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Treatment of chronic migraine with Botox (onabotulinumtoxinA)

Development, insights, and impact

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Abstract

Chronic migraine (CM) is a neurological disease characterized by frequent migraine attacks that prevent affected individuals from performing daily activities of living, significantly diminish quality of life, and increase familial burden. Before onabotulinumtoxinA was approved for CM, there were few treatment options for these seriously disabled patients and none had regulatory approval.

The terminology and recognition of CM evolved in parallel with the onabotulinumtoxinA clinical development program. Because there were no globally accepted classification criteria for CM when onabotulinumtoxinA was in development, the patient populations for the trials conducted by Allergan were determined by the Allergan migraine team in collaboration with headache scientists and clinicians. These trials and collaborations ultimately led to improvements in CM classifications.

In 2010, onabotulinumtoxinA became the first medication and first biologic approved specifically to prevent headaches in patients with CM. Approval was based on 2 similarly designed phase 3, double-blind, randomized, placebo-controlled, multicenter clinical studies. Both studies showed significantly greater improvements in mean change from baseline in headache-day frequency in patients with CM receiving onabotulinumtoxinA compared with those receiving placebo.

The safety and effectiveness of onabotulinumtoxinA have been established globally in >5000 patients with CM with or without medication overuse treated in clinical and observational studies. Benefits also include improvements in quality of life, fewer psychiatric comorbidities, and reduced healthcare resource utilization. Across studies, onabotulinumtoxinA was well tolerated; adverse events tended to be mild or moderate in severity and to decline over subsequent treatment cycles.

Abbreviations: AEs = adverse events, CDH = chronic daily headache, CM = chronic migraine, CTTH = chronic tension-type headache, EM = episodic migraine, FDA = Food and Drug Administration, ICHD = International Classification of Headache Disorders, IHS = International Headache Society, PREEMPT = phase 3 research evaluating migraine prophylaxis therapy, SNAP-25 = synaptosomal associated protein-25kDa.

Keywords: headache, human, neuromuscular agents, prevention, preventive treatment, treatment outcome

1. Introduction and burden of chronic migraine (CM)

Chronic migraine (CM) is a neurological disease that impacts an estimated 1 to 2% of the global population.[1–3] In childhood, migraine can occur with low frequency and then gradually increase in frequency over time and become disruptive in adulthood during a time when higher education, careers, and raising a family are important priorities.[4–6] CM is characterized by headache on ≥15 days per month with at least 8 days per month

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linked to migraine (*International Classification of Headache Disorders* [ICHD]-3).[7] CM affects substantially more women than men, and is more debilitating than episodic migraine (EM) in terms of its greater frequency of headache and migraine days and increased prevalence of comorbid conditions, such as other chronic pain disorders, anxiety, depression, and medication overuse.[8–11] Individuals with CM experience frequent migraine attacks that usually interfere with activities of daily living, greatly diminish quality of life, and result in increased family and societal burden, as well as lead to substantial economic burdens for patients and healthcare systems.[5]

The following historical narrative was compiled based on review of the literature and interviews with the authors, and the quoted portions reflect the personal observations and reflections of the individuals who were interviewed. In some instances, this article describes uses for which Allergan has not sought and/or received regulatory approval in individual countries and are mentioned for historical context or background only.

The burden of CM can be better understood by hearing from the people with the disease and the doctors who treat them.

Dr Dodick: "I would describe the impact of chronic migraine as being pervasive. Patients with chronic migraine are often symptomatic every day. That does not mean that they have a headache every waking moment of every day, but many have one or more migraine symptoms nearly every day because they are either in the beginning or middle of an attack, just recovering from an attack, or in an interictal state between attacks when nonheadache symptoms may persist. Symptoms may include dizziness, cognitive impairment, brain fog, sensitivity to light, or nausea, all of which are pervasive and impact the patients' personal life, professional life, employment, and ability for career opportunities. It impacts their family; they feel guilty as parents and guilty as partners. One of my patients questioned whether it was ethical to bring a child into the world when they were not fit to take care of the child and also noted that they would never want to burden their child with the kind of disease or illness that they were living with. Some patients with chronic migraine are bed-bound or house-bound, so not only are they not employed, they don't make plans; they don't make plans to go on vacation; they don't make plans to go to a movie; they don't make plans to go to dinner; or to go out to meet a friend, because they can't predict when their next severe attack will occur or they may have been told that they are so unreliable because they have had to cancel so often. These patients don't want to put themselves in that potential position again. They already live with the stigma of having migraines; they don't want to have to live with the stigma of being called unreliable."

While numerous patients express similar concerns and feelings, the extent of disability caused by migraine remains poorly recognized and, despite treatment advances and the availability of effective preventive therapies such as onabotulinumtoxinA and, recently, monoclonal antibodies that target the calcitonin gene-related peptide pathway, CM often remains undertreated.[7,9,10,12,13]

Dr Aurora: "Patients want a medication that is going to do what it says it is going to do: prevent migraine pain, improve quality of life, provide them with headache-free time with their family, and be a drug that is not going to cause a lot of intolerable side effects."

2. Evolution of a disease and development of a treatment

2.1. The evolving concept of CM

Our current clinical understanding of CM as a separate diagnostic category is relatively recent, evolving from concepts of chronic daily headache (CDH), mixed headache, and transformed migraine.[14,15] The path to the current definition of CM was not straightforward, and the definition undoubtedly will continue to evolve as additional understanding of the biologic foundations of migraine emerges.

