Botox for Chronic Migraine: Tips and Tricks

Ten Questions for Andrew M. Blumenfeld, MD

Andrew M. Blumenfeld is director of The Headache Center of Southern California. Most of his research has focused on the use of OnabotulinumtoxinA in the treatment of chronic migraine. He helped develop the injection paradigm approved by the United States Food and Drug Administration and has taught providers around the world on practical aspects of this treatment option.

OnabotulinumtoxinA (Botox) has become a well-recognized and frequently used treatment by providers who care for patients with migraine. Use of this medication can be optimized by following a simple set of guidelines.

1. Who are appropriate candidates for Botox treatment?

OnabotulinumtoxinA is the only treatment approved by the United States Food and Drug Administration for the prevention of headaches in adult patients with chronic migraine (CM). CM assessment involves a detailed history to rule out secondary sources of headache, establish migraine features, and assess the total number of headache days. In order to diagnose migraine, the patient should have had at least five attacks that involve migraine features, as outlined below. In adults, untreated attacks usually last 4 or more hours.

A migraine requires only two of the following headache features: a unilateral distribution (one-sided), pulsatile quality (throbbing), moderate or severe pain (more than 5 out of 10), and aggravation by physical activity (such as bending over). In addition, to diagnose migraine, only one of the following is required: nausea or vomiting or sensitivity to light and noise.

Migraine can be subdivided depending on whether there is an aura or not and also on the frequency of the headaches.

Migraine with visual aura involves visual effects that usually precede the headache and last at least 5 minutes. The visual aura is usually an expanding blinding spot or visual scintillations (shimmering objects in the visual field). Other aura features include reversible symptoms of speech and language difficulty such as word-finding problems and aphasia (inability to express words or comprehend words), sensory phenomena such as tingling in the extremities extending to the face, motor effects such as weakness, and brainstem problems such as unsteadiness and features of cranial nerve dysfunction. These aura symptoms usually last 5 to 60 minutes, can precede or start during the headache, and can also occur without a headache.

The number of headache days determines whether the patient has episodic migraine (EM) (14 or fewer headache days a month) or CM (more than 15 days of headache a month). The best method of determining the actual number of headache days is to subtract this from the number of completely headache-free days in a month. If headache is present on more than half the days in the month, and there are migraine features on at least 8 days a month, the condition is termed CM. The migraine features only have to be present on 8 days out of the month and not on every headache day. The other headache days in this condition are considered to be milder forms of migraine, and they do not have all the typical migraine features. If headache is present on fewer than 15 days a month, this is referred to as EM. EM can transform to CM over time. If analgesics are used on 10 or more days per month, this can lead to a transformation to CM. The patient's headache pattern over a 12-month period should be determined, and during this time, there should be at least 3 months with 15 headache days; 8 of these days should meet migraine criteria.[1-3]

2. How do you counsel patients on when to expect efficacy?

The safety and efficacy of onabotulinumtoxinA for CM was demonstrated in the pivotal phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) trial. In this trial, patients were treated every 12 weeks whether or not their headaches had returned to baseline levels and the primary outcome period was after two treatment cycles.

At baseline, these patients had more than 19 headache days, and after two treatment cycles, their headaches had been reduced by 8 to 9 days per 28 days. The responder rate analysis of the study population shows that about 25% of patients improved by 75% in terms of a reduction of migraine days. In my practice, I usually do three cycles 12 weeks apart, and only if there is no change in headache frequency after this, do I change treatments. In the pivotal trials, the first statistical separation from placebo occurred in the first 4 weeks. There is a small subgroup of patients who fail to respond to the first two treatments and only start to respond after the third treatment.[4-10]

3. Is there a needle size and saline dilution that you find most useful?

The ideal needle to use is a 30G or 31G, half-inch needle. Longer needles are problematic as they encourage deeper injections, which can increase the risk of muscle weakness, and most of the side effects such as neck pain stem from muscle weakness. Perseverative-free normal saline is the only diluent that should be used. There is a case study of a patient who died when onabotulinumtoxinA was mixed with a local anesthetic agent. The pivotal trial established an effective dose using 2 mL/100 units of onabotulinumtoxinA. A fact that is often overlooked is that the mean dose in the trial was 165 units. The patients all received 155 units with a fixed dose, fixed-site injection protocol, and an option of an additional 40 units to follow the pain. This resulted in a mean dose of 165 units, which is the standard that should be used to achieve the efficacy results reviewed above.

