Chapter 4
The Role of Botulinum Toxins in Treatment of Headaches

Introduction

Headache is a common ailment. On average, 50% of the population experiences one headache per month and a quarter of population acknowledge having one headache per week. The international society for classification of headaches, categorizes headaches into primary and secondary headaches. Primary headaches are those that occur in individuals with no evidence of brain disease on brain imaging or laboratory testing, whereas secondary headaches arise as a result of brain pathology or systemic disorders. Although secondary headaches reflect a more serious condition (tumor, inflammation, bleeding, etc), primary headaches can be as severe and as disabling.

The major primary headache disorders consist of migraine, tension headaches and cluster headaches. Over the past 17 years, the effects of botulinum neurotoxin therapy on primary headaches has been studied extensively especially with onabotulinum toxin A (Botox) (see Chap. 3 for different types of botulinum toxins used). These studies, so far, have shown the efficacy of Botox in treatment of chronic migraine, an indication which received approval in summer of 2010 in Europe and Canada; it received approval by FDA for use in US, later that year.

Migraine and Chronic Migraine

The word migraine is derived from the French word of migraine (pronounced migren) which itself originates from the Greek word hemikrania (pain involving half of the head – Galen 200 AD). Although in many patients with migraine, pain of migraine involves mainly one side of the head, a sizeable number of migraine victims complain of bilateral headaches. Migraine is much more common among women than men with a reported prevalence of 17% among the former and 6%

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among the latter [1]. The exact cause of this huge gender difference in migraine is not clear but, undoubtedly, hormonal issues play a major role as migraine frequency often diminishes during pregnancy and after menopause following the drop in estrogen levels. Migraine's impact on the quality of life is substantial. Migraine is currently rated as the seventh cause of medical disability [2]. Migraine headaches usually begin during the second and third decades of life and decrease substantially after age 40 [3]. Migraine is considered a genetic disease since over 50% of the patients report a family history of migraine.

The pathophysiology of migraine is still not fully understood. The old concept that a sequence of constrictions of brain vessels followed by dilatation causes migraine is no longer tenable. According to current thinking, before onset of pain, an electrical wave starts and travels over the cortex resulting in depression of brain activity and release of potassium, calcitonin gene related peptide (CGRP) and other substances. These substances lead to inflammation of brain coverings which then conveys signals to the pain sensitive trigeminal system inside and outside of the brain. This system innervates the skull, scalp and blood vessels; irritation and sensitization of this system results in pain. A genetically related mechanism triggers the initial event of this cascade in migraine which is yet to be explained.

Clinically, migraine headaches are often of moderate to severe intensity and on the average, last from 4 to 72 h. Attacks may be one sided, but changing sides is not unusual. During the attacks, patients often complain of nausea and report unusual sensitivity to light or sounds. Most patients prefer to go to a quiet room, close their eyes and avoid noisy environment.

In 20% of the patients, a migraine attack begins with an" aura ". Aura means "breeze" in Greek language and, in migraine denotes a transient objective sensation before the onset of headache. The most common type of aura in migraine is a visual aura. Patients describe seeing lights in part of their visual field. These light auras are usually on one side of the patients' visual fields (sometimes affecting half of the field in both eyes) while taking many shapes and forms. They can present in form of flickering or zigzag lights also called scintillations. These lights often start in a small part of the visual field and then evolve into larger areas. The enlarging lights in the field of vision (positive aura), sometimes end to momentary loss of vision in the same area (scotoma). In some patients, the scotomas or negative auras can occur without positive auras. Another common aura in migraine is a somatosensory aura which presents with experiencing unusual sensations over the face or parts of body. These sensations are usually in form of tingling, numbness or transient loss of sensation, affecting one side. Such experiences in older individuals need to be differentiated from initial symptoms of an impending stroke which is totally different from migraine. Other auras such as experiencing intense smell or taste or having episodes of vertigo are less common.

Patients may explain their first migraine as the most severe headache of their life with a very sudden onset. Such headaches (thunderclap headache) need to be investigated by computed tomography (CT scan) or magnetic resonance imaging (MRI) to ensure that they do not represent bleeding inside the head as a consequence of a

ruptured aneurism that requires immediate and urgent care due to its potentially life threatening nature (re-bleed).

