We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS

BOOK CITATION INDEX

INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Botulinum Toxin for the Treatment of Chronic Migraines

Alberto Jaime Kalach-Mussali and
Daniel Mondlak Algazi

Additional information is available at the end of the chapter

Abstract

Migraines are the third most common disease in the world, with an estimated global prevalence of 14.7%. Migraine has a characteristic throbbing quality, of moderate to severe intensity, generally unilateral, and has associated symptoms including photophobia, phonophobia, and gastrointestinal distress. Episodic migraine occurs less than 15 days per month, while chronic migraines occur more or equal to 15 days per month. Treatment of migraine consists of abortive and preventive therapy. Acetaminophen, aspirin, and NSAIDs are often used for management of mild attacks. For more severe attacks, triptans are recommended. Intravenous administration of some combination of dopamine receptor agonists, dihydroergotamine, and intravenous NSAIDs is recommended for severe episodes. Preventive daily treatment of migraine is recommended when migraine episodes exceed 6–8 days per month, or what is tolerable to the patient. Beta-blockers, topiramate, amitriptyline, and divalproex sodium are commonly used for migraine prevention. Initial anecdotal reports in patients receiving botulinum toxin for facial cosmetic purposes noted the effects of these injections on headache and trigger point-initiated pain syndromes, which appeared to be independent of its effects upon muscle tone. Current thinking is that migraine pain results from activation of intracranial meningeal perivascular afferents with some studies suggesting the role of extracranial afferents.

Keywords: botulinum toxin, chronic migraine, headache

1. Introduction

Headache is the most common nervous system disorder. Migraine headache is one of the most debilitating forms of headache [1]. Together with anemia and hearing loss, the World

Health Organization, migraine is one of the three most prevalent conditions but states that their affects are not dramatic, is overlooked and underestimated [2]. It affects 2–15% of the world's population for a total of 324.1 million migraine sufferers, not of episodes, with women affected three times as often as men and affects mostly socially active and productive people ranging from 25 to 55 years of age [3, 4]. The World Health Organization ranks migraine headache as the nineteenth most disabling disease and characterizes severe migraine to be as disabling as quadriplegia, psychosis, and dementia [1, 2, 5, 6]. Traditional theories regarding its cause attribute it to a vascular or central nervous phenomenon. Migraine is a primary headache, classified by the International Headache disorder in which the headache is by itself the illness. Migraine is characterized by severe headaches and is often associated with nausea, vomiting, and heightened sensitivity to sound and light at the peak of the attack. Many migraneurs even when they have consulted a physician are not satisfied with their therapy and report that typically prescribed medications are not always optimal. Currently, triptan medications are the most effective therapy for acute migraine attacks, reducing pain and associated symptoms in only up to two-thirds of patients. There is a significant need to develop more effective therapies for migraine prevention because up to 35% of affected persons suffers from 2 to 3 severe attacks per month and 25% suffers more than 4 attacks per month [7].

Patients eligible to be considered for prophylactic migraine treatment include frequent headaches, recurring disabling migraines that significantly interfere with daily routine, excessive cost of acute and preventive treatments, failure, contraindication overuse or adverse events with acute migraine therapy, patient preference, and presence of uncommon migraine conditions including hemiplegic migraine, basilar migraine, migraine with prolonged aura, or migrainous infarction [8].

Commonly used treatments for migraine prophylaxis include β-adrenergic blockers, calcium channel blockers, tricyclic antidepressants, and anticonvulsants, most of them with moderate to severe adverse effects. Botulinum toxin type A has been under use for the treatment of migraine and other types of headache. Botulinum toxin type A has been used to treat a variety of disorders including involuntary muscle contraction, blepharospasm, strabismus, cervical dystonia, and for cosmetic purposes [9]. Specifically for the treatment of dystonia and spasticity, botulinum toxin type A has shown an analgesic effect, leading to further investigation for other painful conditions such as migraine and tension-type headache.

Botulinum toxin type A has been used off-label since 2000 for the treatment of migraine headache [10]. Since then, multiple small trials report the effectiveness of botulinum toxin type A for migraine headache prevention. However, the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) 1 and 2 trials that class 1A evidence was concluded that botulinum toxin type A treatment reduces chronic migraine headache impact and improves headache-related quality of life [11–13]. After these evidence-based data were published, the Food and Drug Administration in the United States approved botulinum toxin type A for the treatment of chronic migraine headache on October 15, 2010.

Botulinum toxin has been investigated for the treatment of several headache disorders. The beneficial effect of botulinum toxin type A treatment for migraine was first noted in patients who were given the protein for cosmetic purposes treating facial rhytides and reported relief

from their migraine headaches [14, 15]. The pooled result of these studies showed that botulinum toxin type A was significantly superior to placebo in reducing headache days and multiple quality-of-life measures [16, 17].

2. Migraine

Cephalalgia has affected human beings since the beginning of time, being the earliest description among Sumerian poems circa 3000 BC, which described an individual as being "sick-headed." The first reports of a patient describing alteration in visual perceptions, or aura, came from Hippocrates. During the second century AD, Aretaeus of Cappadocia delineated the symptom structure of what is commonly referred to as migraine with aura. More recently, scientific theories to explain the pathophysiology of migraine headaches have emerged. After the introduction of the neural theory, proposing that certain disturbances within the autonomic nervous system may account for the triggering and sustenance of the headache. Dey subsequently described the phenomenon of cyclical pituitary compression of the trigeminal nerve. In the modern era, Wolff described a phenomenon of episodic extracranial vascular dilatation and constriction, leading to the formulation of the vasogenic theory of migraine.

Worldwide prevalence of migraine is estimated to be 13–17% in women and 8–14% in men. The effect of migraine on quality of life is profound. Nearly all migraineurs experience functional impairment because of their condition; more than half being severe requiring bed rest. Most migraine patients do not seek medical attention, instead relying on over-the-counter medications, because they believe that effective prescribed treatments do not exist [19].