In the early and mid-1980s, the research and clinical observations of the neurologist Dr Ninan T. Mathew (1937–2015) spurred efforts to understand migraine in its entirety. Dr Mathew reported that >75% of patients with CDH had a history of EM, referring to the phenomenon as transformed migraine.[16,17] The first criteria for diagnosing a range of headaches were published by the International Headache Society (IHS) in 1988. The first version of the ICHD redefined CDH as chronic tension-type headache (CTTH) with the main criterion being the presence of headache on at least 15 days a month during at least 6 months.[18] Dr Silberstein et al observed that many patients had long-duration (≥4 hours) headache on at least 15 days a month, but these headaches were not limited to classic tension headaches. Thus, they proposed revised criteria for 4 primary CDH subtypes (CTTH, hemicrania continua, new daily persistent headache, and transformed migraine) and then field-tested the revised transformed migraine criteria.[15] Over time, the terminology "transformed migraine" was replaced by the terminology "chronic migraine" to be consistent with CTTH (i.e., headaches of a particular type occurring on ≥15 days per month). CM was first defined in the 2004 *ICHD, 2nd edition* as migraine headache occurring on at least 15 days per month for >3 months in the absence of medication overuse.[19]

In June 2006, the ICHD of the IHS published revised criteria for diagnosing CM (ICHD-2R) and confirmed their position that CM was the preferred term among other terms used previously (i.e., CDH and transformed migraine).[14] The revised criteria were designed to more accurately reflect the patients seen in clinical practice. The third and most recent version of the ICHD (ICHD-3; 2018) defines CM as headache occurring on at least 15 days per month, for >3 months, which has features of migraine headache on at least 8 days per month.[7] Following incorporation of the term CM, patients classified with CM were deemed too severe, and therefore at risk, for inclusion in clinical trials of acute and preventive medications. Prior to accepted criteria, patients who experienced migraine on ≥15 days per month were excluded from many clinical trials.

Dr Lipton: "Most of my patients with migraine could not be included in clinical trials because they were deemed too ill for controlled trials of acute as well as preventive treatments. Patients with 15 or more days of headache per month and

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patients with medication overuse were often systematically excluded from clinical trials. That meant the results of many clinical trials did not apply to the patients in my practice. Developing criteria that included patients with chronic migraine or transformed migraine in clinical trials was a step towards developing the evidence we needed to treat them."

3. Clinical development pathway of onabotulinumtoxinA

Dr Brin: "In 1976, Dr Andrew Blitzer was chief resident in Otolaryngology at the Mount Sinai Hospital in New York and Dr William Binder was his junior resident. Subsequently, when Dr Blitzer and I were exploring the cosmetic potential of Oculinum® (first brand name for onabotulinumtoxinA, now branded as Botox) at Columbia University, Dr Binder returned to New York to learn about using onabotulinumtoxinA for aesthetic hyperfunctional lines.[20] *Beginning in 1994, we published several papers together.*[21,22]*" Dr. Binder subsequently found that some of his aesthetic patients observed that their migraine symptoms improved.*[23,24]

In the early 1990s, Dr Binder observed that several of his patients treated with onabotulinumtoxinA for hyperfunctional facial lines also experienced alleviation of their migraine headache symptoms. He conducted a small study between 1992 and 1994 and contacted Drs Brin and Blitzer to share his observations. Together, they evaluated their patient charts to determine improvements in migraine headache symptoms in those treated with onabotulinumtoxinA[23] and subsequently studied open-label treatment of 106 patients who initially sought treatment for aesthetic hyperfunctional facial lines or dystonias of the head and neck, and also had concomitant headache disorders.[24] The retrospective case review study demonstrated that onabotulinumtoxinA was safe and effective for acute and preventive treatment of migraine headaches.[24] Because many of the patients identified in the case review had received cosmetic treatment, relatively small doses (mean = 31 U; range 5 U–110 U) were administered.[24] Thus, the initial Allergan phase 2a trials were conducted using low doses of onabotulinumtoxinA (e.g., 25 U and 75 U).[25] The first double-blind, placebo-controlled trial in patients with a history of 2 to 8 moderate to severe migraine attacks per month demonstrated a reduction in attack frequency and severity with low dose (25 U) onabotulinumtoxinA along with a favorable safety profile.[25]

Dr Brin: "Based on physician experience, in 1997 Allergan initiated several early phase 2 studies that focused on a treatment paradigm of the frontal and temporal region. In total, 5 studies were conducted in phase 2a to assess doses and treatment paradigms. These studies evaluated doses that were too low for consistent efficacy, and a clear signal for dose and sites of injection had not emerged. Nevertheless, physicians used the drug off label and explored various doses, cranial injection sites, and headache patient populations. Some physicians were using 'fixed-site, fixed-dose,' 'follow-the-pain,' or combined approaches, and patients were reporting clear benefit. Allergan held advisory boards to better understand how physicians were exploring treatment in their clinics. Together with the early phase 2a results and physicians' experiences, the phase 2b studies were designed."

The development of the clinical program for onabotulinumtoxinA occurred largely in parallel with the evolution of the terminology for CM.

Dr Aurora: "What we were noticing in the clinic in patients that were receiving onabotulinumtoxinA for aesthetic indications was that there were patients with transformed migraine or chronic daily headache with migraine features who were not responding well to the standard of care, but were responding to onabotulinumtoxinA. This observation led us to ponder whether all patients with chronic headache may not respond the same way and, in fact, those with migraine features may respond better. So our experience with onabotulinumtoxinA helped to shape our notion of migraine classification, and we thought that there might be a different classification needed to describe these patients better so that they get the treatment that they deserve and that they would respond to."

When Allergan's phase 2b clinical development program for onabotulinumtoxinA began, it was still unclear as to which patient population might respond to treatment. Therefore, trials focused on patients with "episodic migraine" and trials focused on patients with "CDH" were initiated (Fig. 1). CDH comprised 4 subgroups: transformed migraine, CTTH, new onset persistent daily headache, and hemicrania continua; the most prevalent of these was transformed migraine. The majority of patients enrolled into the CDH trials had transformed migraine. In subsequent discussions with the US Food and Drug Administration (FDA) regarding the phase 3 program, Allergan learned that a labeled indication for a broad patient population of CDH would not be possible without safety and efficacy being demonstrated separately for each of the 4 CDH subgroups. Therefore, a decision was made to enroll only patients with CM (terminology recognized at the time the phase 3 trials were designed) in the phase 3 program.

