Chapter 8

# Management of Migraine Headaches: OnabotulinumtoxinA Injection

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/67308

**Abstract**

Chronic migraines are a common debilitating headache disorder. Recently, there has been increasing interest in the use of onabotulinumtoxinA as a preventative treatment, as studies have shown significant benefits. In line with current accepted theories on the pathophysiology of migraines, the toxin works by both direct and indirect means to prevent peripheral and central nerve sensitization. While efficacy has been established, the technique for extracranial delivery of onabotulinumtoxinA continues to see changes in an effort to seek better outcomes. The PREEMPT injection protocol is the original injection paradigm design targeting broad muscle groups. The ART injection paradigm offers the ability to deliver onabotulinumtoxinA closer to culprit nerves, thus increasing its effect and also decreasing adverse effects. OnabotulinumtoxinA is an effective and well-tolerated option for selective patients seeking relief from migraine headaches.

**Keywords:** BTX, onabotulinum toxin, migraine, ART, PREEMPT, trigger site theory

## 1. Introduction

Chronic migraines are the most common type of headache in patients that seek treatment, according to the data compiled from several specialty headache centers in the United States [1–3]. It is a debilitating disorder that not only has the ability to severely reduce the quality of life, but also causes a heavy economic burden. However, among the high number of patients that suffer from chronic migraines, only a third receive prophylactic treatments [4].

Over the last couple of decades, there has been an increasing interest in the use of onabotulinumtoxinA (BTX-A) as a preventative treatment for migraine headaches. Over time, a number

of well-designed large-scale studies demonstrated that this neurotoxin to be effective in reducing several measures of migraine symptomology [5–11]. The first major landmark study, called the PREEMPT (Phase III Research Evaluating Migraine Prophylaxis Therapy) trials, indicated that BTX-A is indeed effective and safe in treating migraine headaches. These studies showed a statistically significant reduction in the primary endpoint of headache day frequency in chronic migraine patients. They also demonstrated significant reductions in several other measures of migraine symptomology such as cumulative hours of headaches, headache days, and days of moderate/severe headaches [9]. Further studies indicated efficacy in reducing disease burden based on patient quality of life questionnaires [10, 11]. However, studies evaluating the effect of BTX-A on episodic migraines so far have not shown significant benefits [12–15]. This led to BTX-A being approved by the Food and Drug Administration (FDA) for the treatment of chronic migraine headaches. The injection paradigm used in the PREEMPT trails was designed based on the initial injection sites reported in earlier phase II trials [16, 17]. While the PREEMPT injection protocol is proven to be effective, research is ongoing with several other BTX-A injection techniques that have been developed. One in particular is the targeted approach, which was first done to pre-screen surgical decompression and later developed into a more formal technique used solely for preventative treatment purposes.

Currently, BTX-A is used to provide safe and effective long-term treatment for chronic migraine headaches. To appreciate the differences and advantages in BTX-A injection techniques between the two specialties, it is important to understand the different targets of injection, the trigger point and nerve compression hypothesis, mechanism of action of BTX-A in the treatment of migraines, and the anatomy of various muscles and nerves has only recently been elucidated by studies done between Cleveland and Dallas [6, 7, 18–20]. In this chapter, we discuss the PREEMPT injection paradigm and the Anatomical Regional Targeted (ART) BTX-A paradigm.

## 2. Mechanism of onabotulinumtoxinA

OnabotulinumtoxinA, one of the seven serotypes secreted by the *Clostridium botulinum* bacteria, is currently approved for use in several conditions including strabismus, blepharospasm, cervical dystonia, and glabellar lines. Only serotypes A and B are used in the medical context. The toxin works by blocking various activities at neuron junctions that depend on intracellular vesicle trafficking to the membrane, such as neurotransmitter release [21, 22]. Normally, stored acetylcholine is transmitted via intracellular vesicles that fuse at the surface outer membrane. OnabotulinumtoxinA cleaves the SNAP-25 protein at the surface membrane, inhibiting the SNARE complex system of vesicular fusion and thus preventing subsequent neurotransmitter release into the nerve junction [23]. In the context of pure cosmetic treatments, this mechanism inhibits contractions of superficial musculature on the face, eliminating the folding of skin. In the context of migraine treatment, the toxin likely works by inhibiting both motor and sensory neurons. Similar to cosmetic treatment, motor neuron inhibition is beneficial to the migraine patient. If nerve irritation is caused by impingement from an overactive muscle, the myorelaxant effect would reduce this irritation. On the other hand, another