Migraine was classified originally as classic or common. In 1988, the International Headache Society published guidelines for discriminating among 13 major types of headache because of inconsistency of headache definitions and the resulting difficulty in epidemiologic and pathophysiologic study; classic migraine became "migraine with aura," and common migraine became "migraine without aura." Migraine can be episodic or chronic but has unique combinations of neurologic, gastrointestinal, and autonomic symptoms that differentiate it from other headache conditions [19]. In the International Classification for Headache Disorders created in 1988 (ICHD-1), major headache types were categorized and distinguished primary and secondary headache disorders. Revised in 2003, the ICHD-2 defined a primary headache disorder as one for which no identifiable structural or organic cause is known. A secondary headache disorder required a known structural or systemic etiology as the cause of the headache symptom. Examples of these include intracranial bleeding, thrombosis of cerebral veins, infections (e.g., meningitis or encephalitis), tumors, dissection of cerebral arteries, and arteritis.

Migraine, tension-type headache, and trigemino-autonomic headache are the most common primary headaches. Clinical presentation, medical history, clinical, and technical examination allow us to distinguish the distinct types of headache disorders. Headache in migraine

commonly has pulsating or throbbing character and is unilateral. Attacks last 4–72 h, and usually in the moderate to severe presentations are accompanied by photophobia, phono-phobia, or osmophobia, and nausea or vomiting. Typically, physical activity worsens pain. Chronic migraine is defined in the ICHD-2 as migraine headache at least 15 days per month for 3 months, with attack duration lasting more than 4 h. Whereas episodic migraine only lasts less than 15 headache days per month according to the most recent revision by the International Chronic Headache diagnostic criteria in 2014. Other forms of chronic daily headache include chronic tension type headache, hemicrania continua, new daily persistent headache, and chronic cluster headache.

The spectrum of migraine headaches has been coded by the International Headache Society in its last revision (ICHD-III-β-2014) accepted seven subtypes, with notable subforms (**Table 1**). Migraine can be classified into two major subtypes, namely with or without aura. Migraine without aura is the most prevalent subtype and may involve a higher frequency of attacks and greater disability than migraine with aura.

Migraine is a paroxysmal headache disorder, with periods of relative quiescence between acute headache episodes. Headaches typically manifest with moderate to severe throbbing head pain lasting hours to days, in a hemicranial and frontotemporal distribution; however, bilateral and posterior cervical pain can occur. Associated symptoms may include nausea, vomiting, anorexia, malaise, photo- or phonophobia, and blurred vision. Transient neuro-sensory perceptions prior to or concomitant with the pain phase occur in migraine with aura.

Diagnostic criteria for migraine without aura include at least five attacks, lasting 4–72 h, with at least two of the following characteristics: unilateral location, pulsating quality, moder-ate or severe intensity, aggravation by or cause avoiding of routine activity. Also nausea or vomiting or both during the headache of photophobia or phonophobia, in general, cannot be attributed to any other disorder.

Approximately 30% of migraineurs experience auras; for migraine with typical aura, criteria include at least two attacks including an aura consisting in the presentation of fully reversible visual symptoms including positive features (e.g. flickering lights, spots or lines) or negative features (loss of vision) or fully reversible sensory symptoms including positive features (e.g. pins and needles) or negative features (numbness), or fully reversible dysphasic disturbance. Migraneurs also develop at least, two of the following: homonymous visual symptoms or uni-lateral sensory symptoms, at least one aura symptom developing gradually over greater than 5 minutes or different aura symptoms occurring in succession over greater than 5 minutes, and each symptom lasting greater than 5 minutes and less than 60 minutes. The headache ful-filling criteria for migraine without aura begins during the aura or following the aura within 60 minutes must be considered a migraine with typical aura, and as the other classification, it cannot be attributed to any other disorder [20].

2.1. Pathophysiology of migraine

The pathophysiology of migraine is complex and is still a focus of research. Contrary to the previous vascular theory of migraine, which held that migraine resulted from constriction

1.1. Migraine without aura

1.2. Migraine with aura

   1.2.1. Typical aura with migraine headache

      1.2.1.1. Typical aura with headache

      1.2.1.2. Typical aura without headache

   1.2.2. Migraine with brainstem aura

   1.2.3. Hemiplegic migraine

      1.2.3.1. Familial hemiplegic migraine

         1.2.3.1.1. Familial hemiplegic migraine type 1

         1.2.3.1.2. Familial hemiplegic migraine type 2

         1.2.3.1.3. Familial hemiplegic migraine type 3

         1.2.3.1.4. Familial hemiplegic migraine, other loci

      1.2.3.2. Sporadic hemiplegic migraine

   1.2.4. Retinal migraine

1.3. Child. Chronic migraine

1.4. Complications of migraine

   1.4.1. Status migrainosus

   1.4.2. Persistent aura without infarction

   1.4.3. Migrainous infarction

   1.4.4. Migraine aura-triggered seizure

1.5. Probable migraine

   1.5.1. Probable migraine without aura

   1.5.2. Probable migraine with aura

1.6. Episodic syndromes that may be associated with migraine

   1.6.1. Recurrent gastrointestinal disturbance

      1.6.1.1. Cyclical vomiting syndrome

      1.6.1.2. Abdominal migraine

   1.6.2. Benign paroxysmal vertigo

   1.6.3. Benign paroxysmal torticollis

Adapted from the International Classification of Headache Disorders-III-β-2014, International Headache Society, 2014.

Table 1. Classification of migraine headache disorders.

and dilation of blood vessels innervating the head, migraine is now recognized as result-ing fundamentally from a hypersensitive central nervous system that has difficulty properly modulating pain. In the current neurovascular model, the vascular changes that occur are

recognized as secondary phenomena. The primary components involve interactions among the brainstem, the cortex, and the trigeminovascular system. The brainstem is involved in descending modulation of pain, neuronal inhibition that traverses the cortex is the recognized cause of migraine aura, and resulting sensitization and activation of trigeminal afferents are the source of pain. Culminating from this sequence is a release of neuropeptides, dilation of meningeal blood vessels, neurogenic inflammation, and both within attacks and over time central sensitization manifests. Intracranial blood vessels and meninges are pain sensitive. Sterile neurogenic inflammation may evoke migraine pain.

Neurogenic inflammation includes vasodilation, plasma protein extravasation, mast cell activation, and release of proinflammatory mediators. The activation of meningeal nociceptors releases various neuropeptides, including calcitonin gene-related peptide (CGRP) and substance P from trigeminocervical nerve endings. CGRP is a potent dilator of cerebral and dural vessels and has found to be elevated in migraine attacks. Substance P is involved in plasma extravasation in the dura mater during primary headache attacks, and neurokinin receptor antagonists can inhibit neurogenic dural inflammation but have not been found to have effect in acute migraine attacks. In contrast, a clinical trial with CGRP receptor antagonist was successful in treating acute migraine attacks [21]. Also, a sensitization of peripheral and central trigeminovascular neurons seems to take place in migraine.

