OnabotulinumtoxinA in the treatment of patients with chronic migraine: clinical evidence and experience

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Abstract: Chronic migraine is a debilitating neurobiological disorder that affects approximately 1.4–2.2% of the population worldwide. Patients with chronic migraine have 15 or more headache days per month, with at least 8 days per month that meet the criteria for migraine. Injection of onabotulinumtoxinA, using a standardized injection protocol, was approved by the US Food and Drug Administration in 2010 for the treatment of chronic migraine. The approval was made based on results from two large, randomized, double-blind placebo-controlled trials: the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) trials. Since then, numerous studies have been performed investigating the short-term and long-term benefits, risks and complications of the use of onabotulinumtoxinA injections for the treatment of chronic migraine. The purpose of this narrative review is to describe the currently available clinical evidence for the use of onabotulinumtoxinA injections for treating patients with chronic migraine.

Keywords: botulinum toxins, humans, migraine disorders, type A

Introduction

Chronic migraine is a debilitating neurobiological disorder that affects about 1.4–2.2% of the population worldwide.1 According to the International Classification of Headache Disorders, third edition (beta version), chronic migraine is defined as headache occurring on 15 or more days per month for more than 3 months, and on at least 8 days per month, has the features of migraine headache, which include at least two of the following four qualities: unilateral location, pulsatile quality, moderate or severe pain intensity and aggravation by physical activity, as well as at least one of the following: nausea, vomiting, photophobia and phonophobia (Table 1).2

Studies from different parts of the world have shown that patients with chronic migraine have a higher degree of disability and burden, a greater chance of missing family activities, reduced productivity and greater healthcare resource utilization than those who have episodic migraine.3–5 Patients with chronic migraine suffer from a lower health-related quality of life and higher levels of anxiety and depression, and are less likely to be able to work.4 Moreover, chronic migraine is a critical factor for perceived stress that affects the quality of life of migraine patients.6

Despite the high prevalence of chronic migraine, many patients do not receive the appropriate diagnosis and even fewer patients receive appropriate treatment. In the Chronic Migraine Epidemiology and Outcomes (CaMEO) study, a large population-based epidemiology study in the United States, 1254 of the participants met the diagnostic criteria for chronic migraine.7 Of those patients, only 512 (41%) reported discussing headache with a healthcare provider. Of the 512, only 126 (25%) received an accurate diagnosis, and of the 126, only 56 (44%) received both acute and preventive treatment. To help care providers worldwide decrease the burden of chronic migraine, evidence-based discussions of the clinical trials and patient care experiences are crucial.
An adequate treatment plan for chronic migraine includes both acute and preventive medications. Acute medications are those given to alleviate the acute head pain and discomfort of a migraine attack and include nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, triptans, combination analgesics, or less ideally, butalbital and opioid medications. The European Federation of Neurological Societies guideline recommends NSAIDs and triptans for the acute treatment of migraine attacks (level A recommendation). The guideline also recommends the use of metoclopramide and domperidone before the intake of an NSAID or triptan (level B recommendation).\(^8\) The acute medications should only be used on an as-needed basis, and patients should be advised not to take the medications for more than 10 to 15 days per month, according to the type of acute medication, to avoid developing a medication-overuse headache (MOH) (Table 2). Preventive medications are those taken daily to decrease the frequency, duration, and severity of migraine headaches. Preventive medications should be considered when patients are having three or more headache episodes per month or when headache substantially interferes with daily activities. These medications can also be used when acute medications are ineffective, contraindicated, or overused.\(^9\) Preventive medications should be initiated for patients with chronic migraine, and evidence-based prophylactic medications for episodic migraine are often used for the treatment of chronic migraine. Oral medications that are commonly used include antiepileptics, such as topiramate; antihypertensives, such as beta blockers; and antidepressants, such as tricyclic antidepressants.\(^{10,11}\) Flunarizine is also considered a drug of first choice for the prophylaxis of migraine in Europe.\(^8\) Among these medications, topiramate has been shown to be effective in large, randomized placebo-controlled trials of patients with chronic migraine.

In 2010, onabotulinumtoxinA was approved by the US Food and Drug Administration (FDA) for the treatment of chronic migraine. Its approval was based on the results of the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) studies: two large, randomized double-blind, placebo-controlled trials.\(^{12,13}\) However, currently onabotulinumtoxinA is the only treatment option approved by the FDA as a preventive medication for chronic migraine. Since its approval, the use of onabotulinumtoxinA for patients with chronic migraine has been increasing. The purpose of this article is to review the clinical evidence and experience using onabotulinumtoxinA to treat patients with chronic migraine.