There was uncertainty about the clinical development program, both internally at Allergan and within the migraine academic community. Internal skepticism was especially high upon completion of the phase 2 program, as those trials had not met their primary endpoints.

Dr Brin: "I came back from an American Academy of Neurology meeting and reported to Lester Kaplan, the head of Allergan R&D at the time, that many physicians in the headache and nonheadache community had treated patients with onabotulinumtoxinA and observed benefits for their headaches. I urged him to continue the migraine development program so we could seek an effective treatment paradigm."

In part because of the controversies surrounding disease concepts and migraine nomenclature, the phase 3 clinical development program itself was controversial. The IHS diagnostic criteria for CM specifically excluded medication overuse; however, many clinicians did not accept this criterion. Allergan elected to include CM patients with medication overuse, which was operationally defined as the use of a simple analgesic on at least 15 days, or other medication types (e.g., ergotamines, triptans, and opioids) or combination analgesics on at least 10 days, with use at least 2 days per week during the 28 days of the study baseline period. Enrolled patients were then stratified to treatment by this criterion. IHS guidelines for clinical studies in CM subsequently adopted this methodology and allowed for the inclusion of patients with medication overuse, although assignment to treatment groups had to be stratified accordingly.[26]

Dr Turkel: "One key issue in designing the phase 3 program was how to deal with medication overuse headache. At the time, there was widespread belief that chronic migraine was caused by medication overuse. However, the criteria for chronic

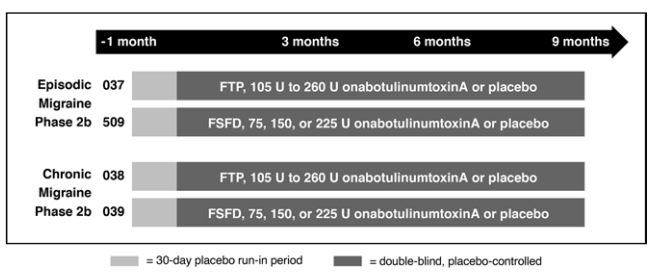

Figure 1. Phase 2b studies of onabotulinumtoxinA conducted between 2001 and 2004. FSFD = fixed-site, fixed-dose, FTP = follow the pain.

migraine at the time did not include medication overuse. We chose to allow enrollment of patients with medication overuse in the phase 3 program despite the objections of many clinicians since our goal was to develop a treatment to meet the needs of suffering patients. Our assumption was that patients were suffering from chronic migraine and, as a result, were overusing their acute treatments in a desperate attempt for pain relief. If the treatment worked to address their underlying disease, then reduction in acute medications would follow."

Dr Brin: "Indeed, because Botox had benefits, including in patients with medication overuse, many patients were able to stop overusing their meds.[27,28] *In this setting, the phrase 'Detox with Botox' was coined and used by some migraine experts.*"

Dr Aurora: "Patients with medication overuse had a big stigma against them because they were overusing medication and were told that preventive therapy was not going to work. The onabotulinumtoxinA trials were the first to show that it does not matter if you are overusing your medication; it is not your fault. The reason is that there has not been good treatment for your migraine, and now when you give a medication that is a good preventive, you do not overuse medication."

The Allergan headache team members working closely with clinical experts examined the phase 2 data extensively and, as a result, identified optimal efficacy endpoints, a standardized treatment paradigm, and patient population for the phase 3 clinical trial program. One of the biggest challenges was to show the efficacy benefit of onabotulinumtoxinA beyond the robust and persistent placebo response rates observed in the phase 2b program, which was assumed to be related to the physical interaction of the physician and the patient due to multiple head and neck injections.

Dr Turkel: "The phase 3 program evolved from treating patients in the phase 2 studies who had chronic daily headache to treating patients with chronic migraine, mirroring the environment at the time and identifying patients with chronic migraine as the responsive candidates for moving forward with clinical development. The injection paradigm was finalized in a hotel suite at the AAN in 2005 with Mitchell, Sheena, David, and myself, after a meeting with the FDA, who requested a standardized injection paradigm for the Phase 3 program that could be easily translated to instructions for use on a package insert."

Accordingly, the **P**hase 3 **RE**search **E**valuating **M**igraine **P**rophylaxis **T**herapy (PREEMPT) clinical development program enrolled adult patients who had a history of migraine and an indication that most headaches were migraine in origin (protocol required at least 50% to be migraine or probable migraine per ICHD-2), intermittent (protocol specified at least 4 episodes), and long-lasting headaches (at least 4 hours) on ≥15 days each month.[29,30] The PREEMPT clinical program consisted of 2 phase 3 studies, each with a 24-week, double-blind, placebo-controlled phase followed by a 32-week, open-label phase.[29,30] PREEMPT I took place at 56 North American sites from January 23, 2006 to July 16, 2008,[29] while PREEMPT II was conducted at 66 sites in Europe and North America from February 7, 2006 to August 11, 2008.[30]

Despite much discussion around the most appropriate efficacy endpoint (debate between headache-episode frequency or headache-day frequency), the primary efficacy endpoint for PREEMPT I ultimately was proposed as the mean change from baseline in *headache-episode frequency* for the 28-day period ending with week 24.[29] *Headache-day frequency* was designated as a secondary endpoint. Unfortunately, the primary endpoint in PREEMPT I (headache-episode frequency) did not demonstrate a significant difference between the onabotulinumtoxinA and placebo treatment groups, but the secondary endpoint of headache-day frequency separated from placebo significantly ($P = .006$). The crucial recognition that the headache-episode frequency endpoint, which had been the gold-standard efficacy endpoint accepted by health authorities for previous trials in patients with EM, was insensitive for assessing CM was a significant finding.

Dr Dodick: "Based on my clinical experience and patient follow-up, we realized that there was a major disconnect between the data and what patients reported. Not unusually, patients would report that they felt 75% better, whereas the data showed only minimal reductions in episodes. We needed to listen to what our patients were telling us. In chronic migraine, going from an episode that could last 3 days to one that was 4 hours was clinically meaningful."