Sensitization of the peripheral trigeminovascular neurons could mediate the throbbing, and sensitization of the central trigeminovascular neurons that propel cutaneous allodynia often observed during migraine attacks. The pathophysiology influences a cascade of interacting events within the nervous system resulting in headache [22, 23].

Another potential mechanism involves the synaptic vesicle glycoprotein 2A protein (SV2A), a synaptic vesicle protein isoform with high affinity for botulinum toxin type A that is involved in the binding and subsequent internalization of the toxin into peripheral neurons. Botulinum toxin interacts with peripheral nociceptive neurons and inhibits release of nociceptive mediators from peripheral nociceptors such as glutamate, substance P, and calcitonin gene-related peptide.

Migraine runs in families and has a strong genetic component, and the best example is familial hemiplegic migraine, an autosomal-dominant subtype of migraine with aura that includes motor weakness. Three genetic mutations corresponding to three variants of familial hemiplegic migraine have been identified of which genes code for the ion-channel transport: *CACNA1A* on chromosome 19, *SCN1A* on chromosome 2, and the *ATP1A2* gene on chromosome 1. However, contributors to other more common forms of migraine have not been firmly established [23].

2.2. Treatment of migraine

Typically, medications for acute attacks include simple analgesics or NSAIDs for mild to moderate attacks as abortive treatments. For moderate to severe attacks, ergot derivatives were originally prescribed but now are replaced by triptans, with a greater receptor specificity

and greater effectiveness for more severe attacks. Opioids are reserved for rescue therapy when other medications are contraindicated. Acute medications have limited efficacy and are only useful for short-term symptom relief, and some of them result also in adverse side effects; further, they do not offer prophylactic benefits and have diminished effectiveness if taken over long periods of time. Long-term prevention is the preferred treatment approach to migraine.

The primary goal of migraine prophylactic treatment is improving quality of life through decreased frequency and intensity of headache, improved function and decreased disability, and reduced use of medications with improved efficacy of acute therapy. Although some of the proposed etiologic factors are out of the patient's control, such as heredity [24] and cyclical hormone changes in females [25], others are amenable to lifestyle changes. Examples of such include stress, smoking, intake of certain foods such as meats and cheeses (high nitrites), nuts, chocolate, caffeine withdrawal and alcohol consumption, lack of exercise, sleep pattern, quality and duration, and, in females, menstruation, oral contraception, and estrogen replacement therapy. Some medications also have hypothesized to initiate or increase the frequency of migraine attacks, such as nitroglycerin, some calcium channel blockers, tetracycline, and sildenafil citrate.

Preventive therapy should be offered to patients with migraine reported six or more days per month, with four or more days of headache with some impairment or three or more days with headache with severe impairment requiring bed rest. Situations in which should be considered include patients with 4–5 migraine days per month, with 3 days with some impairment or 2 days with severe impairment [4]. Currently, anticonvulsants, antidepressants, beta-blockers, calcium channel antagonists, conventional or selective nonsteroidal anti-inflammatory drugs, and serotonin antagonists have been used as prophylactic treatments for migraine. Unpleasant side effects can occur with each of these types of drugs. They include drowsiness, fatigue, dizziness, sexual dysfunction, weight gain or loss, constipation, nausea, dry mouth, and insomnia. None of the abovementioned drugs have been approved by the US Food and Drug Administration or labeled as such for use in headache treatment or prevention [26].

There exists a great demand for long-acting acute and prophylactic therapies that are effective, well tolerated, and devoid of significant systemic toxicities or adverse effects. The interest in the use of botulinum toxin type A as an alternative therapy has gained popularity.

3. Botulinum toxin and chronic migraine

There are seven botulinum toxin serotypes (A, B, C1, D, E, F, and G) with an eighth serotype (H) described by some authors as a hybrid of known serotypes F and A [27]. All serotypes inhibit acetylcholine release, although their intracellular target proteins, physiochemical characteristics, and potencies are different. Botulinum toxin type A has been the most widely used and studied for therapeutic purposes.

Botulinum toxin binds to the motor and sympathetic nerve terminals. It enters the nerve terminals and inhibits the release of acetylcholine. This inhibition occurs as the botulinum neurotoxin cleaves one of several proteins integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. This results in blocking neuro-muscular transmission at the neuromuscular junction. After direct intramuscular injection, botulinum toxin produces partial chemical denervation and paralysis of the muscle, resulting in a decrease of muscle activity [28].

The precise mechanism by which botulinum toxin type A alleviates headache pain is unclear, but the inhibition of release of glutamate and other neuropeptides suggests that its antino-ciceptive properties are distinct from its neuromuscular activity. A peripheral trigger point theory emerged when Binder first noticed the positive effect of onabotulinumtoxin-A while conducting clinical trials for frontal lines and noticing that frontal migraine symptoms improved with either corrugator supercilii muscle paralysis by botulinum toxin type A injection or corrugator muscle resection for the treatment of hyperfunctional facial lines [18, 29–30]. Nonsurgical treatment of migraines includes avoidance of triggers, such as alcohol and caffeine, and pharmacologic control with medications [31]. Current data suggest that botulinum toxin type A modifies the sensory feedback loop to the central nervous system by clocking intrafusal fibers, resulting in decreased activation of muscle spindles. This effectively alters the sensory afferent system by reducing the traffic along IA spindle afferent fibers [32]. Botulinum toxin type A also appears to inhibit the release of glutamate and calcitonin gene-related peptide from primary nociceptive fibers, reduce the firing of wide-dynamic range neurons within the dorsal horn of the spinal cord, and reduce the activity of central nocicep-tive neurons, as demonstrated by decreased expression of immediate early genes (c-Fos) after nociceptor stimulation [28]. A reduction in afferent sensory activity coming from pericranial and cervical muscles and inhibition of peripheral and central trigeminal sensitization may be the potential mechanisms by which botulinum toxin type A exerts its therapeutic effect in migraine, tension-type headache, and other primary headache disorders [33].