Based on the frequency of headaches, migraine is classified as episodic or chronic migraine. The term episodic migraine defines a form of migraine with headache days of less than 15 per month while definition of chronic migraine requires 15 or more headache days per month, with at least 8 of 15 of them being of migraine type.

Treatment of migraine includes abortive and prophylactic (preventive) measures. Abortive medications suppress the acute pain, whereas prophylactic medications, prevent recurrence of severe headaches. Abortive treatments are short term and usually limited to the day of the migraine attack. Prophylactic treatments require taking daily medications. Migraine is an underdiagnosed disease and it is generally believed that preventive treatment in migraine is also underutilized.

Treatment of Acute Attacks

Three categories of medications are capable of inducing significant relief of acute migraine attacks within 2 h, usually in over 50% of the patients. These abortive drugs consist of Triptans, the Ergot derivative DHE and antiemetic (against vomiting) agents (metoclopramide, chlorpromazine). Triptans (sumatriptan, eletriptan and several others) are available in oral and injectable forms as well as nasal spray with the latter two being more useful in patients with nausea or vomiting. Subcutaneous injection of injection or nasal spray DHE have similar effects, while intravenous DHE combined with metochlopromide is often used for aborting severe attacks. For milder attacks, one can use over the counter drugs such as acetaminophen or aspirin. Transcranial magnetic stimulator is a FDA approved device that provides a magnetic pulse to the brain surface (through the skull) and has been shown to make 17% of the patients free from acute migraine headaches within 2 h [3].

Preventive Treatment

A large number of medications are now available for prevention of acute attacks. Among these medications the most commonly used are tricyclic antidepressants (amitryptiline and nortryptiline), betablockers (propranolol, nadolol, metoprolol, timolol), anticonvulsant agents (topiramate and divalproex sodium), and most recently, monolclonal antibodies targeting, CGRP (calcitonin gene related peptide). CGRP is a major pain transmitter and modulator that based on laboratory tests, plays a major role in the pathophysiology of migraine. In high quality, blinded, phase 3 studies (see definition in Chap. 3), this group of drugs has been found to be extremely effective in prevention of migraine [4]. The mode of treatment

application are subcutaneous or intravenous injections, used once every one to three months. Monoclonal antibody treatment is about to be approved by FDA for use in the US.

Unfortunately, all medications used for prevention of acute migraine attacks have a low to medium rate of efficacy especially in chronic migraine when the attacks occur 15 or more days per month. Moreover, the side effects of these medications such as hypotension (low blood pressure) and sexual dysfunction (beta-blockers), unusual sensory experiences, cognitive decline, depression, weight loss (topiramate), tremor and hair loss (divalproex), dry mouth, urinary retention and weight gain (tricyclic antidepressant and divalproex) concerns many patients. Over the counter medications such as co-enzyme Q, magnesium, vitamin B1 and melatonin or acupuncture have questionable preventive effect. Exercise, yoga, and meditation help some patients through relaxation. Furthermore, drugs that are used for aborting the acute migraine attacks, are themselves, sometimes hard to tolerate due to undesirable side effects. For instance, triptans and DHE are contraindicated in coronary artery disease and can cause dizziness, nausea and light headedness, while antiemetic medications cause sedation and acute abnormal movements (dystonia: twisting of the limbs and akathisia: excessive restlessness). For these reasons a mode of preventive treatment which is effective and has a low side effect profile remains desirable for prevention of frequent migraine attacks [1].

Botulinum Toxin Treatment of Migraine

During 1980's and 1990's animal studies demonstrated that onabotulinumtoxinA (Botox) can block the release of pain modulators and pain transmitters from nerve-muscle junction [5]. This made researchers think that Botox injections into muscles around the head, by influencing the pain transmitters, may help patients with headaches. During 1990's several reports indicated that Botox injection into forehead muscles can improve forehead wrinkles. To the surprise of clinicians, some migraine patients who received Botox into forehead for cosmetic purposes reported reduction of intensity and frequency of their headaches. Following these observations, a headache specialist, Stephen Silberstein and his co-workers conducted the first randomized, double blind, placebo controlled clinical trial (see Chap. 2 for definition of clinical trial) of Botox in patients with migraine [6]. In that study, 123 patients with migraine were stratified into three groups receiving either Botox 75 units, Botox 25 units or placebo (normal saline) into the forehead muscles. Although the study did not show a statistically significant improvement of the primary outcome measure – increased pain free days/month, it showed that injection of Botox into forehead muscles reduces the intensity of migraine attacks and the number of pain days/month. It took another 10 years before the role of Botox in treatment of migraine was established. During these 10 years, several studies with Botox in episodic migraine (with pain frequency of <15/month) failed to show any efficacy. However, in 2010 publication of PREEMPT studies demonstrated that injection of Botox into

the pericranial (around the head) muscles with certain injection paradigm and dose can significantly reduce the number of pain days in patients with chronic migraine. The total dose and number of injected sites in PREEMPT studies was substantially higher than that of prior studies.