4. What words or phrases do you use to explain what the injections feel like to lessen patient anxiety?

Injection description is very important. It is best to describe the injections as a pinch rather than a bee sting, and to explain that the injections are shallow, with only a half-inch needle. As a result of the superficial technique used with the injections, deep anticoagulation can be continued. The procedure is short, and talking to the patient during the procedure about something other than the injections can help alleviate the patient's anxiety. It is important to describe onabotulinumtoxinA as a purified protein rather than a toxin or a poison. In addition, stating that it relaxes muscles rather than causing paralysis will be reassuring to the patient. In a very anxious patient, the areas to be injected can be iced first or a local anesthetic cream can be applied. Starting with the trapezius muscle can also help, as these injections are the least painful, and the patient cannot see the needle. Finally, it is important to make sure the injections are performed with a sharp needle, and blunt needles are discarded. Thirty-gauge needles only remain sharp for six to eight needle sticks each.

5. What are best techniques to avoid ptosis?

Ptosis generally occurs from injecting the frontalis incorrectly. The worst mistake is for the injector to move the procerus and corrugator injection points higher, where they will place more onabotulinumtoxinA into the frontalis. It is important to examine patients to determine their pre-existing conditions prior to treatment administration. In particular, patients should be examined for pre-existing eyelid ptosis or pseudoptosis. With pseudoptosis, the lid strength is normal, but soft tissue covers part of the upper lid. With lid ptosis, the lid strength is weak. For both lid ptosis and pseudoptosis, patients will have frontalis compensatory activity, resulting in upgoing eyebrows (reverse Babinski sign). With brow ptosis, the frontalis is weak, and the eyebrow is depressed downward leading to tissue resting on the upper lid. To avoid this, the frontalis should be injected in the upper third of the forehead. The corrugator muscle attaches to bone at the medial end of the superciliary arch. The muscle fibers travel laterally and upward

inserting into the skin in the middle of the supraorbital margin. The corrugator muscle is partially blended with the orbicularis oculi and occipitofrontalis. The supraorbital and supratrochlear nerves pass through the corrugator muscle. The corrugator muscle acts to pull the eyebrows downward and medially, which causes vertical wrinkle lines in the skin between the brows.

According to the PREEMPT injection paradigm, a total of 5 units of onabotulinumtoxinA is injected into each corrugator muscle. To confirm the location of the muscle, the patient is asked to furrow the brow in order to activate the corrugator. Once the muscle has been located, the muscle should be palpated and pinched by holding it between the thumb and index finger. Five units of onabotulinumtoxinA is injected at an approximate 90° angle with the bevel of the needle pointing upward into the medial belly of the muscle. As the needle is inserted, there is skin resistance, which lessens when the muscle is penetrated. This decrease in resistance is termed a muscle pop. Once the muscle pop occurs, inject into the superficial muscle. If the injection is too far superior or above the corrugator muscle, brow ptosis can occur due to depression of the medial brow as the frontalis elevating function is lost and the corrugator depressing function remains unopposed. Whereas weakening the corrugator muscle will cause elevation of the medial eyebrow, alternatively, if the corrugator injection is done too low, then diffusion to the levator palpebral muscle could lead to lid ptosis.

The procerus is a small triangular-shaped muscle that intermingles with the inferior aspect of the frontalis muscle. The muscle runs from the aponeurotic fascia on the nasal bones and inserts into the skin of the inferior forehead. The medial portion of the eyebrow and the skin of the lower forehead are drawn down by the procerus muscle, producing transverse wrinkle lines over the bridge of the nose.

According to the PREEMPT injection paradigm, one injection of 5 units of onabotulinumtoxinA is administered to one site in the procerus muscle. The procerus injection site is approximately midway between the two corrugator injections. In order to confirm the location of the procerus muscle, the patient is asked to furrow the brow, which will activate the belly of the muscle causing the medial furrowing to occur. Once identified, 5 units of onabotulinumtoxinA is injected superficially into the belly of the muscle at a 90° angle to ensure the injection is administered into the procerus rather than the frontalis. Injections placed too superiorly may inadvertently lead to penetration of the frontalis muscle.