Jakubowski explored neurologic markers that might distinguish migraine patients who would benefit from botulinum toxin treatment from those who would not. The prevalence of neck tenderness, aura, photophobia, phonophobia, osmophobia, nausea, and throbbing was simi-lar between responders and nonresponders. However, during clinical investigation of pain semiology, 92% of nonresponders describes a build-up of pressure inside their head or an exploding headache. Among responders, 74% described their head to be crushed, clamped, or stubbed by external forces, what we understand as imploding headache, and 13% perceived an eye-popping pain (ocular headache). Exploding headaches could explain the pain media-tion by intracranial innervation; thus, we infer that extracranial botulinum toxin application will not correspond to a responsive individual. Imploding and ocular headaches respond to botulinum neurotoxin application, suggesting that the migraine pain involves extracranial innervation as well [34].

The physiologic mechanism of migraine treatment suggested by Guyuron is the decompres-sion of peripheral nerves, decreasing peripheral nerve inflammation and excitability, leading to newer treatment techniques such as migraine surgery. Botulinum toxin exerts its mecha-nism chemically, whereas surgery releases such anatomical entrapments mechanically [15].

4. Patient evaluation

A correct diagnosis of patients presenting with chronic headache requires a systematic approach to obtain the necessary information. This may be difficult because of the anxiety, feeling of helplessness, and other mood disorders that obscure migraine symptoms. A careful interview and documentation of headache history and examination can aid in reaching a precise diagnosis and classification.

During the interview, some descriptors will guide in precise identification, such as progression of headache through present time, age of onset, frequency and duration of the attacks, severity of headache episodes, quality of the pain, presence or absence of aura, inciting factors, mitigating factors, systemic reactions, craniofacial disorders, systemic illnesses, medication history, family history of headache, and social history.

Although the patient only complains primarily of cranial discomfort, a complete physical examination is warranted on the initial visit. Cardiovascular, ophthalmologic, or neuromuscular symptoms could be missed; ear, nose, throat, scalp, and neck should be thoroughly examined. Specific aspects of the physical examination that should be systematically examined include: vital signs and affect, cardiopulmonary evaluation, auscultation of the carotid, vertebral arteries, cranium and orbits for bruits, range of motion, tenderness, crepitus of the neck, and jaw/temporomandibular joint. The head, neck, and back should be palpated for trigger points, masses, bruises, or thickened or tender blood vessels. Neurological examination should rule out papilledema and focal signs, such as visual field deficits, pupillary asymmetry, sensory deficits of the face, trunk, or extremities; asymmetric gait or motor weakness.

Ancillary tests may provide additional clinical information. Neuroimaging in the form of computed tomography (CT) or magnetic resonance imaging (MRI) has become an invaluable resource for physical diagnosis. Lumbar puncture may be indicated during a severe headache to detect subarachnoid hemorrhage or meningitis, and can be diagnostic of meningeal carcinomatosis or lymphomatosis, and to detect high or low cerebrospinal fluid pressure. Electroencephalography (EEG) has been used to screen for structural cerebral abnormalities via the detection of altered electrophysiological patterns, but the American Academy in Neurology failed to find in 1995 sufficient evidence supporting the utility of EEG in the routine evaluation of headache. If clinical evidence suggests the possibility of organic brain pathology, only CT and MRI are suggested [20].

5. Safety, indications, and contraindications

According to the Food and Drug Administration in the United States, botulinum toxin type A is indicated for the prophylaxis of headaches in adult patients with chronic migraine. Safety and effectiveness have not been established for the prophylaxis of episodic migraines.

Adverse effects are most commonly related to the injection, with systemic adverse effects being very rare. Injection-related adverse effects are mild and transient and rarely lead to discontinuation of therapy.

Serious and/or immediate hypersensitivity reactions have occurred, including anaphylaxis, serum sickness, urticarial, soft tissue edema, and dyspnea.

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junction disorders (e.g. myasthenia gravis or Lambert-Eaton syndrome) should be monitored closely and have an increased risk of clinically significant dysphagia and respiratory compromise.

Botulinum toxin type A contains albumin, which based on effective donor screening and manufacturing processes carries an extremely remote risk of transmission of viral diseases or Creutzfeldt-Jakob disease.

Specifically, for chronic migraine, it has been shown in double-blind, placebo-controlled efficacy trials, which the discontinuation rate was 12% in the Botox®-treated group and 10% in the placebo-treated group. Discontinuations due to an adverse event were 4% in the Botox® group and 1% in the placebo group. The most frequent adverse events leading to discontinuation were neck pain, headache, worsening migraine, muscular weakness, and eyelid ptosis.

The most common reported adverse reactions following injection of Botox® for chronic migraine include neck pain (9%), headache (5%), migraine (4%), eyelid ptosis (4%), musculoskeletal stiffness (4%), muscular weakness (4%), bronchitis (3%), myalgia (3%), musculoskeletal pain (3%), injection site pain (3%), facial paresis (2%), muscle spasms (2%), and hypertension (2%). Other adverse reactions that occurred more frequently in the Botox® group compared to the placebo group at a frequency less than 1% include vertigo, dry eye, eyelid edema, dysphagia, eye infection, and jaw pain.

Safety and effectiveness in patients younger than 18 years have not been established. Clinical studies also did not include sufficient subjects older than 65 years to determine whether the response to treatment is different from younger patients.

## 6. Dosage and administration

Indication specific dosage and administration recommendations should be followed. In treating adult patients for one or more indications different than migraine, the maximum cumulative dose should generally not exceed 360 Units, in a 3-month interval.

Onabotulinumtoxin-A vacuum-dried vials should be reconstituted prior to injection with sterile, non-preserved 0.9% Sodium Chloride Injection USP. For chronic migraines, the recommended dilution is 200 Units/4 mL or 100 Units/2 mL, with a final concentration of 5 Units/0.1 mL. The recommended dose for treating chronic migraine is 155 Units administered intramuscularly rather than intradermal, avoiding the periosteum, eyelid region, and visible superficial blood vessels while using a sterile 30-gauge, 0.5-inch needle as 0.1 mL (5 Units) injections per each site for a total of 31 injection sites in the head and neck, divided across seven specific head/neck muscle areas. A 1-inch needle may be needed in the neck region for patients with thick neck muscles; the use of needles longer than 1-inch increases the risk of

complications such as pneumothorax, vascular injury, and spinal cord damage. Even though the FDA approved dosage is 155 Units distributed in 31 sites as in the PREEMPT trials, the total dose has ranged from 25 to 300 Units over several injection sites.