http://dx.doi.org/10.5772/67308

mechanism of migraine headaches genesis is hypersensitivity of sensory neurons, specifically nociceptor neurons. BTX-A acts as a direct analgesic by blocking these hyperexcitable nociceptors. Studies have shown that BTX-A blocks the release of a number of nociceptive mediators, preventing the hypersensitization of peripheral nociceptors [24]. By blocking peripheral pain signaling to the central nervous system, BTX-A thus indirectly blocks central sensitization. Additionally, BTX-A has direct effects on nerves. In animal studies, BTX-A has been shown to both prevent and reverse sensitization of nociceptors [25]. If given prophylactically, BTX-A reduces the increase in spontaneous firing rate caused by later sensitization. It also reduces the spontaneous firing rate of already sensitized nociceptors [25]. Due to inhibition of the SNARE complex, the activity of chemoreceptors (TRPA1 and TRPV1) required for nociception is also reduced [26]. Importantly, recent evidence suggests that depositing BTX-A closer to nerves increases its effect, versus being distributed within a muscle group [26]. Therefore, the toxin's benefit in the prophylactic treatment of chronic migraines is likely due to several interacting effects including the inhibition of overactive motor neurons and the prevention/reversal of nociceptor sensitization [27].

## 3. Diagnosis of chronic migraines and candidacy for onabotulinumtoxinA

Prior to being treated for migraine headaches by BTX-A injection, it is critical for the patient to be seen by a board-certified neurologist, preferably one who specializes in headache medicine. If the neurologist does not offer BTX-A injection, collaboration with other specialties such as plastic surgery, ENT, or pain management for the injections can be done. A multidisciplinary team approach with plastic surgery, neurology, psychiatry, sleep medicine, and pain management working in conjunction with each other is an effective and preferred approach. The neurologist should evaluate and confirm the diagnosis of chronic migraine headache, ruling out other likely causes of recurring headaches that may not respond to BTX-A injection. Results from the PREEMPT part 1 and part 2 trials established BTX-A as safe and effective for chronic migraine patients. However, BTX-A should be avoided in patients who have previous hypersensitivity reactions to the toxin. Other contraindications include pre-existing neuromuscular disorders (myasthenia gravis and Lambert-Eaton syndrome), peripheral motor neuropathies, and amyotrophic lateral sclerosis that can increase the risk of significant side effects. It is unclear how effective BTX-A is in treating other commonly seen headache types, such as cluster, tension, and episodic headaches, as results have been mixed [15–17, 28–30]. Lastly, the majority of insurance carriers in the United States require documentation of migraine and headaches days, and previous failure of several classes of migraine medications.

## 4. Trigger sites and peripheral nerve irritation hypothesis

Because of its complex and multifactorial etiology, the exact pathophysiology of migraine headaches has yet to be completely elucidated. There are several commonly accepted theories based on central and peripheral mechanisms. In the context of onabotulinumtoxinA injection

for migraine headaches, local inflammation sensitizes sensory neurons and upregulates the recruitment of sensory nociceptors [31–38]. As alluded to earlier, migraine pathophysiology involves irritation of peripheral nerves. Specifically, it involves several branches of the trigeminal nerve. Subsequent repeated irritation of the nerve causes an augmented perception of pain. The trigger point hypothesis attempts to explain this cycle of inflammation and trigeminal neuronal hypersensitivity. It takes into account that patients are often able to describe the origin of their migraine pain in a specific area, and that each site of origin leads to a different constellation of symptoms. Among other mechanisms, irritation of extracranial nerves in the periphery can be caused by overactivity of surrounding musculature, tight fascial bands, and intimate neurovascular relationships. Therefore, irritation of peripheral nerves by adjacent muscular contraction or other contact points can cause release of inflammatory factors, triggering the onset of migraine headaches. In this context, onabotulinumtoxinA can be targeted to these potential trigger sites in an attempt to prevent or inhibit the inflammatory cycle leading to peripheral and central sensitization. This theory and its implication in the success or failure of migraine surgery should not influence the fact that anatomical knowledge of the nerve locations can improve BTX-A injection techniques. Even if some neurologists do not hold the peripheral nerve compression theory correct, evidence now shows that BTX-A is most effective when deposited closer to nerves, acting by means of either direct reduction of chemoreceptors on the nociceptor membrane surface, or indirect decrease in activity by reducing mechanosensitivity [25, 26].