Dr Diener: "While some patients only had a small decrease in headache frequency, they had improvements in quality of life and related disability and wanted to continue on the drug."

These observations, combined with significant results in PREEMPT I for the endpoint of mean change from baseline in *headache-day frequency*, resulted in changing, before database lock, the primary endpoint of the PREEMPT II trial to mean change from baseline in *headache-day frequency* for the 28-day period ending at week 24.[30] In the end, both the initial and the revised primary endpoints were met, allowing onabotulinumtoxinA to become the first medication and the first biologic approved by the US FDA specifically for the prevention of CM. After this first registration of onabotulinumtoxinA in October 2010 as a treatment specific for CM prevention, approval followed in 86 additional countries. It is important to note that unit doses are not interchangeable among different botulinum toxin products,[31] as each has its own dosing guidelines and clinical profile.

4. Efficacy, tolerability, and safety highlights

The effectiveness of onabotulinumtoxinA has now been demonstrated in >5000 patients with CM treated in clinical and observational studies.[28–30,32–42] The PREEMPT trials compared the efficacy and safety of onabotulinumtoxinA with that of placebo over a 24-week double-blind period, which was followed by a 32-week open-label phase, in 1384 adults with CM.[29,30,32] Treatment with onabotulinumtoxinA provided sustained and significant reductions from baseline in headache-day frequency with incremental benefits over succeeding treatment cycles (Fig. 2).[43,44] Importantly, the data demonstrated that patients who failed to respond to the first treatment cycle of onabotulinumtoxinA may respond to the second or third cycle with clinically meaningful improvements.[44] In a pooled analysis of the PREEMPT trial data, a significantly greater percentage of onabotulinumtoxinA-compared with placebo-treated patients experienced at least a 50% decrease from baseline in the frequency of headache days at all time points ($P < .001$), demonstrating a responder rate that was clinically meaningful.[32] Data from the long-term, open-label Chronic Migraine OnabotulinuMtoxinA Prolonged Efficacy open Label study augment the results from the PREEMPT program. The Chronic Migraine OnabotulinuMtoxinA Prolonged Efficacy open Label study provided additional evidence of the consistency and long-term safety, efficacy, and tolerability in patients treated every 12 weeks with onabotulinumtoxinA over 108 weeks (9 treatment cycles).[33] Assessments of headache impact (total 6-item Headache Impact Test score),[33] migraine-related disability (Migraine Disability Assessment Questionnaire),[45] health related quality of life (scores of all 3 Migraine-Specific Quality-of-Life questionnaire domains),[45] sleep disturbance (Pittsburgh Sleep Quality Index),[46] fatigue (Fatigue Severity Scale),[46] depression (9-item Patient Health Questionnaire),[46] and anxiety (7-item Generalized Anxiety Disorder Assessment)[46] were also significantly ($P < .0001$) improved from baseline at week 108. Additional ongoing and completed Allergan-sponsored onabotulinumtoxinA trials are summarized in the timeline in Figure 3.

In people with migraine, the broad array of benefits associated with onabotulinumtoxinA treatment is well documented in the published literature.[47,48] The benefits include improvements in quality of life and reduction of burdens and psychiatric comorbidities associated with CM.[27,29,30,32,33,43,44,48–53] Treatment with onabotulinumtoxinA

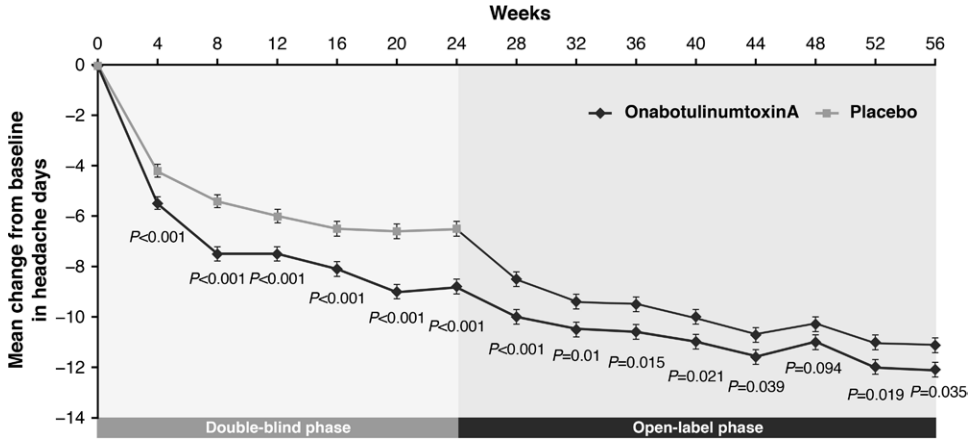

Figure 2. Mean (standard error) change from baseline in frequency of headache days in patients who completed 5 treatments of onabotulinumtoxinA versus placebo in the PREEMPT trial. Reprinted with permission from Aurora SK, et al.[43] PREEMPT = Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy.