With the exception of the procerus muscle, which should be injected at one site (midline), all muscles should be injected bilaterally with half the number of injection sites administered to the left and half to the right side of the head and neck; even if the patient has strictly unilateral headaches. The recommended re-treatment schedule is every 12 weeks. **Figure 1** shows the recommended injection sites for chronic migraine.
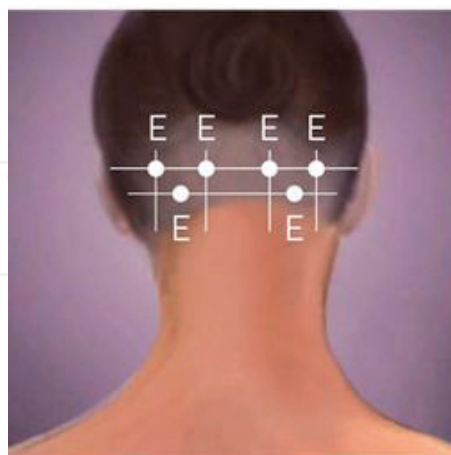
Botox dosing by muscle for chronic migraine is as follows: (1) frontalis muscle—20 Units divided in four sites distributed bilaterally; (2) corrugator muscles—10 Units divided in two
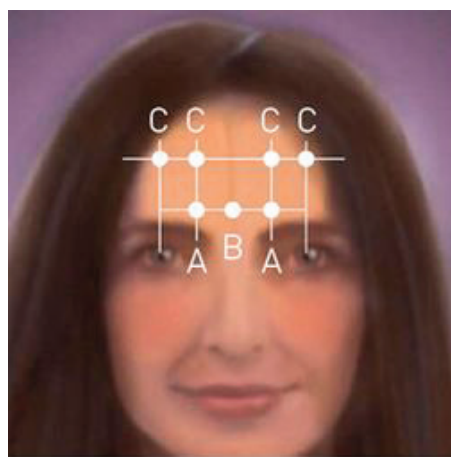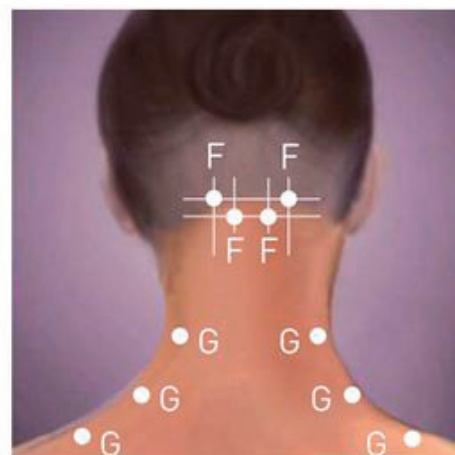

A. Corrugator: 5 Units each side
B. Procerus: 5 Units (1 site)
C. Frontalis: 10 Units each side
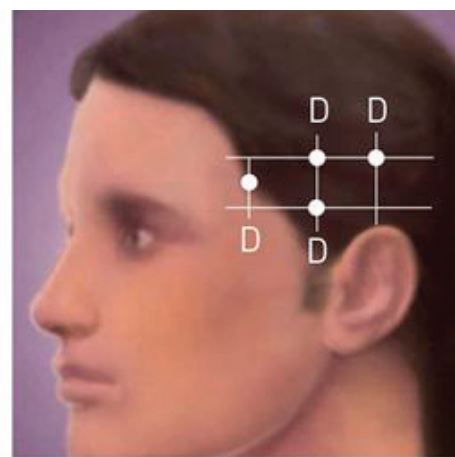
D. Temporalis: 20 Units each side

E. Occipitalis: 15 Units each side

F. Cervical paraspinal: 10 Units each side
G. Trapezius: 15 Units each side

Figure 1. Injection sites.

sites distributed bilaterally; (3) procerus muscle—5 Units in one site; (4) occipitalis muscle—30 Units divided in six sites distributed bilaterally; (5) temporalis muscles—40 Units divided in eight sites distributed bilaterally; (6) trapezius muscles—30 Units divided in six sites distributed bilaterally; and (7) cervical paraspinal muscle group—20 Units divided in four sites distributed bilaterally.

The target of these injections is superficial to the peripheral sensory nerves, namely the trigeminal nerve branches, the occipital nerves, and the cervical sensory rami from C3 to C5, rather than the muscles themselves.

Upper cervical-occipital muscles, especially the splenius capitis and splenius cervicis, may trigger migraine. Frequently, these muscles also contribute to pain and headache by irritating the adjacent greater occipital nerve and causing the concomitant neuralgic symptomatology. Thoracic paraspinal and periscapular muscles are frequently symptomatic and can also trigger headache. Unwanted weakness of the supraspinatus and infraspinatus muscles, which form part of the rotator cuff, allows the humeral head to rise, while injected trapezius and levator scapulae may cause the acromion to sag inferiorly and anteriorly. This can result in painful shoulder impingement 8–10 days after injections.

Onabotulinumtoxin type A reaches its clinical effect at 7–10 days and plateaus at 3 weeks. The neuromuscular blocking action of BTX-A lasts 3–4 months; however, the reduction of pain can last substantially longer, and an effect more specific for migraine may continue to develop beyond 2–3 months after the injection session [35].

A combination of a fixed-dose/fixed-site injection plan and a follow-the-pain method is appropriate. Following this premise, Guyuron has identified trigger points and has proposed another method of peripheral nerve decompression, through surgical release of mechanical entrapment, reducing effectively migraine severity and frequency with surgical deactivation of peripheral trigger points. Even though other trigger point identification methods have been described, botulinum toxin type A injections can serve as a prognosticator of migraine surgery success because of its significant positive association with surgical outcomes [36–38].

Follow-the-pain injection sites are identified by history and examination of the cervical-shoulder girdle and temporomandibular musculature being most useful for patients with tension-type headaches. These sites include the frontalis, temporalis, occipitalis, trapezius, splenius capitis, suboccipital, and cervical paraspinal muscles. Guyuron has identified four major and several minor trigger sites, and botulinum toxin type A injections for trigger site identification and migraine surgery planning are administered at one trigger site per visit based on the constellation of symptoms. The frontal trigger site (Site I) involves the supraorbital and supratrochlear nerves. In the temporal trigger site (Site II), the zygomaticotemporal branch of the trigeminal nerve is compressed by the temporalis muscle and the tight deep temporal fascia. In the rhinogenic trigger site (Site III), contact points among the septum, turbinates, and concha bullosa or sinus inflammation can irritate the trigeminal nerve, obviously when the symptoms suggest Site III as the main trigger, this site should not be injected. In the greater and/or third occipital nerves (Site IV), the semispinalis capitis muscle, fascial bands, and occipital artery could irritate the nerves triggering migraines. The minor triggers consist of the auriculotemporal nerve (Site V) and the lesser occipital nerve (Site VI) [39].