Trigger sites are identified by regions where the pain originates, rather than other final locations where the pain may travel. To assess which sites are active, a Migraine Diary should be completed by patients each day for at least 4 weeks. Since patients often do not pay especially close attention to the exact location where pain begins, this log is very useful in keeping track of trigger origin sites. In addition to the migraine diary, a thorough history should be obtained to differentiate between sites where pain begins and sites where pain may radiate to. Because trigger sites are where the pain originates, injection of targeted BTX-A should be focused in these sites and not where the pain ends. However, a more liberal approach to targeted injection is to inject all the regions. Currently, there are six major trigger sites relevant to available treatment methods, which can be categorized into several "regions": frontal (Site I), temporal (Site II), rhinogenic (Site III), occipital (Sites IV and VI), and auriculotemporal (Site V). **Site I** refers to headaches beginning in the lateral and central forehead areas, with central and cephalad radiation. Patients often describe the pain beginning above the eye and moving from outside to inside. At times, palpation with a single finger at the area of the supraorbital and supratrochlear nerve will reveal tender areas where the supraorbital nerve (SON) and supratrochlear nerve (STN) are involved. In some cases, hypertrophy of the corrugator supercilii muscle may be visible on physical exam. **Site II**, or the temporal trigger site, is associated with headaches originating in the temple. Often times, pain radiates toward the lateral temporal and posterior auricular areas. The temporalis muscle may be larger than normal, or tighter than usual. However, it is important to differentiate temporomandibular joint (TMJ) pathology, as it is not a trigger site for migraine headaches. In this region, the zygomaticotemporal branch of the trigeminal nerve (ZTBTN) is involved in the generation of pain. **Site III** refers to pain of nasoseptal origin. This pain is usually associated with weather changes and

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atmospheric pressure changes, usually beginning in the early hours of the morning. Patients may complain of rhinitis, hyposmia, anosmia, halitosis, and dental pain. Because of this, they can also complain of breathing problems. In addition, this pain is generally described as starting behind the eye and radiating outward. Oxymetazoline nasal spray is used to temporarily abort headaches originating from this site. Of note, septal triggers should be considered if pain persists despite BTX-A injection in other trigger sites. To confirm an active trigger site in the septal area, imaging via computed tomography scan is required. Intranasal pathology such as septal deviation contacting turbinates, concha bullosae, and other masses can be identified and surgically treated. It is important to rule out septonasal origin, as BTX-A generally does not improve pain originating from site III. **Site IV** occipital trigger site refers to headaches originating in the back of the neck and radiating anteriorly. This area usually correlates with the anatomical course of the greater occipital nerve (GON). Palpation in this area usually reveals a point of maximal tenderness that corresponds to the location where the nerve pierces the semispinalis capitis muscle. Some injection techniques target the semispinalis and splenius capitis, as well as the occipitalis muscle, but generally BTX-A is deposited as close to the nerve as possible. Patients may also complain of retroauricular pain associated with this site. Of note, it is possible that an intimate neurovascular relationship between the greater occipital nerve and occipital artery at this trigger site plays a major role in migraine development [6, 18, 20, 39]. The close relationship of the greater occipital nerve with the occipital artery can cause pain to fluctuate with weather, as arterial vascular tone changes. In general, pain in the occipital region mostly involves the GON, while the third occipital nerve (TON) may be involved to a lesser degree. **Site V** refers to pain in the area corresponding to the auriculotemporal nerve (AT). Pain in this area is caused by TMJ facial bands inferiorly and the temporal artery more superiorly, causing irritation to the AT nerve [40]. Finally, **Site VI** refers to the area around the lesser occipital nerve.

While these areas are the major sites relevant to currently available treatment modalities, a number of other sites have been reported to cause significant pain. The trapezius muscle group, TMJ muscle group, sternocleidomastoid muscle, and masseter are few examples. While patient description should aid in the selection and specific location of injection sites, actual injection is based on the anatomy of the culprit nerves and surrounding tissue.

## 5. Techniques for injection

### 5.1. PREEMPT injection paradigm [24]

The injection protocol used in the phase III PREEMPT trials were based on, and developed upon, earlier phase II studies that demonstrated safety and efficacy in the use of onabotulinum toxin for chronic migraine patients. Using this PREEMPT injection paradigm, the phase III part 1 and part 2 studies confirmed significant reduction in the frequency of headache days and low rates of adverse events [9, 41]. At 24 weeks, pooled data from both trials reported a significant difference in the reduction of headache days compared to placebo. Specifically, those who underwent 24 weeks of BTX-A injection had a 7.4 day reduction, while placebo

had a 4.7 reduction in headache days [10]. Thus, the PREEMPT injection protocol is a proven prophylactic treatment for chronic migraine patients.

As the first formal injection protocol described, the PREEMPT technique is a combination of a "fixed site" and "follow the pain" approaches. This was based on a number of earlier studies employing different approaches. From these studies, this combination approach was determined as the most optimal protocol to be used in the PREEMPT trials [24]. A total of 155 units are injected into 31 fixed sites, targeting a number of muscle groups. In addition to these fixed site and fixed dose (FSFD) sites, an additional eight sites and 40 units can be injected according to physician discernment in a "follow the pain" approach. Therefore, the PREEMPT injection paradigm uses a minimum of 155 units and a maximum of 195 units, which corresponds well with the determined optimal dosage range between 150 and 200 units [24]. **Figure 1** shows the PREEMPT injection protocol in each area. A standard 30-gauge 0.5-inch syringe is used, and an injection interval of 12 weeks is followed.