### Currently available guidelines

In 2016, the Guideline Development Subcommittee of the American Academy of Neurology published an updated practice guideline summary for the use of botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache.\(^{14}\) In this guideline, level A means that the intervention is effective and should be offered. Level B means that the intervention is probably
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The investigators reviewed the clinical trials published after the previous 2008 guideline and concluded that level A evidence exists to support the established and effective use of onabotulinumtoxinA for chronic migraine and recommended its use to increase patients’ headache-free days. In addition, the guidelines stated that level B evidence existed for the probable effectiveness of onabotulinumtoxinA in improving health-related quality of life (HRQoL) for patients with chronic migraine. For episodic migraine, the updated guideline provided level A evidence that onabotulinumtoxinA was ineffective and should not be offered. For chronic, tension-type headaches, there was level B evidence that onabotulinumtoxinA was probably ineffective (Table 3).14

**Table 2. The International Classification for Headache Disorders (ICHD)-3 Beta Diagnostic Criteria for Medication-Overuse Headache.**

| Medication-overuse headache |
|----------------------------|
| A. Headache occurring $\geq 15$ days per month in a patient with a preexisting headache disorder |
| B. Regular overuse for $>3$ months of one or more drugs that can be taken for acute or symptomatic treatment of headache. Patients should be coded for one or more subtypes of medication-overuse headaches, according to the specific medication(s) overused and the criteria for each below (MOH subtypes). |
| C. Not better accounted for by another ICHD-3 diagnosis |

**MOH subtypes**

| Ergotamine-overuse headache: |
| Regular intake of ergotamine on $\geq 10$ days per month for $>3$ months |

| Triptan-overuse headache: |
| Regular intake of one or more triptans in any formulation, on $\geq 10$ days per month for $>3$ months |

| Simple analgesic-overuse headache: |
| Paracetamol (acetaminophen)-overuse headache |
| Regular intake of paracetamol on $\geq 15$ days per month for $>3$ months |
| Acetylsalicylic-acid-overuse headache |
| Regular intake of acetylsalicylic acid on $\geq 15$ days per month for $>3$ months |
| Other NSAID-overuse headache |
| Regular intake of one or more NSAIDs other than acetylsalicylic acid on $\geq 15$ days per month for $>3$ months |

| Opioid-overuse headache |
| Regular intake of one or more opioids on $\geq 10$ days per month for $>3$ months |

| Combination-analgesic-overuse headache |
| Regular intake of one or more combination analgesic medications on $\geq 10$ days/month for 3 months |

(The term combination analgesic is used specifically for formulations combining drugs of two or more classes, each with analgesic effect or acting as adjuvants)

| Medication-overuse headache attributed to multiple drug classes not individually overused |
| Regular intake of any combination of ergotamine, triptans, simple analgesics, NSAIDs, or opioids on a total of $\geq 10$ days per month for $>3$ months without overuse of any single drug or drug class alone |

| Medication-overuse headache attributed to unverified overuse of multiple drug classes |
| Both of the following: |
| 1. Regular intake of any combination of ergotamine, triptans, simple analgesics, NSAIDs, or opioids on $\geq 10$ days per month for $>3$ months |
| 2. Identity, quantity or pattern of use or overuse of these classes of drug cannot be reliably established |

| Medication-overuse headache attributed to other medication |
| Regular overuse on $\geq 10$ days per month for $>3$ months of one or more medications other than those described above, taken for acute or symptomatic treatment of headache |

*ICHD-3, International Classification of Headache Disorders, 3rd edition. Adapted from Headache Classification Committee of the IHS. Used with permission.*