When only a follow-the-pain approach is used in patients with migraine or migrainous headache, there is a risk for a poor cosmetic outcome and/or shifting of the headaches to the previously unaffected side. Even in these cases, cosmetic effects in the frontal region need to be obtained, which also assure good compliance with continued treatment; but asymmetric injections can be given in the temporalis, occipitalis, splenius capitus, cervical, and subcervical paraspinal muscles. The doses injected in the cervical-shoulder girdle muscles are low to prevent any possible weakness that could cause headache. Patients need to be carefully assessed for associated cervical dystonia, which requires injection of the dystonic muscles. Current available data do not appear to indicate a dose-response benefit from BTX-A injection therapy.

For patients with migraine or migrainous headache features identified by history, treatment with a fixed-site approach may be required for successful results.

Therefore, further randomized, placebo-controlled clinical trials are needed to identify the optimal dosing regimen and injection sites. However, some studies have reported greater efficacy with repeated dosing [8, 14].

Migraine improvement can be monitored with the use of a diary or another self-reporting method. Progress is indicated by reduction of oral prophylactic medications, improved response from abortive therapies, as well as reduced frequency, intensity, and severity of migraine headache symptoms. Nonpharmacologic headache therapies, such as biofeedback, cognitive-behavioral pain management strategies, and relaxation therapies, which were previously ineffective, may prove more successful after BTX chemodenervation and should be reconsidered as adjuncts to treatment [35].

Currently, only Botox® has been approved by the FDA for the treatment of chronic migraines, but in studies of botulinum toxin type A, Dysport® has shown efficacy when administered for tension-type headache using a dosage of 200–500 Units per application.

After injection, patients should be informed that (1) from time to injection to symptomatic benefit is between 3 and 14 days, peaking at 3 weeks, (2) duration of benefit is 12–16 weeks, (3) maximum effect may take several treatments, (4) duration of reduction in headache symptoms may not be synchronous with the return of muscle function, and (5) postinjection site blebs in the forehead region will disappear within a few hours and will reduce the hyperfunctional lines of the face in 3–5 days.

Patients should be instructed on keeping headache diaries, which document the frequency and location of headache, severity, and medications used over a 4-month period. The Migraine Disability Assessment (MIDAS) can be used as a measure of treatment success. Objective measurements of treatment effectiveness are important, so that clinical response can be evaluated and future treatment sessions can be modified as necessary [30].

7. Efficacy

Guidelines indicate that quality clinical trials in patients with migraine should always be double-blind, randomized, placebo-controlled trials [40]. Clinical evidence supporting the

use of botulinum toxin injections is mixed. Binder demonstrated that 51% of migraineurs reported complete response, and an additional 38% reported partial responses for a mean of 4.1 and 2.7 months, respectively [30]. Data from the double-blind phase of studies demonstrate significant improvement with onabotulinumtoxin A versus placebo observed over 24 weeks of treatment, demonstrating that the benefits persist over 56 weeks of treatment using measures of headache impact (HIT-6) and quality of life questionnaires (HRQoL). Patients who switched from placebo to onabotulinumtoxin A at 24 weeks experienced significant improvements from baseline at a rate of change not different than observed among patients that received onabotulinumtoxin A from the start of the double-blind period. This indicates that efficacy persists even if the treatment is delayed.

All patients improved, as indicated by a change from baseline in the frequency of moderate to severe migraines. Botulinum toxin type A is a safe treatment that significantly reduces migraine frequency and severity. It is still discussed to what extent the way of application of botulinum toxin may influence its efficacy, and in most studies, the fixed-site approach has been employed. This creates a systematical approach injecting the same predetermined sites with predetermined doses. For the follow-the-pain method, the authors conducting trials have been acknowledged that their results do not confirm efficacy but may be useful for chronic migraines [11].

Silberstein published the first placebo-controlled, double-blind study in migraine patients with 123 patients who were randomized into three groups and treated with placebo, 25, or 75 Units of Botox®. The treatment with 25 Units was superior to placebo in reducing the frequency of the attacks but no different than the 75 U group [8].

Multiple studies have shown a tendency to reduce headache days in distinct period of time but have failed to reach criteria for statistical significance [34, 41–43].

Dodick has found a statistically significant difference in an analysis of 228 patients without prophylactic medication [12]. The breakthrough of onabotulinumtoxin-A in the treatment of chronic migraine came in 2010, when Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) study group published the results of the PREEMPT I and PREEMPT II trials, totaling 1384 patients who were included in a 28-day baseline screening period, a 24-week double-blind, parallel-group, placebo-controlled phase, and a 32-week open-label phase. Both studies completed three injection trials, with the same study design but different endpoint conclusions.

In the PREEMPT I trial, significant differences were found in the reduction of headache and migraine days but missed the amount of migraine episodes. The PREEMPT II confirmed the efficacy in the reduction of headache days [12, 16]. The positive results of the two PREEMPT trials led to approval of onabotulinumtoxin-A in September 2011 by the US FDA and many other registration authorities worldwide.

Medication overuse is a major problem in chronic migraine patients, and the PREEMPT pooled data show effectiveness in a reduction in headache days and a reduction in medication overuse. Beside reduction in headache frequency and severity, botulinum toxin also improves quality of life [3, 4]. In a more recent study [44], it was demonstrated that monthly headache

days, migraine days, days with nausea/vomiting, and days with intake of pain medications were significantly reduced after the first treatment, maintaining such effect throughout the entire study period. Also health-related and migraine-related quality of life improved after the treatment. Patients also had a decrease in depression symptoms, theoretically mediated by improving quality of life.

In all the mentioned studies, approximately a 10% of patients did not respond to treatment with botulinum toxin. The development of antibodies, intrinsic worsening of migraine, and an initial placebo effect have also been discussed as causes of resistance to treatment [45].