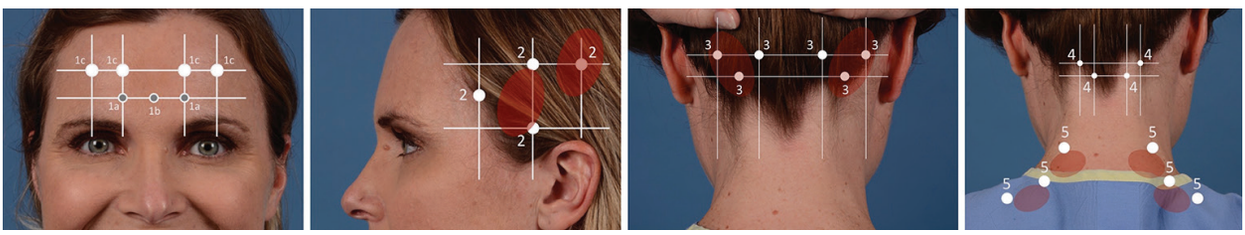


**Figure 1.** PREEMPT injection protocol. Locations of fixed site, fixed dose injections: (1a) procerus, (1b) corrugators, (1c) frontalis, (2) temporalis, (3) occipitalis, (4) cervical paraspinal, and (5) trapezius muscle. Follow-the-pain injection areas are indicated in red color.

### *5.1.1. Frontal*

In the frontal region, a total of 35 units are injected in a shallow manner into four muscle groups. First, the corrugator muscle is injected bilaterally 1.5 cm above the medial superior edge of the orbital ridge, with 10 units into each side. In the midline, the procerus is injected with 5 units in a location midway between the two corrugator injections. Finally, injection of the frontalis is divided into four sites, with 20 units total. On one side, the medial injection is 1.5 cm above the corrugator injection, and the lateral injection is 1.5 cm away from the medial injection in the same horizontal plane. This is repeated on the opposite side of the forehead.

### *5.1.2. Temporal*

In the temporal region, the temporalis muscle is the main muscle group targeted. Injection in this area consists of four sites on each side of the head. A total of 20 units are injected into each side. The first injection is behind the anterior border of the temporalis muscle. The second injection is 0.5 cm above and 1.5 cm posterior to the first injection. The third and fourth injection is 0.5 cm posterior and inferior to the second injection, respectively. This is repeated on the opposite side. As mentioned earlier, additional units can be injected on both or just one side, and is based on palpation for significant tenderness and pain that requires additional treatment.

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*5.1.3. Occipital*

The occipitalis muscle group is injected with 15 units in three sites on each side, totaling 30 units. The first injection is 1 cm lateral to and above the occipital protuberance. The second injection is given 1 cm lateral and 1 cm above the first injection. Finally, the third injection is 1 cm medial and 1 cm above the first injection. Similar to the temple area injection, physicians can follow the pain by palpating for significant areas of tenderness, and inject additional units.

*5.1.4. Cervical spine and paraspinal muscle groups*

In the area of the back of the neck, the PREEMPT protocol targets the semispinalis and splenius muscle groups. Injection consists of two sites on each side with 20 units total. On each side, the first injection is 3–5 cm inferior and just lateral to the occipital protuberance. Another injection is made 1 cm superior and lateral to the first.

*5.1.5. Trapezius*

The trapezius muscle is injected superiorly into three sites on each side, with 30 units total. The fixed dose is 5 units into each of the six total sites. One injection is made into the lateral portion of the muscle, another to the middle aspect, and one medially and superior within the medial portion of the muscle. With results from palpation for tenderness and pain, the physician can inject additional sites within the muscle group.

**5.2. ART injection technique: Anatomical, Regional, and Targeted [42]**

While the PREEMPT trials and its associated injection paradigm have paved the way for the development of BTX-A injection in migraine headaches, several other injection techniques have been developed, including the Anatomical, Regional, and Targeted (ART) injection paradigm. In contrast to the "fixed site" and "follow the pain" approach of the PREEMPT protocol, the ART technique offers a dynamic injection paradigm based on anatomical studies and surgical experiences in the decompression of nerves [42].