PREEMPT Studies

The two PREEMPT studies were multi-center and investigated the efficacy of Botox in chronic migraine (15 or more pain days per month), on a total of 1384 patients. PREEMPT studies were double blind, meaning that the patients did not know what they were receiving; physicians and raters of the response were also blinded to the type of the injections. Both studies also had a follow up, open label (unblinded arm). The blinded arm of the studies lasted for 24 weeks with placebo or Botox injection every 12 weeks. Patients were evaluated with weekly visits during which they had several ratings of pain, sleep, and quality of life throughout the duration of the study. The open, unblinded arm which began after completion of the blinded arm, lasted 32 weeks during which the patients received Botox only and were evaluated the same way for response. Evaluation of the pooled data from the two PREEMPT studies showed that a single injection of Botox produced not only reduction of pain days and migraine episodes per month but also reduced the pain intensity within each episode [7]. All findings had a high level of statistical significance ($P < 0.0001$). Since then, Botox has been used for treatment of chronic migraine on thousands of patients. The positive results of PREEMPT studies raised several practical questions:

- Can the positive effect of Botox treatment in chronic migraine be sustained over a long period of time (years) with repeat injections?
- A sizeable number of patients with chronic migraine also have superimposed medication overuse headaches i.e. they have a second pain issue. Does this population of patients with chronic migraine also respond to Botox therapy?
- Generally, patients with chronic migraine have a poor quality of life. Do the positive effects of Botox therapy in chronic migraine lead to improvement of quality of life?
- Is long term- treatment of chronic migraine with Botox safe? Are there any serious side effects with long-term use?

Aurora and co-workers [8], studied the sustenance of Botox effect on 1005 patients with chronic migraine who received Botox injections into pericranial (around the head) muscles after 5 cycles of treatment (every 3 months). Patients continued to enjoy pain relief during all five cycles of treatment (56 weeks) and also showed a substantial improvement in their quality of life as measured by migraine-specific quality of life questionnaire scores. Another group of investigators demonstrated that quality of life improved significantly in both in blinded and open label phase of the PREEMPT study in the Botox group (607 patients) compared to the

placebo group (629 patients) [9]. Silberstein and co-workers [10], studied another cohort of PREEMPT population. Of 688 patients who received Botox, 49.3% demonstrated 50% or more reduction in the frequency of headache days after first injection with additional 11% and 10% first time responders observed during the second and third cycle of injections. In another study which focused on patients with migraine and medication overuse headaches [11], treatment with Botox decreased the frequency of headache and migraine days, headache intensity, number of severe headache days and percentage of patients with severe HIT-6 scores (poor quality of life). The authors concluded that Botox treatment is effective in patients with chronic migraine and medication overuse.

In recent years, a number of authors have investigated the utility of Botox therapy in migraine outside clinical trials and in real- life situations. These studies [12, 13], have confirmed the positive results of clinical trials of Botox therapy in chronic migraine. A recent, large survey conducted in 28 Italian health centers also concurred with the conclusion of these real-life studies [14].

Sites of Botox Injection, Recommended Dose Per Site and Per Session

The most common injection technique currently used for treatment of chronic migraine is the one used in the PREEMPT studies [15]. The PREEMPT protocol recommends injecting 5 pericranial (around the head) muscles consisting of three forehead muscles (corrugator, procerus, and frontalis), one muscle at the temple (temporalis) and one muscle at the back of the head (occipitalis). Two other injection locations are into the upper neck and shoulder muscles (splenius and trapezius muscles) (Fig. 4.1). The function of these muscles and the number of injections per muscle and does per injection sites are presented in Table 4.1. The total dose per session is 165 units with an option to increase it to 195 units, per the discretion of the injecting physician.