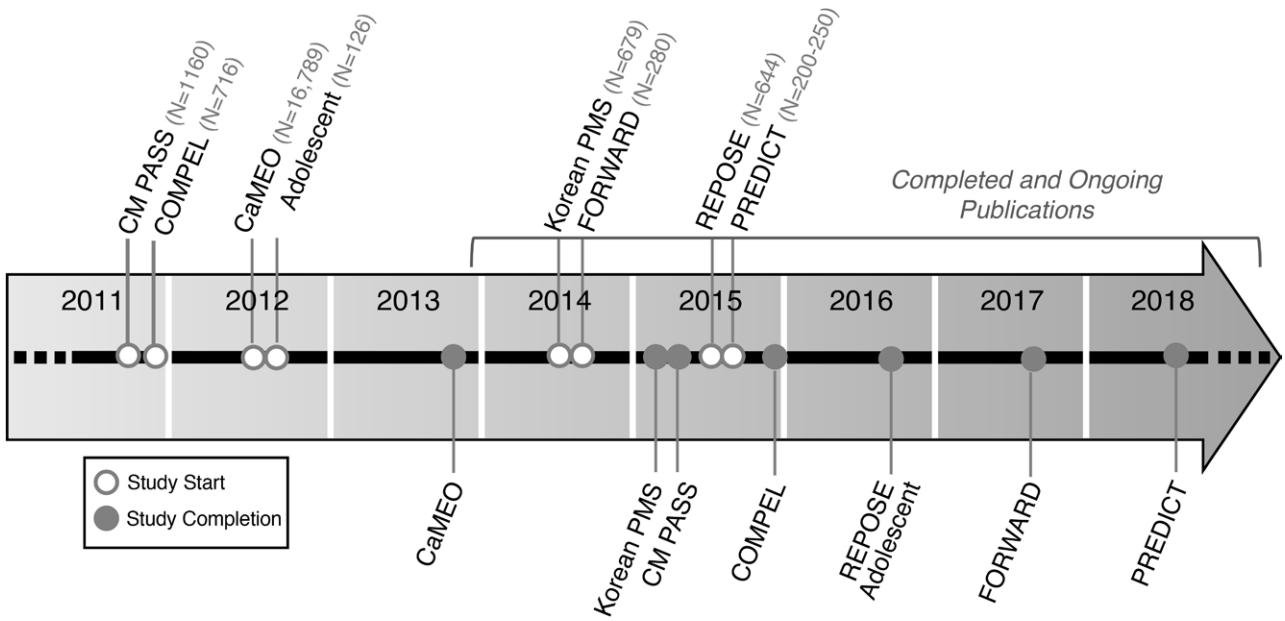

Figure 3. Ongoing and completed Allergan-sponsored onabotulinumtoxinA trials. CaMEO = Chronic Migraine Epidemiology and Outcomes, CM PASS = Chronic Migraine Post-Authorization Safety Study, COMPEL = Chronic Migraine OnabotulinuMtoxinA Prolonged Efficacy open Label, PMS = Post-Marketing Surveillance, PREDICT = Patient Reported Outcomes in Patients With Chronic Migraine Treated With Botox, REPOSE = REal-life use of botulinum toxin for the symptomatic treatment of adults with chronic migraine, measuring healthcare resource utilization, and Patient-reported OutcomeS observed in practicE.

has also been shown to be cost-effective compared with placebo and reduce healthcare resource utilization and costs.[54,55] The effectiveness of onabotulinumtoxinA for the management of CM has been further documented through extensive real-world experience.[33,48,49] To date, in the US alone, >2 million treatments have been administered to 500,000 unique patients with CM.

A local treatment, onabotulinumtoxinA is safe and well tolerated with low rates of adverse events (AEs) that are typically mild to moderate in severity and resolve without sequelae, as reported in both clinical trials and real-world studies in CM.[27,29,30,32,33,43,44,49,50,52,56,57] In long-term studies, the incidence of overall AEs and the most common individual AEs (which include neck pain, muscular weakness, eyelid ptosis, muscle tightness, injection-site pain, headache, myalgia, musculoskeletal stiffness, and musculoskeletal pain) tend to decrease with repeated administration.[50,52] Also, in routine clinical practice, the incidence of treatment-related AEs is consistent with rates in clinical trials, also tending to decrease over treatment cycles.[50] Region-specific information regarding safety and efficacy can be found in local labeling.

5. The mechanisms of action of onabotulinumtoxinA in CM

When investigators first began reporting benefits of onabotulinumtoxinA in open-label studies of migraine, little was understood of the mechanisms by which it acted.[5,24] Clinicians initially considered the possibility that its effectiveness was due to muscle relaxation, but several observations called this interpretation into question, including a dissociation between muscle effects and pain relief.[24]

Dr Brin: "We noticed a symptomatic dissociation between pain relief and reduction of muscle spasm when treating dystonia patients in the 1980s, and, for some, the pain relief exceeded reduction of muscle contractions.[58] *This dissociation was also reported during a discussion session at the*

International Toxins Meeting in Munich in 1995 on spasticity, where an expert pointed out that the pain associated with spasticity improved and resolved faster than the muscle spasm. In our migraine study published in 2000, we discussed the clinical observation that the duration of pain relief sometimes exceeded the duration of muscle relaxation and some patients showed benefits on migraine-associated nausea/vomiting, visual disturbances, and phonophobia, arguing against an exclusive neuromuscular mechanism.[24] *The sensory nature of migraine and the dissociation between the muscle effects and pain reduction, as demonstrated in spasticity*[59] *and a migraine analysis,*[60] *provide support for our early clinical observations. We now understand that onabotulinumtoxinA modulates release of pain-inducing neurotransmitters at the synapse and inhibits insertion of nociceptors into the nerve terminal membrane.*[61]*"*

Over the past 3 decades, understanding of both the pathophysiology of migraine and the mechanisms by which onabotulinumtoxinA acts in migraine has expanded substantially.[11,62] CM is now recognized as a highly complex neurological disease, involving multiple peripheral pathways and portions of the central nervous system.[6] The trigeminovascular system has emerged as central to migraine pathophysiology.[6] Early during a migraine attack, peripheral sensitization can occur, resulting in a decreased threshold for response in the trigeminal nerve. With repeated attacks and progression, generalized central sensitization can occur and is thought to lead to cutaneous allodynia, hyperalgesia, and ongoing pain.[11,63]

Following injection into head and neck muscles that are innervated by sensory terminals of trigeminal neurons, onabotulinumtoxinA is internalized into nerve terminals where it ultimately cleaves the protein synaptosomal associated protein-25kDa (SNAP-25).[64,65] SNAP-25 is an integral component of the soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptor complex, which is necessary for synaptic vesicle docking and fusion. Without the formation of the soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptor complexes, neurotransmitter/neuropeptide exocytosis is inhibited, as is the insertion of membrane receptors that depend on vesicle fusion with the neuronal membrane. Thus, onabotulinumtoxinA cleavage of SNAP-25 inhibits the release of neuropeptides and neurotransmitters such as calcitonin gene-related peptide and glutamate, that are associated with the genesis of pain.[11,66] OnabotulinumtoxinA also reduces the number of ion channel receptors in sensory nerve membranes; these include transient receptor potential cation channel subfamily V member 1, transient receptor potential cation channel subfamily A member 1, and P2X3 – receptors that are upregulated due to sensory afferent neuron activation that characterizes migraine.[5,6,11,67]

6. Lessons learned and the impact of onabotulinumtoxinA in CM

The successful development of onabotulinumtoxinA for CM underscored the critical value of teamwork and commitment. Initially, the efficacy of onabotulinumtoxinA was not fully accepted by the clinical community, particularly since the mechanism of action was not well understood; however, this waned significantly over time with expanded evidence of its clinical benefit.

