ABSTRACT

Botulinum toxin type A has been studied for the treatment of headache disorders since the early 1990s when its usefulness for this diagnosis was coincidentally discovered during the course of treatments for hyperfunctional glabellar lines and certain movement disorders. This article reviews the data from clinical studies using botulinum toxin type A for chronic daily headache (CDH) leading up to current, ongoing phase III trials. The Mathew and Silberstein late phase II double-blind, randomized, placebo-controlled trials using a modified “follow-the-pain” approach and a fixed-site approach are discussed, including a summary of primary and secondary endpoint results. In addition, results from the subanalyses conducted by Dodick are included. Several key aspects to optimize use of botulinum toxin type A for CDH also are discussed, including dosage and injection sites.

A BRIEF HISTORY OF THE USE OF BOTULINUM TOXIN TYPE A FOR HEADACHES

The concept of using botulinum toxin type A for headache is relatively new. The first citation in the literature that refers to a possible connection between botulinum toxin type A and headache first appeared in 1994 when a double-blind trial for the use of botulinum toxin type A for hyperfunctional glabellar lines yielded the surprising finding that incidental, coexistent headaches might also be relieved. In the same year, Zwart et al conducted a small study of 6 patients with chronic tension-type headache (CTTH) to attempt to ascertain the role of pericranial muscle tension in the pathophysiology of tension-type headache (TTH).2 The pericranial muscles were paralyzed in 6 patients with CTTH, using botulinum toxin. The investigators injected the temporal muscle on 1 side, using the other side as a control. In this study, the authors failed to find any significant reduction in pain intensity, as measured by the visual analog scale, or any changes in pressure pain threshold, as measured by an algometer. However, they only treated a limited number of patients, and only 1 pericranial muscle was injected systematically. Despite the results, this small investigation opened the door to the study of botulinum toxin type A as a treatment for headache.2

In 1998, Binder et al conducted a larger, retrospective study of 96 patients with chronic migraine (CM) identified through movement disorder and cosmetic surgery clinics.3 All received botulinum toxin type A injections into the glabellar, temporalis, and occipitalis regions. This was a fixed-site, variable-dose protocol, with a mean total dose of 26 ± 14 U. Treatment response was defined as complete (ie, elimination of headaches), partial (ie, ≥50% reduction in frequency or severity of headaches), or no response (ie, <50% reduction in frequency or severity of headaches). Their results revealed that 51% of patients had a complete response, 28% of patients showed a partial response, and 21% of patients showed no response.3

The first double-blind study of botulinum toxin type A for headache was published in 1999, reporting on research conducted by Relja and Korsic.4 In 2000, Binder et al’s full report of the improvement in migraine frequency with glabellar injection appeared,
as did the first double-blind trial examining the use of forehead injections for headache. Silberstein et al conducted a double-blind, vehicle-controlled investigation of patients \((n = 123)\) who experienced 2 to 8 moderate-to-severe migraines per month. Researchers randomly assigned these patients to 1 of 3 groups: placebo \((n = 41)\), 25 U botulinum toxin type A \((n = 42)\), or 75 U of botulinum toxin type A \((n = 40)\). This was a fixed-site, fixed-dose trial, and subjects were injected into muscles of the frontalis, glabellar, and bilateral temporalis regions. The study endpoint was a significantly greater reduction in monthly headaches from baseline as compared to placebo. Compared to the placebo group, the 25-U group demonstrated significant improvement \((P < .05)\) for frequency of moderate-to-severe migraines at months 2 and 3. Interestingly, the 75-U group was not differentiated from the placebo group.

Additional migraine measures improved with the administration of 25 U of botulinum toxin type A, including the frequency of all migraines, migraine severity, days per month requiring acute medication use, and migraine-associated vomiting. Treatment-related adverse events were transient and dose-dependent. They included blepharoptosis, diplopia, and muscle weakness in the immediate region of injection. Clinical experience has since shown that these adverse events may be avoided by more cautious placement of injections and appropriate dose adjustments.