The frontalis muscle attaches to the skin of the lower forehead and ascends to join the fronto-occipital aponeurosis. The action of the frontalis muscle involves elevation of the eyebrows to produce expressions such as surprise, and can cause deep transverse wrinkles on the forehead. The antagonists for brow depression are the corrugators, procerus, and orbicularis oculi muscles.

According to the PREEMPT paradigm, one injection of 5 units of onabotulinumtoxinA into four sites (total 20 units) into the frontalis muscle is done. The injection points are located by visually drawing a line up from the medial edge of the supraorbital rim. Patients will be injected into the muscle in the upper third of the forehead at least 1 to 2 fingerbreadths above the corrugator injection site. The lateral muscle injection areas are parallel and approximately 1 fingerbreadth lateral to the medial injection site, which is roughly in line with either the midpupillary line or the lateral edge of the cornea, which is the limbus line. In cases in which I am worried about ptosis, I inject the frontalis close to the hairline. In order to reduce the risk of these unwanted effects, injections should be administered in the upper third of the forehead only. The needle should be inserted at a 45° angle superiorly. Because the frontalis is an elevator muscle, weakening can cause brow ptosis or exacerbate preexisting brow ptosis.

6. Patients have reported neck pain and/or weakness with Botox injections. What tips do you have to avoid/minimize this?

The patient's neck stability, posture, torsion, and symmetry should be assessed to determine whether he or she may be at increased risk for adverse events prior to the first injection cycle. A patient with preexisting neck pain and/or weakness may be at higher risk for exacerbation of the condition upon injection of the occipitalis, cervical paraspinal, or trapezius muscle groups. Patients with smaller frames may be at higher risk for neck weakness. Indicated injection sites can still be injected with minimal side effects and unwanted outcomes as long as correct injection sites are targeted and treatments are administered using a superficial approach with avoidance of the mid and lower cervical regions. The cervical paraspinal muscle group is made up of multiple muscles including the trapezius, splenius capitis and cervicis, and semispinalis capitus. This group of muscles helps support the neck, including extension of the head.

According to the PREEMPT injection paradigm, 5 units of onabotulinumtoxinA is to be administered to two sites on each side for a total dose of 20 units across four sites in the cervical paraspinal muscle group near the midline. The first injection site is approximately 1 cm left of the midline of the cervical spine and approximately 3 cm (2 fingerbreadths) inferior to the occipital protuberance. The second site is measured approximately 1 fingerbreadth diagonally up at a 45° angle from the first injection. The injections should be administered in the most superficial aspect of the muscle, angling the needle 45° and superiorly. To aid in the placement of the injections, the patient

should be positioned upright with the head in a neutral position. If the neck is flexed too far forward, injections may be too deep. Injections that are too low or too deep in this muscle group can lead to muscle weakness and neck pain. Injectors should use a suboccipital approach to ensure that the injection sites are not too low. In addition, a horizontal line can be visualized across the neck, approximately 2 fingerbreadths down from the occipital protuberance, to make certain the injections remain above the line and are not administered too low in the neck. The higher these injections are, the more likely that they will be in the muscle fascial condensation, which will minimize the potential for neck weakness. These injections should not be done below the hairline. Patients who have trigger points in the neck should not be injected at these sites as these are generally areas where muscles may be weakened and injections of onabotulinumtoxinA at these sites might worsen their neck issues.

The trapezius muscle is a large, triangular, superficial muscle. It attaches proximally in the medial third of the superior nuchal line, external occipital protuberance, nuchal ligament, and spinous processes of the C7-T12 vertebrae. Distal attachment of the trapezius occurs at the lateral third of the clavicle and acromion and spine of the scapula. The action of the muscle includes neck extension and stabilization of the scapula and support for the arm. The muscle fibers proximal to the inflection point of the neck (ie, necklace line) run vertically and are involved with neck extension. According to the PREEMPT injection paradigm, one injection of 5 units of onabotulinumtoxinA to each of three sites on either side of the trapezius, for a total of 30 units divided across six sites, is given. The first injection site can be identified by visually divid-