Dr Turkel: "This program needed a champion, and I was fortunate to be in the position and to have such highly motivated, committed, and supportive colleagues within Allergan and in the research/clinical community. I had firsthand experience seeing my father suffer for decades with chronic migraine; I was hopeful that onabotulinumtoxinA would prove to be the breakthrough treatment that he and so many other patients needed. I worked very hard to ensure that Allergan pursued a scientifically rigorous development program to evaluate this drug's potential in patients who were otherwise excluded from clinical trials."

The approval from the US FDA provided important validation to clinicians who had been witnessing improvements in their patients in the clinic but had encountered resistance in the academic community. Overall, the scientifically based clinical trial program was acknowledged and well received in the academic community (Fig. 4).[5]

After regulatory approval, educating physicians worldwide about the treatment paradigm for CM required the development and implementation of a completely new level of training from Allergan. An unprecedented level of detail and infrastructure was required to teach neurologists and headache specialists. In general, headache specialists did not have experience using onabotulinumtoxinA to treat spasticity and dystonia and, therefore, were unlikely to have experience administering onabotulinumtoxinA into 31 to 39 sites in 7 muscles of the head and neck for migraine treatment.

Dr Brin: "Considerations when developing the administration protocol included practical, therapeutic, and physician experience, which all came together in the end. Training headache specialists to inject into the head and neck muscles on a worldwide basis had never been done before."

Dr Aurora: "When developing the administration protocol, we wanted to make it simple: simple math and simple translation. When we developed the postmarketing training materials, we kept the approach uniform with the PREEMPT injection paradigm and utilized many training materials that had been developed to train the more than 100 global physician investigators who participated in the PREEMPT trials."

The development of protocols that clearly defined and standardized inclusion and exclusion criteria, the use of electronic

Figure 4. Drs Mitchell Brin and Catherine Turkel at the 4th Galien Forum and the 2013 Prix Galien USA Awards ceremony in New York City in October 2013.

diaries to capture patient-specific information daily, and the requirement of hands-on injection training overseen by regional coordinating physician injector experts made the PREEMPT clinical trials possible. The value of evidence of onabotulinumtoxinA overall cannot be overstated. The importance of the onabotulinumtoxinA clinical trial program for improving the understanding of CM as a disease and its impact on patients and global health systems had implications far beyond the approval of onabotulinumtoxinA as a specific treatment to prevent CM.

Dr Diener: "Operational criteria [such as that used in the PREEMPT program] had a major impact on clinical trials in migraine and allowed us to approach chronic migraine as a disease."

Dr Turkel: "Because many migraine thought leaders in Europe didn't recognize chronic migraine as a disease at the time we sought approval, Dr Diener had to present extensive clinical and research data to convince the European Medicines Agency that chronic migraine existed, and that onabotulinumtoxinA was an effective and safe treatment needed by European patients and physicians. Ultimately, they agreed and the product has since been registered in many European countries."

Dr Silberstein: "With the revised [chronic migraine] criteria [as defined in the PREEMPT trials], the patient population was now defined, and this informed the future of clinical development in this field."

In turn, the ability to conduct longitudinal studies, uncover potential risk factors associated with the use of medications, and better understand how to manage patients was enhanced. In addition, for a complicated disease state such as CM, it has been recognized that no one single endpoint can best define the totality of benefits.

Dr Lipton: "When medication works, that can help legitimize a disease and redefine best medical practice. OnabotulinumtoxinA is a serious medication that did more than change the lives of individual patients. It helped to reduce the stigma of migraine and establish chronic migraine as a serious, disabling, and treatable neurologic disorder."

Before onabotulinumtoxinA was approved for CM, there were few options for seriously disabled patients. OnabotulinumtoxinA treatment has changed patients' lives for the better by reducing the frequency of headache days and improving their quality of life. It was not associated with many side effects seen with other preventive oral medications such as topiramate and β-blockers. For some, that also means a life that is more normal.

Dr Silberstein: "Following onabotulinumtoxinA's approval for chronic migraine, more and more physicians reported that their clinics were happier places because they now had a very effective therapeutic to prevent chronic migraine. One of my patients noted that for the first time in years, they were able to get out of the house without pain. For the first time in years, they were able to be with their children."

Dr Brin: "The success of this program helped to validate thinking about pain being a separate dimension and therapeutic target with onabotulinumtoxinA, and it spurred forward new directions for both clinical and basic science research. It expanded the research community's consideration of novel hypotheses about the mechanism of onabotulinumtoxinA in treating medical conditions with a pain or sensory component."