The ART injection paradigm can be described as Anatomical, Regional, and Targeted [42]. In this approach, injection is not necessarily targeted to a broad muscle group. Rather, this injection paradigm is designed based more on the *direct* effects of onabotulinum toxin on peripheral nerves, which have been previously described [25, 26, 43, 44]. As a result, injections rely heavily on accurate understanding of nerve anatomy and delivery of the toxin as close to the nerve as possible. The term "Anatomical" refers to injections based on the accurate location and depth of a nerve, and its surrounding musculature. "Regional" refers to focused injections at regions where pain originates (frontal, temporal, or occipital). "Targeted" refers to injections based on the topography of tender areas, which may not always correspond with known anatomical compression points. Therefore, the ART injection approach has the potential to be more individualized to each patient's unique picture of migraine pain.

While the PREEMPT injection paradigm dictates the exact dosage delivered to each site, the ART injection protocol is less strict on how much is injected. Previous studies have showed

the optimal dosage range per injection cycle is between 150 and 200 units [24]. The standard ART dosage consists of 155 units delivered across several sites: 45 units into the frontal site, 25 units into the temples, 50 units to the GON, 10 units to the LON, 15 units split into the tails of the GON and LON, 5 units in the area of the AT nerve, and finally 5 units in the area of the tail of the AT nerve. This standard is the injection pattern given to patients who report pain in all trigger sites. However, upon physician discretion, more units can be delivered to certain areas, or none in certain trigger sites, according to what the patient reports.

*5.2.1. Site I: Frontal*

In Site I, injection of BTX-A is based on irritation of the supraorbital and supratrochlear nerves (SON and STN). In this site, the injection is more anatomical than targeted. If BTX-A is injected in areas of maximal tenderness here closer to the orbital rim, the risk for lid ptosis and diplopia is high. Therefore, injection is more fixed in this area. The corrugator supercilii muscle (CSM) is thought to compress the SON and STN, but any of the other glabellar muscles has the potential to as well (procerus, depressor supercilii). In addition, fibrous bands in the supraorbital foramen, or a boney foramen, could also be sources for proximal compression and pain. Before injecting into this area, the topographical anatomy of the corrugator muscle can be clearly visualized by asking the patient to frown. Of note, studies in plastic surgery literature have further outlined the anatomy of the corrugator, which is not followed accurately in the PREEMPT/Allergan injection protocol (**Figure 2**). The CSM begins 3 mm lateral to the midline and extends 43 mm laterally. Superiorly, it extends 33 mm from the pupil. An ice pack is used to cool the area before injection, as it is important to reduce anxiety and pain in the migraine patient. Digital occlusion of the supraorbital and supratrochlear vessels with the non-dominant thumb reduces the risk of "microhematomas". A short 0.5 inch 30-gauge needle with 0.1 cc graduation is used to inject 12.5 units into each side with a five-point standard injection (**Figure 3**). Based on correct anatomy, injection should be deeper medially and more superficial laterally. Single injections can be done on each side using a longer needle inserted superficially on the lateral side and extended deeply toward the medial side. Injection should be done as the needle is advancing, as it provides for the best control. If bleeding is present, gauze can be used, but it is critical not to press with excess pressure as the toxin can diffuse into unwanted areas in the upper lid.

Injection into the frontalis muscle should be only in the upper half of the forehead (**Figure 3**). Injecting lower on the forehead leads to a higher rate of lid ptosis. A total of 15–20 units is injected. This injection not only targets the distal portions of the SON and STN, but relaxation of the frontalis muscle reduces cephalic pull that can cause tension in the proximal nerve areas.

*5.2.2. Site II: Temporal*

Injection into the temporal area is again more anatomical than targeted. The zygomaticotemporal branch of the trigeminal nerve (ZTBTN) emerges approximately 17 mm posterolateral and 6.5 mm cephalad to the lateral canthus. This point of exit from the temporalis muscle is seen consistently in cadaver studies [45]. A long 30-gauge needle should pierce the temporalis muscle 1 cm posterolateral to this point to deposit 12.5 units on each side (**Figure 4**). The injec-

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tion should be fanned deeply in a 1.5 cm radius. Additionally, a single deep injection at the point of nerve exit over the deep temporal fascia should also be performed.