8. Conclusions

Migraine is a major cause of disability worldwide. Chronic migraine can reduce quality of life and is one of the most prevalent conditions. Physicians treat day-to-day and must precisely diagnose and effectively treat headache disorders. An adequate examination will guide to a specific disorder, so the indicated therapeutic plan can be started to assure patient satisfaction. Acute medications have shown variable efficacy, and patients commonly seek preventive therapy to avoid the inconvenient impairment chronic migraines that can cause. Botulinum neurotoxin, even if not fully comprehended in its precise pathophysiology for the treatment of pain, has provided relief from headache pain, reducing severity, frequency, and duration of episodes and improving quality of life. Currently, the FDA has approved only a fixed-point technique; together with the follow-the-pain injection, technique can relief migraine for 12 weeks or more. Further studies have to be conducted to demonstrate the mechanism of action pathways and to perfect the administration, but currently, botulinum toxin is a safe, effective, and with minimal adverse effects to be considered in migraine therapy.

Author details

Alberto Jaime Kalach-Mussali* and Daniel Mondlak Algazi

*Address all correspondence to: albertokalach@gmail.com

Hospital Ángeles Lomas, Mexico City, Mexico

References

[1] Menken M, Munsat TL, Toole JF. The global burden of disease study: Implications for neurology. Archives of Neurology. 2000;**57**:418-420. DOI: 10.1001/archneur.57.3.418

[2] World Health Organization. The Global Burden of Disease. Geneva: World Health Organization; 2004. Available from: http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf [Accessed: 2018-05-10]

[3]   Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M, et al. Headache. 2001;**41**: 646-657. DOI: 10.1046/j.1526-4610.2001.041007646.x

[4]   Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;**68**:343-349. DOI: 10.1212/01.wnl.0000252808. 97649.21

[5]   World Health Organization. World Health Report 2002: Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization; 2002. Available from: http://www. who.int/whr/2002/en/whr02_en.pdf?ua=1 [Accessed: 2018-05-10]

[6]   Patel NV, Bigal ME, Kolodner KB, Leotta C, Lafata JE, Lipton RB. Prevalence and impact of migraine and probable migraine in a health plan. Neurology. 2004;**63**:1432-1438. DOI: 10.1212/01.WNL.0000142044.22226.54

[7]   Goadsby PJ, Lipton RB, Ferrari MD. Migraine: Current understanding and treatment. The New England Journal of Medicine. 2002;**346**:257-270. DOI: 10.1056/NEJMra010917

[8]   Silberstein S, Mathew N, Saper J, et al. Botulinum toxin type A as a migraine preventive treatment. Headache. 2000;**40**:445-450. DOI: 10.1046/j.1526-4610.2000.00066.x

[9]   Carruthers J, Carruthers A. Botulinum toxin (Botox) chemodenervation for facial rejuvenation. Facial Plastic Surgery Clinics of North America. 2001;**9**:197-204

[10]   Schulte-Mattler WJ, Krack P, BoNTTH Study Group. Treatment of chronic tensión-type headache with botulinum toxin type A: A randomized, doublé-blind, placebo-controlled multicenter study. Pain. 2004;**109**(1-2):110-114. DOI: 10.1016/j.pain.2004.01.016

[11]   Silberstein S, Lipton R, Dodick D, Freitag F, Mathew N, et al. Topiramate treatment of chronic migraine: A randomized, placebo-controlled trial of quality of life and other efficacy measures. Headache. 2009;**49**(8):1153-1162. DOI: 10.1111/j.1526-4610.2009.01508.x

[12]   Dodick DW, Mauskop A, Elkind AH, DeGryse R, Brin MF, et al. Botulinum toxin type A for the prophylaxis of chronic daily headache: Subgroup analysis of patients not receiving other prophylactic medications: A randomized, double-blind, placebo-controlled study. Headache. 2005;**45**(4):315-324. DOI: 10.1111/j.1526-4610.2005.05068.x

[13]   Dodick DW, Turkel CC, DeGryse RE, Aurora SK, Silberstein SD, et al. PREEMPT chronic migraine study group – Onabotulinumtoxin A for treatment of chronic migraine: Pooled results from the double-blind randomized, placebo-controlled phases of the PREEMPT clínica program. Headache. 2010;**50**(6):921-936. DOI: 10.1111/j.1526-4610.2010.01678.x

[14]   Binder WJ, Brin MF, Blitzer A, Schoenrock LD, Pogoda JM. Botulinum toxin type A (BOTOX) for treatment of migraine headaches: An open-label study. Otolaryngology and Head and Neck Surgery. 2000;**123**(6):669-676. DOI: 10.1067/mhn.2000.110960

[15]   Guyuron B, Tucker T, Kriegler J. Botulinum toxin A and migraine surgery. Plastic and Reconstructive Surgery. 2003;**112**(Suppl):171S-173S; discussion 174S. DOI: 10.1097/01. PRS.0000082206.71638.E9

[16] Aurora SK, Dodick DW, Turkel CC, et al. Onabotulinumtoxin A for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia. 2010;**30**:793-803. DOI: 10.1177/0333102410364676

[17] Diener HC, Dodick DW, Aurora SK, et al. Onabotulinumtoxin A for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia. 2010;**30**:804-814. DOI: 10.1177/0333102410364677

[18] Mannix LK. Epidemiology and impact of primary headache disorders. The Medical Clinics of North America. 2001;**85**(4):887-895. DOI: 10.1016/S0025-7125(05)70349-7

[19] Headache Classification Committee of the International Headache Society. The international classification of headache disorders, 3rd edition (beta version). Cephalalgia. 2013;**33**(9):629-808. DOI: 10.1177/0333102413485658

[20] Schwartz JS, Blitzer A, Young N, Benson BE. Migraine. In: Blitzer A, Benson BE, Guss J, editors. Botulinum Neurotoxin for Head and Neck Disorders. 1st ed. Thieme; 2012. pp. 165-184

[21] Olesen J, Diener HC, Hussedt IW, Goadsby PJ, Hall D, Meier U, Pollentier S, Lesko KM, BIBN 4096 BS Clinical Proof of Concept Study Group. Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine. The New England Journal of Medicine. 2004;**350**(11):1104-1110. DOI: 10.1056/NEJMoa030505

[22] Burstein R, Levy D, Jakubowski M. Effects of sensitization of trigeminovascular neurons to triptan therapy during migraine. Revue Neurologique (Paris). 2005;**161**(6-7):658-660. DOI: RN-07-2005-161-6-7-0035-3787-101019-200503797