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References

[1] Manack A, Turkel CC, Kaplowitz H. Role of epidemiological data within the drug development lifecycle: a chronic migraine case study In: Lunet N, ed. Epidemiology – current perspectives on research and practice. Rijeka, Croatia: InTech. 2012:155–70.
[2] Natoli JL, Manack A, Dean B, et al. Global prevalence of chronic migraine: a systematic review. Cephalalgia. 2010;30:599–609.
[3] Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390:1211–59.
[4] Grosberg B, Bigal ME, Ricci J, et al. Epidemiology of chronic daily headache in adolescents [abstract]. Neurology. 2007;68(Suppl 1):A180.
[5] Whitcup SM, Turkel CC, DeGryse RE, et al. Development of onabotulinumtoxinA for chronic migraine. Ann N Y Acad Sci. 2014;1329:67–80.
[6] Burstein R, Noseda R, Borsook D. Migraine: multiple processes, complex pathophysiology. J Neurosci. 2015;35:6619–29.
[7] The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38:1–211.
[8] Katsarava Z, Buse DC, Manack AN, et al. Defining the differences between episodic migraine and chronic migraine. Curr Pain Headache Rep. 2012;16:86–92.
[9] Buse DC, Manack AN, Fanning KM, et al. Chronic migraine prevalence, disability, and sociodemographic factors: results from the American Migraine Prevalence and Prevention Study. Headache. 2012;52:1456–70.
[10] Manack Adams A, Serrano D, Buse DC, et al. The impact of chronic migraine: the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study methods and baseline results. Cephalalgia. 2015;35:563–78.
[11] Aurora SK, Brin MF. Chronic migraine: an update on physiology, imaging, and the mechanism of action of two available pharmacologic therapies. Headache. 2017;57:109–25.
[12] Dodick DW, Loder EW, Manack Adams A, et al. Assessing barriers to chronic migraine consultation, diagnosis, and treatment: results from the Chronic Migraine epidemiology and Outcomes (CaMEO) Study. Headache. 2016;56:821–34.
[13] Dodick DW. CGRP ligand and receptor monoclonal antibodies for migraine prevention: Evidence review and clinical implications. Cephalalgia. 2019;39:445–58.
[14] Olesen J, Bousser MG, Diener HC, et al. New appendix criteria open for a broader concept of chronic migraine. Cephalalgia. 2006;26:742–6.
[15] Silberstein SD, Lipton RB, Sliwinski M. Classification of daily and near-daily headaches: field trial of revised IHS criteria. Neurology. 1996;47:871–5.
[16] Mathew NT, Stubits E, Nigam MP. Transformation of episodic migraine into daily headache: analysis of factors. Headache. 1982;22:66–8.
[17] Mathew NT, Reuveni U, Perez F. Transformed or evolutive migraine. Headache. 1987;27:102–6.
[18] International Headache Society, Headache Classification Committee. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Headache Classification Committee of the International Headache Society. Cephalalgia. 1988;8(Suppl 7):1–96.
[19] Olesen J, Bousser M-G, Diener H-C, et al. Second Headache Classification Subcommittee The International Classification of Headache Disorders, 2nd ed. Cephalalgia. 2004;24(Suppl 1):9–160.
[20] Blitzer A, Brin MF, Keen MS, et al. Botulinum toxin for the treatment of hyperfunctional lines of the face. Arch Otolaryngol Head Neck Surg. 1993;119:1018–22.
[21] Keen M, Kopelman JE, Aviv JE, et al. Botulinum toxin A: a novel method to remove periorbital wrinkles. Facial Plast Surg. 1994;10:141–6.
[22] Keen M, Blitzer A, Aviv J, et al. Botulinum toxin A for hyperkinetic facial lines: results of a double-blind, placebo-controlled study. Plast Reconstr Surg. 1994;94:94–9.

[23] Binder W, Brin MF, Blitzer A, et al. Botulinum toxin type A (BTX-A) for migraine: an open label assessment [abstract P4-104]. Mov Disord. 1998;13(Suppl 2):241.

[24] Binder WJ, Brin MF, Blitzer A, et al. Botulinum toxin type A (BOTOX) for treatment of migraine headaches: an open-label study. Otolaryngol Head Neck Surg. 2000;123:669–76.

[25] Silberstein S, Mathew N, Saper J, et al. Botulinum toxin type A as a migraine preventive treatment. For the BOTOX Migraine Clinical Research Group. Headache. 2000;40:445–50.

[26] Tassorelli C, Diener HC, Dodick DW, et al. Guidelines of the International Headache Society for controlled trials of preventive treatment of chronic migraine in adults. Cephalalgia. 2018;38:815–32.

[27] Silberstein SD, Blumenfeld AM, Cady RK, et al. OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline. J Neurol Sci. 2013;331:48–56.

[28] Ahmed F, Zafar HW, Buture A, et al. Does analgesic overuse matter? Response to onabotulinumtoxinA in patients with chronic migraine with or without medication overuse. SpringerPlus. 2015;4:589.

[29] Aurora SK, Dodick DW, Turkel CC, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia. 2010;30:793–803.

[30] Diener HC, Dodick DW, Aurora SK, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia. 2010;30:804–14.

[31] Botox [package insert]. Madison, NJ: Allergan USA, Inc. 2021.

[32] Dodick DW, Turkel CC, DeGryse RE, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache. 2010;50:921–36.

[33] Blumenfeld AM, Stark RJ, Freeman MC, et al. Long-term study of the efficacy and safety of onabotulinumtoxinA for the prevention of chronic migraine: COMPEL study. J Headache Pain. 2018;19:13.

[34] Ahmed F, Gaul C, Garcia-Monco JC, et al. An open-label prospective study of the real-life use of onabotulinumtoxinA for the treatment of chronic migraine: the REPOSE study. J Headache Pain. 2019;20:26.

[35] Andreou AP, Trimboli M, Al-Kaisy A, et al. Prospective real-world analysis of onabotulinumtoxinA in chronic migraine post-National Institute for Health and Care Excellence UK technology appraisal. Eur J Neurol. 2018;25:1069–e83.

[36] Dominguez C, Pozo-Rosich P, Torres-Ferrus M, et al. OnabotulinumtoxinA in chronic migraine: predictors of response. A prospective multicentre descriptive study. Eur J Neurol. 2018;25:411–6.

[37] Khalil M, Zafar HW, Quarshie V, et al. Prospective analysis of the use of onabotulinumtoxinA (BOTOX) in the treatment of chronic migraine; real-life data in 254 patients from Hull, U.K. J Headache Pain. 2014;15:54.