In practice, patients often express concern about the number of injections, thirty one, recommended by the PREEMPT group. Jabbari and co-workers at Yale have demonstrated that similar results can be achieved with a different injection paradigm that includes only 21 injection sites (Fig. 4.2) . In this injection scheme, injection sites at the temples are reduced to two on each side (using a larger dose of 15 units per site) and occipital injections to one on each side (5 units). Three injections, each 10 units are given into the posterior neck muscle (splenius), on each side. The six trapezius injection sites that are recommended by PREEMPT group, are eliminated from this paradigm [16]. Although some authors expressed concern that injection of higher doses into the neck may cause muscle weakness, the Yale group did not notice any weakness of neck or temporalis muscle after thousands of Botox injection sessions performed for treatment of chronic migraine. The total dose per session is 175–200 units, comparable with that of PREEMPT (165–195).

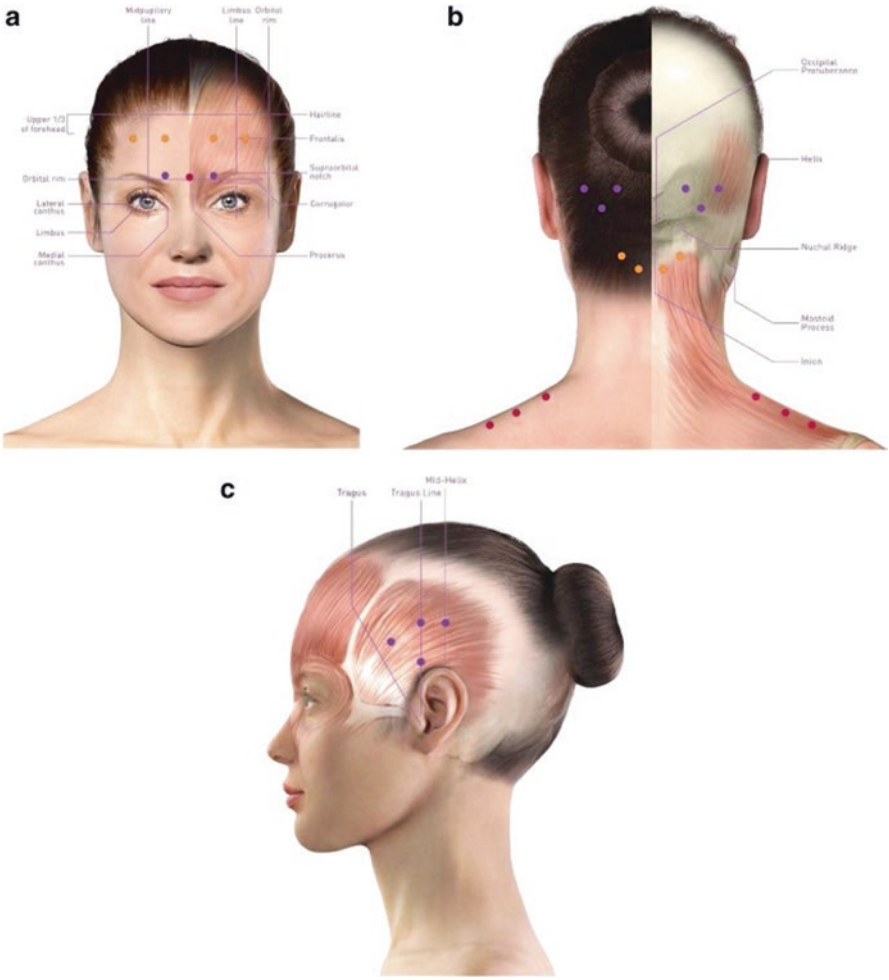

Fig. 4.1 Sites of Botox injections for treatment of chronic migraine as recommended by the PREEMPT Study group. From Blumenfeld et al. 2017 [15]. In Headaches. With permission from the Publisher, Wiley & Sons

How to Inject?