MOH, medication-overuse headache; NSAID, nonsteroidal anti-inflammatory drug.
The PREEMPT studies are two class I trials that established the efficacy of onabotulinumtoxinA for chronic migraine prophylaxis. The multicenter, phase III, 24-week, double-blind, parallel-group, placebo-controlled studies were followed by a 32-week, open-label, single-treatment onabotulinumtoxinA phase. A total of 1384 patients were included from 122 sites across 6 countries in Europe and North America. In the double-blind phase, patients were randomized to onabotulinumtoxinA (155–195 U, \( n = 688 \)) or placebo (\( n = 696 \)). Following the double-blind phase, all patients received onabotulinumtoxinA, administered every 12 weeks as 31 fixed-site, fixed-dose injections (5 U/site) across seven specific head and neck muscle areas. The data from PREEMPT 1 and 2 were then pooled for analysis. The results showed a statistically significant decrease in the frequency of headache days at week 24, which was the primary endpoint for the pooled analysis, and favored those who received onabotulinumtoxinA compared with placebo (−8.4 versus −6.6; \( p < 0.001 \)). There was a significantly greater reduction in all secondary endpoints, including mean change from baseline compared with week 24 in frequency of migraine days, total cumulative hours of headache, frequency of headache episodes, and the proportion of patients with a severe score (>60) on the Headache Impact Test-6 (HIT-6), with the exception that there was no significant difference for frequency of acute headache medication intake between the onabotulinumtoxinA and placebo groups. The results showed that onabotulinumtoxinA is an effective preventive treatment for patients with chronic migraine.13,15–17

Other than the primary and secondary outcomes outlined above, studies also demonstrated that onabotulinumtoxinA injections improved HRQoL in patients with chronic migraine. The validated HIT-6 score and the Migraine-Specific Quality of Life Questionnaire (MSQ) score were used as the outcome measures. The HIT-6 score assessed how headaches influence a patient’s life in domains such as pain, psychological distress, social limitations and cognitive functioning. The MSQ questionnaire evaluated the quality of life from domains including the effects of migraine on daily social or work-related activities (including restricting or prohibiting activities) and the emotions associated with migraine. There was a significant between-group difference favoring onabotulinumtoxinA versus placebo during the 24-week double-blind phase for HRQoL measures. There was continued improvement in the HIT-6 score and the HRQoL measures during the 32-week open-label phase, when all patients were receiving onabotulinumtoxinA injections. This study showed that the benefits of onabotulinumtoxinA injections on HRQoL persisted throughout the 56-week study period.18

### Table 3. American Academy of Neurology Practice Guideline Summary for onabotulinumtoxinA in the treatment of headache.a

| For the treatment of chronic migraine: | 1. OnabotulinumtoxinA is established as effective and should be offered to increase headache-free days (level A)  
2. OnabotulinumtoxinA is probably effective and should be considered to improve health-related quality of life (level B) |
| For the treatment of episodic migraine: | 1. OnabotulinumtoxinA is established as ineffective and should not be offered for episodic migraine (level A) |
| For the treatment of chronic tension-type headaches: | 1. OnabotulinumtoxinA is probably ineffective for chronic tension-type headaches (level B) |

*a Level A: recommendation for effectiveness signifies intervention should be offered. Level B: recommendation for effectiveness signifies intervention should be considered. Data from Simpson et al.14*

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*Effect of onabotulinumtoxinA injections in chronic migraine: clinical experiences*

After the PREEMPT trials were published, several groups of clinicians also shared real-life experiences of using onabotulinumtoxinA injections, according to the PREEMPT protocol, to treat patients with chronic migraine.

A group in Spain reported the effect of onabotulinumtoxinA injections in patients with chronic migraine who did not respond to two different
preventive medications (topiramate and at least one other preventive therapy). Among the initial 52 patients enrolled, 39 received second injections, and others received one injection. There was a significant decrease in all variables compared with baseline after two injection sessions (headache days, migraine days, medication intake days, triptan intake days). Similarly, another group from England reported their experiences from a large cohort of patients recruited from a tertiary headache center. Full data were available for 254 of 284 patients injected who had one or two sessions of onabotulinumtoxinA injections. Most patients (94%) had three different preventive treatments fail before onabotulinumtoxinA, in accordance with the United Kingdom’s National Institute for Health and Clinical Excellence (NICE) guideline. This prospective study reported significant differences in endpoints before and after treatment, including decreased headache days per month (−7, *p* < 0.001) and increased number of crystal-clear (headache free) days (+7, *p* < 0.001). In addition, there was a significant increase in their HRQoL from the HIT-6 score (reduction of 10 units, *p* < 0.001).

From the results of this trial and the responder rate in the PREEMPT trial, the authors suggested that onabotulinumtoxinA could be given after first-line oral preventive treatment. However, its cost may hinder the use to more refractory headaches and three failed oral preventive treatments.