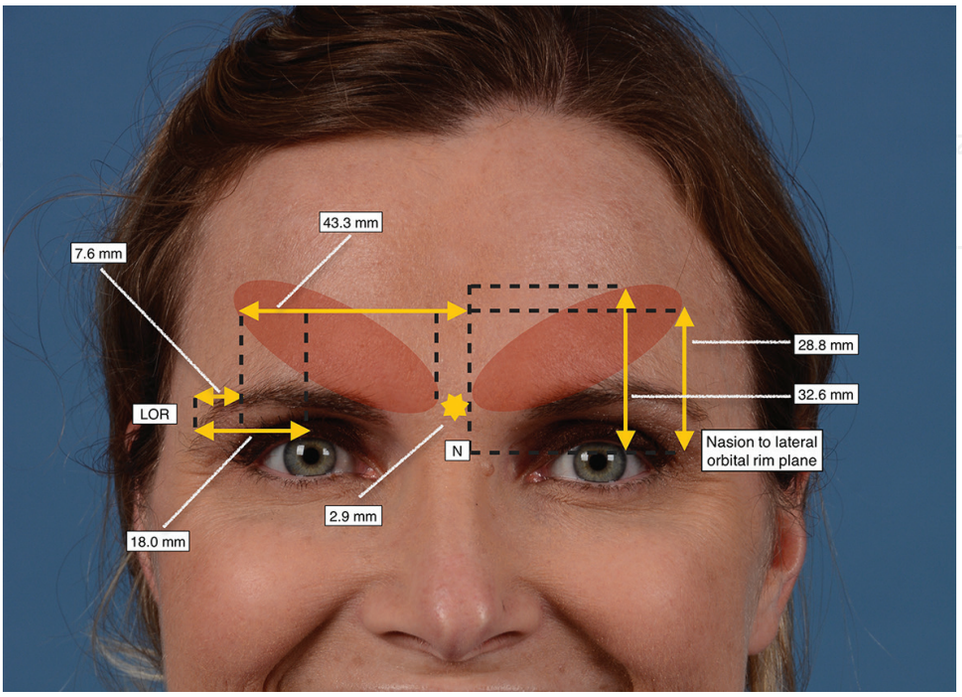


**Figure 2.** The location of the corrugator muscle.

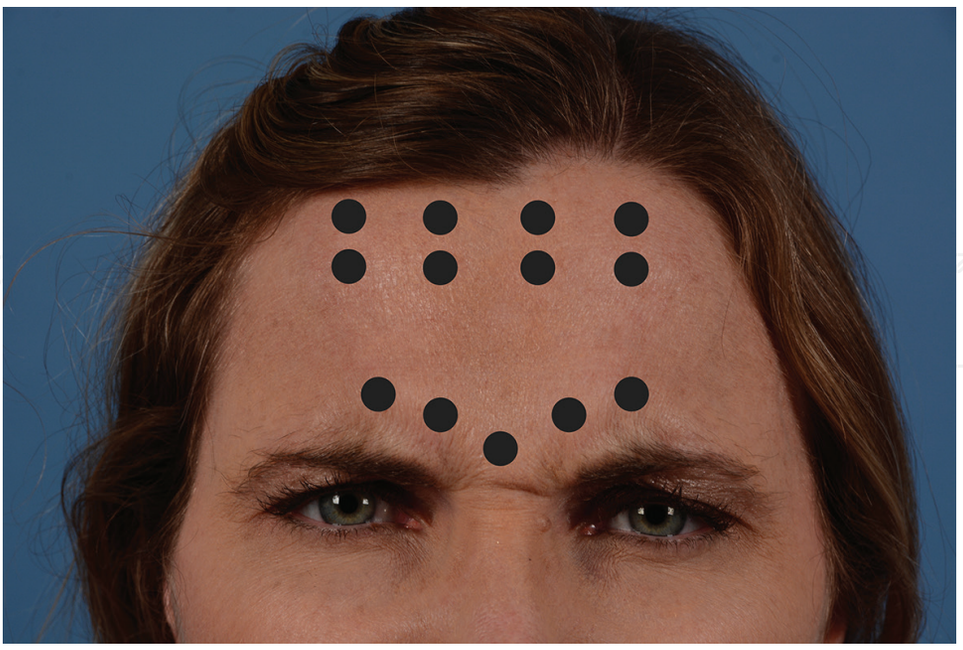

**Figure 3.** ART frontal trigger site injection. Image demonstrating injection sites over the corrugator muscle. The patient frowns to assist in finding the correct locations. The SON and STN nerves are targeted here, as well as the frontalis muscle.