[23] Peck KR, Johnson YL, Smitherman TA. Migraine. Handbook of Clinical Neurology. 2016;**138**:283-293. DOI: 10.1016/B978-0-12-802973-2.00016-1

[24] Hickey JV. The Clinical Practice of Neurological and Neurosurgical Nursing. 7th ed. Philadelphia: Lippincott; 2014

[25] Edelson RN. Menstrual migraine and other hormonal aspects of migraine. Headache. 1985;**25**(7):376-379. DOI: 10.1111/j.1526-4610.1985.hed2507376.x

[26] Binder WJ, Blitzer A. Treatment of migraine headache with botulinum toxin type A. Facial Plastic Surgery Clinics of North America. 2003;**11**(4):465-475. DOI: 10.1016/S1064-7406(03)00076-2

[27] Kalb SR, Baudys J, Raphael BH, Dykes JK, Luquez C, Maslanka SE, Barr JR. Functional characterization of botulinum neurotoxin serotype H as a hybrid of known serotypes F and A (BoNT F/A). Analytical Chemistry. 2015;**8**(7):3911-3917. DOI: 10.1021/ac5047116v

[28] Aoki R. Review of a proposed mechanism for the Antinociceptive action of Botulinum toxin type A. Neurotoxicology. 2005;**26**(5):785-793. DOI: 10.1016/j.neuro.2005.01.017

[29] Poggi JT, Grizzell BE, Helmer SD. Confirmation of surgical decompression to relieve migraine headaches. Plastic and Reconstructive Surgery. 2008;**122**(1):115-122; discussion 123-4. DOI: 10.1097/PRS.0b013e31817742da

[30] Binder WJ, Blitzer A, Brin MF. Treatment of hyperfunc- tional lines of the face with botulinum toxin A. Dermatologic Surgery. 1998;**24**:1198-1205

[31] Rollnik JD, Tanneberger O, Schubert M, Schneider U, Dengler R. Treatment of tensión-type headache with botulinum toxin type A: A double-blind, placebo-controlled study. Headache. 2000;**40**(4):300-305. DOI: 10.1046/j.1526-4610.2000.00044.x

[32] Rosales R, Arimura K, Takenaga S, et al. Extrafusal and intrafusal muscle effects in experimental botulinum toxin A injection. Muscle & Nerve. 1996;**19**:488-495. DOI: 10.1002/(SICI)1097-4598(199604)19:4<488::AID-MUS9>3.0.CO;2-8

[33] Burstein R, Yarnitsky D, Goor-Aryeh I, et al. An association between migraine and cutaneous allodynia. Annals of Neurology. 2000;**47**:614-624. DOI: 10.1002/1531-8249(200005)47:5<614::AID-ANA9>3.0.CO;2-N

[34] Dirnberger F, Becker K. Surgical treatment of migraine headaches by corrugator muscle resection. Plastic and Reconstructive Surgery. 2004;**114**(3):652-657; dicussion 658-9. DOI: 10.1097/01.PRS.0000131906.27281.17

[35] Wheeler AH, Goolkasian P. Open label assessment of botulinum toxin A for pain treatment in a private outpatient setting. Journal of Musculoskeletal Pain. 2001;**9**:67-82. DOI: 10.1300/J094v09n01_08

[36] Ashkenazi A, Blumenfeld A. Onabotulinumtoxin A for the treatment of headache. Headache. 2013;**53**(Suppl 2):54-61. DOI: 10.1111/head.12185

[37] Guyuron B, Reed D, Kriegler JS, Davis J, Pashmini N, Amini S. A placebo-controlled surgical trial of the treatment of migraine headaches. Plastic and Reconstructive Surgery. 2009;**124**:461-468. DOI: 10.1097/PRS.0b013e3181adcf6a

[38] Lee M, Monson MA, Liu MT, Reed D, Guyuron B. Positive botulinum toxin type a response is a prognosticator for migraine surgery success. Plastic and Reconstructive Surgery. 2013;**131**:751-757. DOI: 10.1097/PRS.0b013e3182818b7f

[39] Guyuron B, Nahabet E, Khansa I, Reed D, Janis JE. The current means for detection of migraine headache trigger sites. Plastic and Reconstructive Surgery. 2015;**136**(4):860-867. DOI: 10.1097/PRS. 0000000000001572

[40] Tfelt-Hansen P, Block G, Dahlöf C, Diener HC, Ferrari MD, Goadsby PJ, Guidetti V, Jones B, Lipton RB, Massiou H, Meinert C, Sandrini G, Steiner T, Winter PB, International Headache Society Clinical Trials Subcommittee. Guidelines for controlled trials of drugs in migraine: Second edition. Cephalalgia: An International Journal of Headache. 2000;**20**(9):765-786. DOI: 10.1046/j.1468-2982.2000.00117.x

[41] Gaul C, Holle-Lee D, Straube A. Botulinum toxin type A in headache treatment: Established and experimental indications. Der Nervenarzt. 2016;**87**(8):853-859. DOI: 10.1007/s00115-016-0138-5

[42] Ondo W, Vuong K, Derman H. Botulinum toxin A for chronic daily headache: A randomized, placebo-controlled, parallel design study. Cephalalgia. 2004;**24**:60-65. DOI: 10.1111/j.1468-2982.2004.00641.x

[43] Mathew N, Kailasam J, Meadors L. Predictors of response to Botulinum toxin type A (BoNTA) in chronic daily headache. Headache. 2007;**48**:194-200. DOI: 10.1111/j.1526-4610. 2007.00914.x

[44] Kollewe K, Escher CM, Wulff DU, Fathi D, Paracka L, Mohammadi B, Karst M, Dressler D. Long-term treatment of chronic migraine with Onabotulinumtoxin A: Efficacy, quality of life and tolerability in a real-life setting. Journal of Neural Transmission (Vienna). 2016;**123**(5):533-540. DOI: 10.1007/s00702-016-1539-0

[45] Cernuda-Morollón E, Martínez-Camblor P, Ramón C, Larrosa D, Serrano-Pertierra E, Pascual J. CGRP and VIP levels as predictors of efficacy of Onabotulinumtoxin type A in chronic migraine. Headache. 2014;**54**(6):987-995. DOI: 10.1111/head.12372. Epub 2014 May 6