BOTOX NOTE

History:

The patient is here for Botox treatment.
Botox treatment cycle number:
Botox side effects:
Headache frequency: /90 days
Headache intensity: /10
MIDAS:
HIT-6 score:
PHQ-9 score:
Secondary illnesses:

Examination:

Speech is fluent
No aphasia or confusion
Extraocular movements (EOMs) are full
No lid or pseudoptosis
Full cervical range of motion (ROM)
No neck weakness
No focal limb weakness
No ataxia
Masseter muscle hypertrophy
Trigger points in the cervical-shoulder girdle muscles

Procedure:

Time out taken
Risks and benefits reviewed
Consent obtained
Dilution: 100 units in 2 mL preservative-free normal saline
Lot number documented
Total dose 200 units
Procerus 5 units
Corrugators 5 units each
Frontalis 10 units each
Temporalis 20 units each
Occipitalis 15 units each
Cervical paraspinals 10 units each
Traps 15 units each
Rest discarded
Well-tolerated
No complications

Diagnosis: Chronic migraine

ICD-10 code:

Plan: Botox 200 units in 12 weeks

ing the upper portion of the trapezius muscle in half, from the inflection point of the neck (ie the necklace line) to the acromion (acromio-clavicular joint); the midpoint of this location is where the injection should be administered. The second injection is located at the midpoint of the first injection site and the acromion. The third injection should be administered at the midpoint between the first injection site and the necklace line. Injections should occur in the supraclavicular portion of the muscle, lateral to the neckline, and medial to the deltoid and the acromio-clavicular joint. The injections into the trapezius should be administered horizontally and superficially to avoid injecting too deep.

7. What tricks do you have for the patient who responds well to Botox, but the effect wears off by week 8 to 9?

I increase the dose at each treatment cycle to 195 units. This is based on experience with patients with cervical dystonia, in whom higher doses result in a longer duration of effect. In addition, I transition to the next onabotulinumtoxinA treatment at 12 weeks by using occipital and trigeminal nerve blocks at 10 weeks. Most insurance companies will not cover onabotulinumtoxinA treatments earlier than 12 weeks, but in rare cases, 10-week cycles have been approved.

8. Do you always follow the 155-unit PREEMPT paradigm, or are there occasions when you increase/decrease the dose or inject other muscles?

The 5-unit dose that is injected at each site is a very low dose. Earlier studies with total dosing below 155 units failed to show separation from placebo. As a result, I encourage all patients to get a minimum of 155 units, even if they have a small frame. The optional component of the injection paradigm is the 40 units that are used for following the pain sites. The pain sites are the temporalis, occipitalis, and trapezius. These can be held if the injector is concerned. I do not reduce the dose below 155 units as lower doses have not separated from placebo, and thus I may not achieve an adequate headache effect with a lower dose. In fact, most of the time I increase the dose to at least 165 units, as this was the mean dose in the PREEMPT trials. I inject 5 units behind each ear for a bilateral headache and 5 units in two sites behind one ear in a side-locked headache.

Documentation is important for patients to continue receiving coverage for their Botox.

9. What can you share about what should go into the chart, and how to do that most efficiently?

My macro note is shown on the previous page. All my patients complete a Migraine Disability Assessment (MDAS), Headache Impact Teat–6 (HIT-6) score, and Patient Health Questionnaire–9 (PHQ-9) on arrival for their appointment.

10. Assuming a patient is doing well on Botox injected quarterly, how long do you continue before broaching the subject of discontinuation?

I use a similar approach to that which has been established for oral preventives; ie, once on a therapeutic dose with adequate headache control, the treatment is continued for a full year before considering weaning.

The Chronic Migraine OnabotulinumtoxinA Prolonged Efficacy Open Label (COMPEL) trial is the longest trial that assessed the long-term effects of this treatment. In this trial, patients with CM were treated with nine treatments, 12 weeks apart, and showed progressive headache improvement.

When I wean patients off of treatment, I do not change the dose but rather delay the treatment cycle to 16 weeks and monitor headaches in the last 4 weeks. If the patient remains well-controlled, I increase the treatment window to 20 weeks, and so on. I use this method to establish the level at which patients need reinjection to prevent breakthrough headaches.[11-13] ■

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