Recently, several Allergan-initiated studies (Allergan, Irvine, CA, USA), such as the REPOSE trial, reported the treatment effect of onabotulinumtoxinA in a real-world clinical setting. Efficacy, safety, and tolerability data were collected every 12 weeks. The results showed that most patients and physicians were satisfied or very satisfied with continued onabotulinumtoxinA treatment. There was a sustained reduction in headache days, as well as a significant improvement in quality of life. Another study reported a satisfaction and safety profile for onabotulinumtoxinA for chronic migraine. More than one treatment-related adverse event (including neck pain, eyelid ptosis, worsening of migraine) was reported in 25.1% patients. The authors concluded that the satisfaction and safety profile were consistent with published data from the PREEMPT trials.

Researchers have also investigated the effect of onabotulinumtoxinA injections on depression in patients with chronic migraine. A group of researchers in the US performed a retrospective analysis of 359 patients with chronic migraine who received onabotulinumtoxinA injections. The HIT-6 score was used to indicate improvement in headache severity, and the Patient Health Questionnaire-9 (PHQ-9) score was used as an indicator for depression. They compared the group of patients who had significant improvement in the HIT-6 score with those who did not and computed the proportion of patients who had significant improvement in their PHQ-9 score in both groups. They concluded that the improvement in patients’ depression after onabotulinumtoxinA injections correlated with the improvement in headache severity.

Although studies of real-life experiences are useful, they have limitations, including a potentially high placebo-response rate, lack of a control group, and lack of data for long-term responses to onabotulinumtoxinA injections. Therefore, safety, efficacy and tolerability of onabotulinumtoxinA for patients with chronic migraine are also being addressed in other types of studies. Researchers have designed an open-label, multicenter international study called the Chronic Migraine OnabotulinumtoxinA Prolonged Efficacy Open Label (COMPEL), which is currently ongoing. According to protocols published in 2015, this study will enroll approximately 500 patients. The primary outcome is the mean change in headache frequency (headache days per 28-day period) at 108 weeks (after nine treatments, one every 12 weeks) compared with baseline. Other secondary endpoints include the change in headache frequency at 60 weeks (after five treatments), the change in total HIT-6 score at 108 weeks (after nine treatments) compared with baseline, and long-term (108 weeks) safety and tolerability. This study should contribute to understanding whether onabotulinumtoxinA will be effective long-term as a prophylactic treatment for those who suffer from chronic migraine.

**OnabotulinumtoxinA versus oral preventive treatment**

Several studies have compared the efficacy of onabotulinumtoxinA with that of oral migraine medications for prophylaxis of chronic headache. One group of investigators randomized 72 patients with chronic migraine to two groups and treated them with 25 or 50 mg of amitriptyline or 250 U of onabotulinumtoxinA. They concluded that onabotulinumtoxinA was as effective as amitriptyline for the prophylactic treatment of chronic

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migraine in that there was no significant difference in endpoints, including the percentage of patients who reached a 50% reduction in headache days [67.8% of the patients in the onabotulinumtoxinA group and 72% of the patients in the amitriptyline group, \( p = 0.78 \); relative risk (RR) = 0.94; confidence interval (CI) = 0.11–8.0] and the reduction in pain intensity (50% in the onabotulinumtoxinA group and 55.6% in the amitriptyline group, \( p = 0.79; \text{RR} = 1.11; \text{CI} = 0.32–3.8 \)).

Other than onabotulinumtoxinA, topiramate is the only other treatment option that has undergone double-blind placebo-controlled studies to support its efficacy for chronic migraine prophylaxis. A group of investigators used data from the PREEMPT trial and the topiramate trial to compare the safety and efficacy of onabotulinumtoxinA with topiramate, noting the limitations for a cross-trial comparison. They compared outcome measures by using the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) framework and concluded that there were significant and clinically relevant treatment benefits for both onabotulinumtoxinA and topiramate, and there is evidence to support similar efficacy of both treatments as preventive therapy for patients with chronic migraine. Ultimately, individual patients will decide which treatment is of more clinical meaningfulness to them.

In a large study from a US-based, healthcare claims database, the authors analyzed healthcare utilization of patients with chronic migraine who received either onabotulinumtoxinA or oral preventive medication. Patients treated with onabotulinumtoxinA had significantly fewer headache-related visits to the emergency department and hospitalizations than patients who received prophylactic oral migraine medication at 6, 9, and 12 months after starting therapy; the significant difference remained when only level A oral migraine medications were included. The study was limited by its retrospective nature and the use of the commercial insurance claims database, with the assumption that the codes of the International Classification of Disease, 9th Revision for chronic migraine and comorbidities reflected accurate headache diagnoses.