Botox comes in small vials with the active powdered ingredient sitting at the bottom of the vial. Botox has to be diluted with normal saline before injection. Some injectors like to add 1 cc and some add 2 cc of normal saline into the Botox vial containing 100 units of the toxin. This author prefers 1 cc dilution which allows injecting smaller volumes per site. After adding saline into the Botox vial, the solution is shaken gently and then is drawn into a small, thin 1 cc syringe with 10 divisions each representing 0.1 cc. When using 1 cc dilution, each 0.1 cc division of the

Table 4.1 Injection paradigm recommended by the PREEMPT study: injected muscles, muscle location, muscle function and the dose of Botox administered per site(s)

Muscle	Location	Function of muscle	Number of injection sites per muscle	Dose per injected site
Corrugator	Above the medial edge of eyebrow	Draws the eye brows together and downward	One on each side	5 units x 2
Procerus	Helps to pull the skin between eyebrows downward	Pulling eyebrows together	Single muscle One injection at midline	5 units x 1
Frontalis	Whole forehead	Pulling eyebrows up	Two on each side, total 4	5 units x 4
Temporal	Temple	Closes the mouth	Four on each side, total 8	5 units x8
Occipitalis	Back of the head	Moves the scalp back	Three on each side, total 6	5 units x 6
Splenius	Upper neck	Turns and tilts the head to the same side	Two on each side, total 4	5 units x 4
Trapezius	Shoulder	Moves the shoulders up	Three on each side	5 units x 6

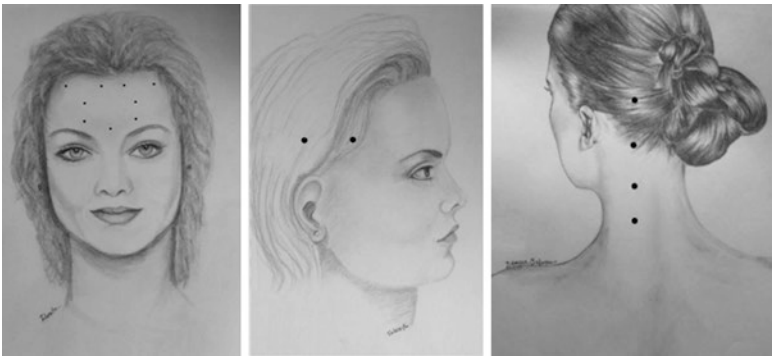

Fig. 4.2 The site of injections in the method used by Yale group for treatment of chronic migraine [16]. Drawings courtesy of Tahereh Mousavi M.D. and Damoun Safarpour M.D.

syringe will contain 10 units of Botox. Botox injections into the skin and muscles for migraine are superficial and performed with a small and thin needle (¾ inch, 27.7 or gauge 30 needle). In experienced hands, injections into pericranial sites, upper neck and shoulder muscles cause minor discomfort. Usually there is no bleeding, but when there is some bleeding, it stops quickly when wiped by a dry gauze. The injections can be done with the patient lying down or sitting up. This author prefers injecting migraine patients in the sitting up position. The whole procedure takes approximately 15 min.

Accuracy of dilution is very important in botulinum toxin therapy. This is particularly true when treating migraine patients since several muscles are small, hence, inaccurate dilution lead to overdosing and unpleasant side effects. For instance, small corrugator and procerus muscles are too close to the eye (see Figs. 4.1 and 4.2), and wrong dilution can lead to weakening of small muscles around the eye causing drooping of the eye lid or double vision. If the Botox solution is prepared and dilution is done by someone other than the injecting physician, it is the responsibility of the injecting physician to double check the accuracy of the dilution before injecting the patient.

Side Effects of Botox Therapy in Chronic Migraine

Side effects that develop following Botox treatment of migraine are minor and transient. In the large PREEMPT study consisting of 1384 patients, temporary pain at the site of injection, minor local bleedings (when the tip of the needle nicks a small blood vessel), mild muscle weakness and eyelid drooping occurred in 2–6% of the patients [8] Drooping of the upper eye lid can last for several weeks, but in my experience, can be easily avoided by careful placement of the thin needle into the lower forehead muscles (procerus and corrugator -see Figs. 4.1 and 4.2), away from the upper eye lid. PREEMPT authors reported no serious side effects, safety and tolerability issues that concurred with the experience of clinicians in the real-life situations.

Several studies have compared the preventive effect of Botox therapy in chronic migraine with the effect of two major headache preventive drugs, topiramate and divalproex. Side effects were more common in topiramate and divalproex groups. More patients in topiramate and divalproex groups discontinued treatment due to undesirable side effects than the group that received Botox (24% versus 7% and 27% versus 3% for topiramate versus Botox and Divalproex versus Botox, respectively) [17, 18].