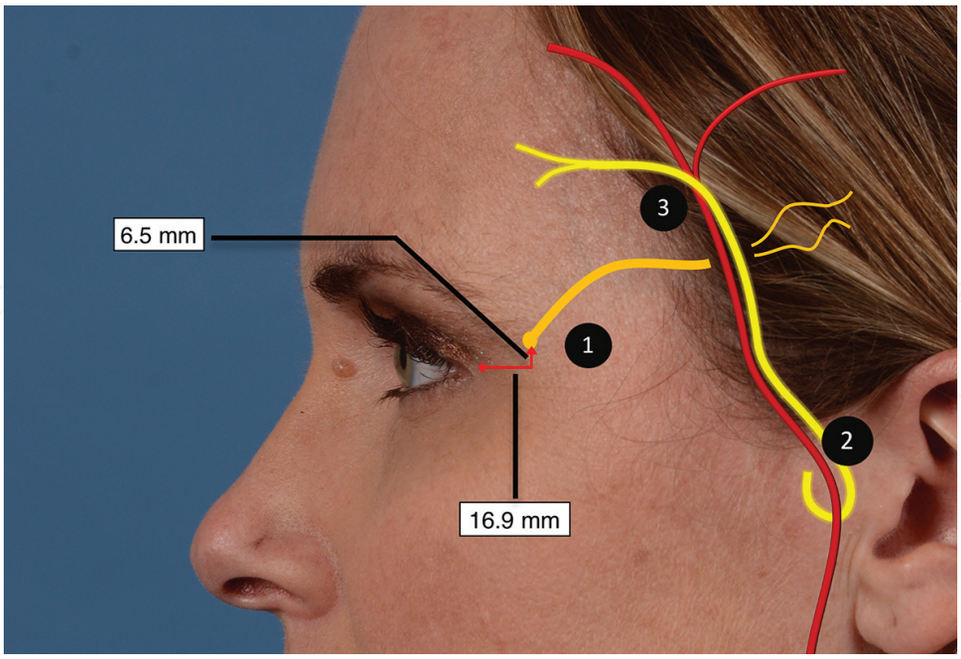


**Figure 4.** ART temporal trigger site injections. Figure demonstrating the relationship between the auriculotemporal nerve (AT), zygomaticotemporal nerve (ZTBTN), and the superficial temporal artery. It is important to note that the ZTBTN is on a different fascial plane, and does not normally contact the AT nerve or temporal artery. Injection sites include: (1) 1.5 cm posterolateral emergence of ZTBTN from deep temporal fascia. (2) fascial band compression at proximal AT. (3) Distal AT area corresponding to crossing with the superficial temporal artery.

The auriculotemporal nerve (AT) is another potential source of nerve irritation in the temporal area. This nerve is referred to as **Site V**. Injection at this site is more targeted than anatomical. BTX-A delivery should be guided by the patient's descriptions of tender areas, which may not always correspond with areas of anatomical compression. Injections should be in two sites: one near the proximal AT area where fibrous bands can compress the nerve, and one near the distal AT where it crosses the superficial temporal artery [42] (**Figure 4**).

*5.2.3. Site III: Nasoseptal*

BTX-A cannot be delivered to this area. A computed tomography scan should be done to elucidate areas of turbinate contact or other masses. Currently, the only treatment for this site is surgical correction.

*5.2.4. Site IV: Occipital*

Injection in Site IV is based on irritation of the occipital nerves: greater occipital nerve (GON), lesser occipital nerve (LON), and the third occipital nerve (TON). Although the LON can be referred to as **Site VI**, its treatment is considered together with other occipital sites. The GON is most commonly the primary site of pain. This injection is both targeted and anatomical. The nerve consistently pierces the semispinalis capitis muscle at a point 1.5 cm lateral to the midline and 3 cm below to the occipital protuberance (**Figure 5**). However, the area of maximal tenderness is often 0.5–1 cm lateral to this point. Therefore, BTX-A injection should

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be targeted to this area. When injecting this nerve, it is critical to inject deeply enough to pierce the trapezius fascia, where the nerve resides. A sturdier 27-gauge long needle is used to ensure penetration of the thick fascia, with 25 units injected into each side. The LON is injected similarly in a targeted and anatomical approach, using 10 units total for both sides (**Figure 5**). The point of maximal tenderness often corresponds anatomically within 0.5 cm of the emergence of the LON behind the sternocleidomastoid muscle [46]. The LON emerges 6.4 cm lateral to the posterior midline drawn through cervical spine, and 7.5 cm caudal from a horizontal line drawn between the most superolateral aspects of the external auditory canals [47]. Additionally, patients sometimes describe pain in the areas corresponding to the distal tails of the GON and LON. In these areas, terminal branches of the occipital artery intertwine with the occipital nerves.