**OnabotulinumtoxinA in chronic migraine with medication overuse**

Chronic migraine is commonly associated with medication overuse. A systematic review of global prevalence indicated that about half of the individuals with chronic migraine reported associated medication overuse, although the range of the estimate varied from 31% to 69%. Similarly, in large randomized controlled trials investigating the effect of preventive medications for chronic migraine, 65–85% of patients had medication overuse at baseline.

In the PREEMPT studies, medication overuse was used as a stratifying variable when patients were randomized to onabotulinumtoxinA or placebo. Of the 1384 patients enrolled, 65% met medication-overuse criteria and were randomized 1:1 to two arms. A planned secondary analysis for chronic migraine within the medication-overuse subgroup showed similar results to those of the chronic migraine group. At week 24, significant differences existed between the mean changes for the treatment group from baseline, favoring onabotulinumtoxinA over placebo for the primary endpoint (8.2 vs. 6.2) and for the secondary endpoints, including frequency of days with migraine, days with moderate to severe headache, and cumulative hours of headache on headache days, migraine episodes, and the percentage of patients with a severe HIT-6 category.

Other studies have demonstrated that onabotulinumtoxinA is effective for patients with chronic migraine and medication overuse. A tertiary care headache center in the United Kingdom reported real-life experiences of using onabotulinumtoxinA to treat patients with chronic migraine, with or without medication overuse. Patients were enrolled according to the NICE guideline, and all patients had treatment failures with at least three headache preventive medications. About half of the enrolled patients were overusing acute headache medications. Comparisons were made between the groups (chronic migraine with medication overuse and chronic migraine without medication overuse). For both groups, there were significant decreases after treatment in headache days, migraine days, days of medication overuse, and days of triptan intake compared with baseline. Between-group comparisons showed no significant difference in headache days at a 50% or 75% responder rate. A responder was defined as a patient who had a 50% or 75% reduction in the number of days with symptoms. The results suggested that onabotulinumtoxinA was equally effective for patients with chronic migraine, with or without medication overuse. The study was...
limited by its open-label design. In addition, the data were collected after only one set of onabotulinumtoxinA injections, so the long-term response is unknown.

Another study reported the long-term (21 months) effects of onabotulinumtoxinA injections for 57 patients with chronic migraine and medication overuse who received the injections according to the PREEMPT protocol: every 3 months and uninterrupted for at least seven cycles. The patients were overusing triptans, NSAIDs, codeine-containing drugs, tramadol or others, often daily. The results showed that there was a significant reduction of the headache index (number of headache days/days observed) and the mean number of analgesic agents taken daily compared with baseline at any injection session. Of note, the headache index was powerfully reduced to 22% after two treatment cycles and continued to decrease to 38% after seven cycles. This report indicated the importance of continuous treatment to sustain and improve the outcome of patients with chronic migraine and medication overuse. The limitation of this study was the lack of a control group.

In terms of the dosage of onabotulinumtoxinA to treat patients with chronic migraine and medication overuse, the PREEMPT trial used 155 to 195 U at the physician’s discretion. The efficacy of this dosage was compared by one group during a 2-year period. To be included, patients needed to have one treatment failure of a preventive medication or one withdrawal attempt. Among the patients enrolled, 143 patients were treated with 195 U of onabotulinumtoxinA, and 132 patients were treated with 155 U. The baseline demographic characteristics of the groups were similar. The authors found that there was significant improvement in all headache parameters compared with baseline. Moreover, between-group comparisons showed a significantly larger reduction in migraine days, headache days, and HIT-6 scores at every treatment session for those treated with 195 U of onabotulinumtoxinA compared with those treated with 155 U. There was no significant difference in the safety and tolerability profile. Although the authors suggested that 195 U of onabotulinumtoxinA appeared to be more effective than 155 U for patients with chronic migraine with medication overuse, the study was limited by lack of randomization and double-blind process, which raised the concern of a potential placebo effect.

