein (SNAP-25). BTX suppresses muscle overactivity, which is highly prevalent in CM, preventing the excitation of nociceptive neurons, limiting local ischemia and the release of proinflammatory mediators such as glutamate and calcitonin gene-related peptide. Because patients commonly experience pain relief before muscle paralysis begins, BTX most likely acts on nerve as well as muscle. In animal models, BTX blocks the release of proinflammatory mediators, including substance P, effectively preventing activation of second-order neurons, which transmit pain, within the spinal cord. New formulations of botulinum toxin, which may better target nerves, are being developed.

**PRACTICAL ISSUES**

Because of the success of the PREEMPT trials and the subsequent FDA approval of BTX for CM, insurance companies are beginning to reimburse for both the medication and the injections. However, multiple issues can make it difficult to use BTX for CM in clinical practice. First, BTX is expensive, with a cost of $1000-1200 for a 200 unit vial. It is a biologic drug, and because the FDA does not currently have a pathway for approving generic biologic drugs, there is no potential for lower drug costs.

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**PREDICTING RESPONSE**

_Some early data and experience suggest that BTX responders were_

- More likely to describe their migraines as pressure from the outside (imploding) or ocular pain vs. exploding pain
- Women
- Patients with allodynia
- Patients with headache-free days before treatment.

_Of note_, patients with unilateral pain may also experience greater relief

“Because patients commonly experience pain relief before muscle paralysis begins, BTX most likely acts on nerve as well as muscle.”
Most insurance companies require documentation that treatment with other migraine preventives from at least two to three other drug classes (antihypertensives, anticonvulsants, antidepressants) have been tried, despite the fact that many of these medications are not proven effective against CM and none are FDA-approved for the indication. Some insurance companies require a demonstrated response to treatment, including headache-free time. As an example, they can deny BTX coverage if a patient does not experience headache-free time, even if daily moderate-to-severe migraine remits to only mild pain. Making sure that patients keep careful diaries and documenting improvement could become even more important.

**PREDICTING EFFICACY IN MIGRAINE: WHOM TO INJECT?**

A few recent studies have attempted to predict BTX responders. In studies, BTX responders were more likely to describe their migraines as pressure from the outside (imploding) or ocular pain, while non-responders were more likely to report exploding pain. Women, patients with allodynia, and those with unilateral pain may also experience greater relief, and patients with headache-free days before treatment are also likely to respond.

In clinical practice, the most effective strategy is to offer BTX to CM patients who have failed to respond to multiple standard preventive treatments. Avoid stopping other medications for migraine prophylaxis after administering BTX, especially for the first two injection cycles, to avoid the possibility that drug withdrawal make BTX ineffective. Advise patients to avoid known triggers, obtain regular sleep and exercise, and treat all medical conditions, such as hypertension, insomnia, and affective disorders, that could worsen migraine control.

**PREEMPT protocols allow for additional injections (up to 195 units) in temporalis and occipitalis areas for more severe pain, so ask about any particular areas of pain. Patients should schedule a follow-up visit one to two months after the first set of injections to review treatment effectiveness and arrange for a second set of injections.**

Ask patients to document both migraine days and headache days before and after treatment. (Patients often notice a wearing-off before the next set of injections in three months.) As a significant minority of patients improved only after the second set of injections, we usually perform at least two sets of injections before deciding that BTX is ineffective. BTX can be effective for CM subjects with MOH, but is most likely to work in patients not using opioids or barbiturates frequently.

**“As a significant minority of patients improved only after the second set of injections, we usually perform at least two sets of injections before deciding that BTX is ineffective.”**

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