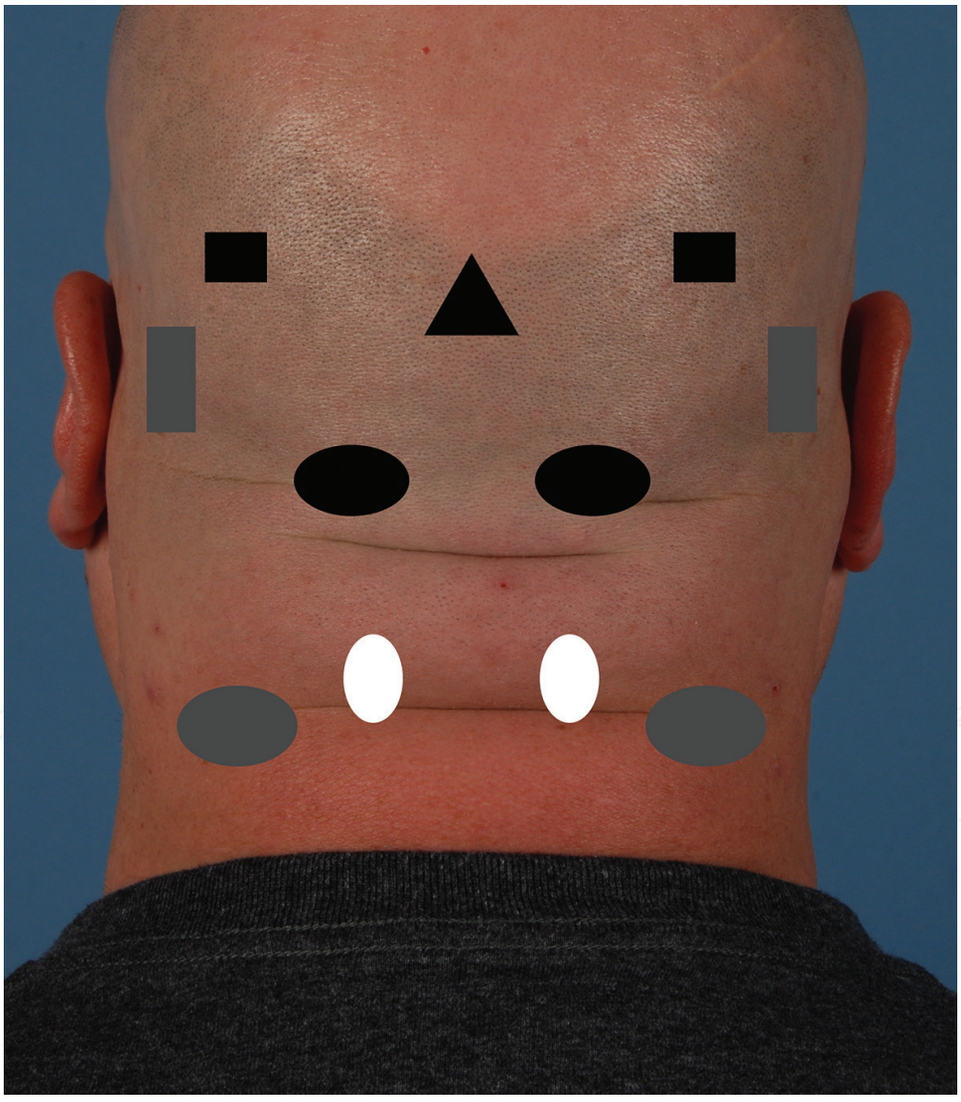

**Figure 5.** ART occipital trigger site injection sites and landmarks. Occipital protuberance (triangle), GON (black oval), tail of GON (black square), LON (gray oval), tail of LON (gray square), 3rd occipital nerve (white circle).

## 6. Conclusion

OnabotulinumtoxinA injection is an effective strategy to treat chronic migraine. At 56 weeks, the percentage of patients in the PREEMPT trials that received at least 50% reduction in headache days was 68%, significantly better than the reduction seen in patients who received placebo [48]. In addition to being effective, BTX-A has also been shown to cause very minimal adverse effects. Some commonly seen complications include neck pain/weakness, eyelid ptosis, and injection site pain. There have been no reported deaths among migraine BTX-A studies, and only 1.4–3.8% of patients discontinued treatment due to adverse effects [9, 10, 16, 17, 24].

BTX-A injection is an effective and well-tolerated treatment option for chronic migraine patients who have previously failed a number of traditional medications. It is most effective in patients who suffer from a higher frequency of headache days, such as those seen in chronic migraines. Additionally, it is well known that chronic migraine patients often suffer from medication overuse. In a subanalysis of PREEMPT trial results, BTX-A demonstrated significant effectiveness in reducing frequency of headache days even in patients who are designated with medication overuse [49]. Sometimes, patients may not respond from the first injection interval. It has been shown even among patients that fail to respond initially, a meaningful proportion of patients responded in the second and third treatment cycles [50]. ART injection on the other hand is a newer, expanded, and more refined version of the targeted injection based on recent neurology data and theories suggesting that BTX-A is more effective if deposited closer to nerves. Although available studies are less robust, preliminary clinical results show less complications than PREEMPT.

While onabotulinumtoxinA injection has been shown to be both safe and effective among a broad group of patients, demonstrating versatile and robust efficacy, research is ongoing to develop the best and most efficient ways to deliver this treatment. Knowledge of potential culprit nerves and the accurate understanding of surrounding tissue anatomy are essential to maximize efficacy and efficiency in chronic migraine pain management.

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