Cost-based analysis

Although the efficacy of onabotulinumtoxinA for chronic migraine prophylaxis has been established, few reports have described the cost savings of this relatively expensive treatment option. A US-based group analyzed data from an open-label study of 230 patients with chronic migraine who had more than two preventive medications fail and who had received two courses of onabotulinumtoxinA. They investigated the utilization of healthcare, including migraine-related visits to the emergency department, urgent care clinic or hospital at 6 months before the initial onabotulinumtoxinA session and 6 months after the onabotulinumtoxinA treatments. They estimated costs as follows: onabotulinumtoxinA, $1050 each session; urgent care, $130.28 per visit; hospitalization, $6155.42 per time; emergency department, $483.72 per visit. There was a significant reduction in the mean number of emergency department and urgent care visits after onabotulinumtoxinA treatment. The mean number of hospitalizations also decreased, although the number did not reach significance at $p < 0.05$. The authors analyzed the average reduction of the treatment-related costs from the decreased emergency department and urgent care visits, as well as hospitalizations and found the decrease to be $1219.33 per patient, which would offset 50% of the total estimated cost for a 6-month treatment with onabotulinumtoxinA. The limitation of this study was the open-label design and the region-specific results, as healthcare systems differ substantially around the world. Long-term data would also be needed to further investigate the cost effectiveness of onabotulinumtoxinA treatments.

Other methods of using onabotulinumtoxinA for the treatment of chronic migraine

Other methods are being investigated for using onabotulinumtoxinA as a preventive headache medication, other than according to the PREEMPT protocol. In a pilot study of 10 patients, a sphenopalatine injection of onabotulinumtoxinA was used to treat intractable chronic migraine. All 10 patients had previous, intolerable adverse effects or contraindications to at least three oral preventive medications. Patients recorded baseline headache characteristics in diaries for 4 weeks, after which they received bilateral sphenopalatine injections with 25 U of onabotulinumtoxinA suspended in 0.5 mL of normal saline. The injections were done in
outpatient settings with the patients awake. To inject the onabotulinumtoxinA accurately, a percutaneous, infrrazygomatic approach was used, and surgical navigation aided placement of the injection device. The primary outcomes were safety and adverse events. All patients experienced adverse events, such as local symptoms, dry eye, visual disturbances, and temporomandibular joint problems, although none of the adverse events were considered serious, and most resolved within 12 weeks after the injections. For efficacy outcome, an intention-to-treat analysis showed a significant reduction of moderate and severe headache days 2 months after the injections compared with baseline (7.6 ± 7.6 days at month 2; 16.3 ± 6.2 days at baseline), and most patients had sustained improvement 3 months after treatment. The authors indicated that these results supported the need for a future randomized placebo-controlled study to establish the safety, efficacy, and duration of response of this novel treatment.

Adverse events of onabotulinumtoxinA injection for chronic migraine
During the double-blind phase (first 24 weeks) of the PREEMPT program, 4% of patients in the onabotulinumtoxinA group and 1% of patients in the placebo group left the study because of an adverse event. The most common treatment-related events were muscle weakness, neck pain, eyelid ptosis, facial paresis, muscle tightness, myalgia, and injection site pain. Neck pain was the most common side effect during the double-blind phase, occurring in 7% of the patients in the onabotulinumtoxinA group and 2% of patients in the placebo group; no unexpected adverse events were reported. A few recent reports have described unusual adverse effects after onabotulinumtoxinA administration for chronic migraine. One reported a case of a 72-year-old woman with chronic migraine who had been receiving onabotulinumtoxinA injections for approximately 3 years when she developed a painful vesicular rash in her right trigeminal nerve V1 (RV1) distribution, 48 hours after receiving her regular injection.37 She had a history of herpes zoster on her lower back with subsequent postherpetic neuralgia. The authors postulated that local trauma from the minor procedure might have been sufficient to activate the herpes zoster, such as in this case of herpes zoster ophthalmicus. Another recent report described an unusual adverse effect of onabotulinumtoxinA injection.38 A 50-year-old man with chronic migraine received his first onabotulinumtoxinA injection, which was done according to the PREEMPT protocol (155 U injected into 31 sites). At 2 weeks after his first injection, he developed two symmetrical lumps in the forehead, which gradually disappeared over 3 months. However, after his second injection, the lumps developed again. Interestingly, the providers injected an additional 5 U of onabotulinumtoxinA in the middle of the frontalis muscles bilaterally, which gradually normalized his forehead shape. The authors recommended careful clinical evaluation of the static and dynamic movement of the upper face before injections to determine if any abnormal muscle morphology or contractions existed that might cause similar effects.

Conclusion
OnabotulinumtoxinA is a well-tolerated, effective preventive medication for patients with chronic migraine. However, more long-term reports of efficacy and analyses of cost-effectiveness are needed to assist clinicians in deciding on the best preventive medication for patients with chronic migraine.

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