[38] Negro A, Curto M, Lionetto L, et al. A two years open-label prospective study of onabotulinumtoxinA 195 U in medication overuse headache: a real-world experience. J Headache Pain. 2016;17:1.

[39] Negro A, Curto M, Lionetto L, et al. OnabotulinumtoxinA 155 U in medication overuse headache: a two years prospective study. SpringerPlus. 2015;4:826.

[40] Stark C, Stark R, Limberg N, et al. Real-world effectiveness of onabotulinumtoxinA treatment for the prevention of headaches in adults with chronic migraine in Australia: a retrospective study. J Headache Pain. 2019;20:81.

[41] Vernieri F, Paolucci M, Altamura C, et al. OnabotulinumtoxinA for chronic migraine: a real-life Italian multicenter experience. Neurol Sci. 2018;39(Suppl 1):171–2.

[42] Vikelis M, Argyriou AA, Dermitzakis EV, et al. Onabotulinumtoxin-A treatment in Greek patients with chronic migraine. J Headache Pain. 2016;17:84.

[43] Aurora SK, Dodick DW, Diener HC, et al. OnabotulinumtoxinA for chronic migraine: efficacy, safety, and tolerability in patients who received all five treatment cycles in the PREEMPT clinical program. Acta Neurol Scand. 2014;129:61–70.

[44] Silberstein SD, Dodick DW, Aurora SK, et al. Per cent of patients with chronic migraine who responded per onabotulinumtoxinA treatment cycle: PREEMPT. J Neurol Neurosurg Psychiatry. 2015;86:996–1001.

[45] Blumenfeld A, Stark R, Manack Adams A, et al. Efficacy and safety of onabotulinumtoxinA in an open-label study for the prophylactic treatment of chronic migraine in adult patients: COMPEL [abstract]. Cephalalgia. 2016;36(Suppl 1):27–8.

[46] Blumenfeld AM, Tepper SJ, Robbins LD, et al. Effects of onabotulinumtoxinA treatment for chronic migraine on common comorbidities including depression and anxiety. J Neurol Neurosurg Psychiatry. 2019;90:353–60.

[47] Herd CP, Tomlinson CL, Rick C, et al. Cochrane systematic review and meta-analysis of botulinum toxin for the prevention of migraine. BMJ Open. 2019;9:e027953.

[48] Ray JC, Hutton EJ, Matharu M. OnabotulinumtoxinA in migraine: a review of the literature and factors associated with efficacy. J Clin Med. 2021;10:2898.

[49] Frampton JE, Silberstein S. OnabotulinumtoxinA: a review in the prevention of chronic migraine. Drugs. 2018;78:589–600.

[50] Matharu M, Halker R, Pozo-Rosich P, et al. The impact of onabotulinumtoxinA on severe headache days: PREEMPT 56-week pooled analysis. J Headache Pain. 2017;18:78.

[51] Lipton RB, Rosen NL, Ailani J, et al. OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine over one year of treatment: pooled results from the PREEMPT randomized clinical trial program. Cephalalgia. 2016;36:899–908.

[52] Aurora SK, Winner P, Freeman MC, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. Headache. 2011;51:1358–73.

[53] Rothrock JF, Manack Adams A, Lipton RB, et al. FORWARD study: evaluating the comparative effectiveness of onabotulinumtoxinA and topiramate for headache prevention in adults with chronic migraine. Headache. 2019;59:1700–13.

[54] Rothrock JF, Bloudek LM, Houle TT, et al. Real-world economic impact of onabotulinumtoxinA in patients with chronic migraine. Headache. 2014;54:1565–73.

[55] Khanal S, Underwood M, Naghdi S, et al. A systematic review of economic evaluations of pharmacological treatments for adults with chronic migraine. J Headache Pain. 2022;23:122.

[56] Mathew NT, Jaffri SF. A double-blind comparison of onabotulinumtoxin a (BOTOX) and topiramate (TOPAMAX) for the prophylactic treatment of chronic migraine: a pilot study. Headache. 2009;49:1466–78.

[57] Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2016;86:1818–26.

[58] Brin MF, Fahn S, Moskowitz C, et al. Localized injections of botulinum toxin for the treatment of focal dystonia and hemifacial spasm. Mov Disord. 1987;2:237–54.

[59] Wissel J, Ganapathy V, Ward AB, et al. OnabotulinumtoxinA improves pain in patients with post-stroke spasticity: findings from a randomized, double-blind, placebo-controlled trial. J Pain Symptom Manage. 2016;52:17–26.

[60] Jakubowski M, McAllister PJ, Bajwa ZH, et al. Exploding versus imploding headache in migraine prophylaxis with botulinum toxin A. Pain. 2006;125:286–95.

[61] Burstein R, Blumenfeld AM, Silberstein SD, et al. Mechanism of action of onabotulinumtoxinA in chronic migraine: a narrative review. Headache. 2020;60:1259–72.

[62] Goadsby PJ, Holland PR, Martins-Oliveira M, et al. Pathophysiology of migraine: a disorder of sensory processing. Physiol Rev. 2017;97:553–622.

[63] Bigal ME, Lipton RB. Concepts and mechanisms of migraine chronification. Headache. 2008;48:7–15.

[64] Blasi J, Chapman ER, Link E, et al. Botulinum neurotoxin A selectively cleaves the synaptic protein SNAP-25. Nature. 1993;365:160–3.

[65] Pirazzini M, Rossetto O, Eleopra R, et al. Botulinum neurotoxins: biology, pharmacology, and toxicology. Pharmacol Rev. 2017;69:200–35.

[66] Blumenfeld AM, Silberstein SD, Dodick DW, et al. Insights into the functional anatomy behind the PREEMPT injection paradigm: guidance on achieving optimal outcomes. Headache. 2017;57:766–77.

[67] Hubbard CS, Becerra L, Smith JH, et al. Brain changes in responders vs. non-responders in chronic migraine: markers of disease reversal. Front Hum Neurosci. 2016;10:497.