Episodic Migraine

The term episodic migraine defines headaches with a frequency of less than 15 times per month. Seven high quality, blinded Class I and II studies (see Chap. 3 for definition of study class) assessed the efficacy of botulinum toxin therapy in episodic migraine. Three of the seven studies have used similar or higher doses than PREEMPT studies. All studies failed to show efficacy of botulinum toxin treatment in episodic migraine. In one study, however, investigation of a subset of the studied cohort, showed that Botox treatment, significantly reduces the intensity and frequency of headaches in patients with 12–14 headaches per month but not among

those with less than 12 headache days per month. In 2016, the Development Guideline Subcommittee of the American Academy of Neurology(AAN), based on the above data, reported Botulinum toxin treatment as ineffective in management of episodic migraine [19].

Tension–Type Headaches

Tension Headaches are the most common type of headaches with a prevalence of 38% in the US population [20]. Compared to migraine, tension headaches are more often bilateral and associated with scalp tenderness and less often associated with nausea and vomiting. Also, most tension headaches are less severe than migraine. The prevalence of chronic tension headaches (15 or more headaches per month) is similar to that of chronic migraine it is 2% in the general population [21]. Six high quality clinical trials (class I and II), two with Botox and four with Dysport (both type A toxins), assessed the efficacy of botulinum toxin A in tension headaches, but none showed efficacy. A meta-analysis study (see Chap. 3 for definition) of the reported data on tension-type headaches, published in 2012, also found botulinum toxin treatment ineffective in tension-type headaches [22]. A close scrutiny of these studies, however, demonstrates that the doses and number of injections in these studies was less than that of PREEPT investigation that had proved efficacy of Botox in management of chronic migraine. The most recent report from the Guideline Development Subcommittee of AAN defines botulinum toxin therapy in TTH as "probably ineffective." [19]

Secondary Headaches

The efficacy of botulinum toxin treatment has been rarely studied in patients with secondary headaches. Approximately 20% of patients suffer from recurrent headaches after head trauma. Although no controlled and blinded studies have been reported on the efficacy of botulinum toxin treatment in patients with post-traumatic headaches, some preliminary, open label (unblinded) observations suggest that Botox may help some of these patients. Yerry and co-workers [23], evaluated the results of Botox injection into the pericranial (around the head) muscles in 64 war veterans with head injury. Most patients had blast injury and 63 of them were male. Botox was injected according to the PREEMPT protocol for chronic migraine. Forty one patients (64%), reported improvement of their headaches.

Economic Issues

Several recent studies have shown that Botox treatment of chronic migraine (despite high cost of Botox) is economically sound and advantageous to the patients. In a recent study of 230 patients with chronic migraine [24], treatment with Botox over the six- month period resulted in 55% and 57% reduction in emergency department visits and hospitalizations, respectively. The investigators reported a cost reduction (saving) of $1219 per patient over the six- month period of Botox treatment. More recently, Hepp and co-workers [25], have assessed headache-related health care utilization at 6, 9 and 12 months in a group of chronic migraine patients treated with Botox and compared it with another group treated with oral migraine prophylactic medications (OMPM). Using a regression analysis method (a form of statistical method), they found that the group that received Botox had 20%, 21%,19% less emergency department visits over 6, 9 and 12 months and also 47%, 48%, 56% less hospitalizations compared to the OMPM group, respectively.

Conclusion

In 2010, after approval of Botox in Europe, Canada and US, a new era was reached in the medical management of chronic migraine. In many patients, Botox treatment eliminated the need for additional daily oral medications or led to the reduction of existing medications. Long-term follow up of patients with chronic migraine has shown that efficacy of Botox continues over years of treatment and actually improves after the second and third injection sessions. Comparative studies have demonstrated that Botox has less side effects compared to major preventive medications for migraine and fewer patients discontinue Botox treatment compared to those who take oral preventive medications. One treatment session every 3–4 months versus taking daily oral medications is another advantage of Botox therapy for management of chronic migraine. Over the long run, despite its expense, treatment of chronic migraine with Botox has proven economically feasible due the reduction of expensive emergency department visits and hospitalizations. To date, all high quality studies (Class I and II) of botulinum toxin therapy in chronic migraine have been conducted with Botox. Additional studies are needed to assess the efficacy of other types of botulinum toxin A (for example Xeomin or Dysport) and the botulinum toxin B (Myobloc) in management of chronic migraine.

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