Beginning in 2001, late phase II studies were initiated to examine the use of botulinum toxin type A for patients with episodic migraine (EM) in addition to chronic daily headache (CDH). Blumenfeld conducted a retrospective, open-label trial of 271 patients with various headache disorders including CDH \((>15\) headache-days/month; 40%), episodic TTH (12%), EM (12%), and patients with so-called mixed headache \(<15\) headache-days/month, combination of migraine and TTH; 36%). These patients were selected because they were refractory to conventional oral medication regimens (76%), had experienced medication overuse (49%), and/or experienced neck and shoulder pain (18%). In addition, 32% of patients reported depression as a comorbidity. The methodology was a follow-the-pain regimen with a mean dose of 63.2 ± 14.5 U and an average of 3.4 ± 1.6 treatments administered at approximately 12-week intervals. The author collected headache frequency and intensity data for 117 patients (Figures 1 and 2). Blumenfeld determined that botulinum toxin type A significantly reduced the frequency of headache from an average of 18.9 ± 10.3 (at baseline) to 8.3 ± 8.9 (at last treatment) headache days per month \((P < .001)\), representing a
56% reduction for all headache types. Headache intensity scores decreased from 2.4 ± 0.6 (at baseline) to 1.8 ± 0.8 (at last treatment, \(P < .001\))—a 25% reduction. In this investigation, treatment significantly lowered headache intensity scores for patients with migraine (\(P < .001\)), CDH (\(P < .001\)), and mixed headache (\(P = .002\)) and showed a trend toward significance with episodic TTH (\(P = .064\)).^7

Recent late phase II data from randomized, controlled trials for the use of botulinum toxin type A in prophylaxis of CDH have been published.^9,10 Although these trials did not meet their primary endpoint (a significant mean change from baseline in the frequency of headache-free days at day 180 for the placebo nonresponder group), the treatment did result in patients having, on average, approximately 7 more headache-free days compared to baseline. The treatment met secondary efficacy outcome measures, including the percentage of patients experiencing at least a 50% decrease in the frequency of headache days, in addition to the reduction in headache frequency. In a subanalysis of the 228 subjects (64%) not taking prophylactic medication, the mean frequency of headaches per 30 days at baseline was 14.1 for the botulinum toxin type A group and 12.9 for the placebo group (\(P = .205\)). After 2 injection sessions, the change in the mean frequency of headaches per 30 days was \(-7.8\) in the botulinum toxin type A group compared with \(-4.5\) in the placebo group (\(P = .032\)) and continued to improve after a third injection session. Botulinum toxin type A treatment resulted in a more than 50% reduction in headache frequency in more than 50% of patients after 3 injection sessions as compared to baseline. Statistically significant differences between botulinum toxin type A and placebo also were evident for headache severity and use of acute medication.^9,10

Given this framework of clinical trials indicating a role for botulinum toxin type A in the treatment of headache, scientists have speculated as to its mechanism of action and precisely how to administer the toxin to most effectively treat various types of headache disorders.

**THEORETICAL MECHANISM OF ACTION: WHY AND WHERE TO TREAT?**

Botulinum toxin type A blocks neuromuscular transmission by binding to high-affinity receptors on motor and sympathetic nerve terminals. On binding, botulinum toxin type A enters nerve terminals and inhibits the release of acetylcholine from vesicles locat-

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**Figure 3. Common Sites for BoNTA Injection in Headache Treatment**

BoNTA = botulinum toxin type A.
ed on nerve endings. When injected in therapeutic
doses, the toxin effects a partial chemical denervation
and subsequent weakening of muscle. In addition, it
impedes pain pathways by inhibiting the release of
neuropeptide neurotransmitters associated with pain
sensitization, and this is hypothesized to account for
its effect on headache symptoms. Clinicians and
researchers have studied the innervation of the head
and neck to determine, based on this mechanism of
action, optimal treatment locations and doses.

Currently, there are 2 injection paradigms for CDH:
the fixed-site and follow-the-pain approaches. For the
fixed-site protocol, injection sites are predetermined and
standardized for all patients, whereas for the follow-the-
pain concept, injections are administered into regions
where patients report pain or tenderness, and thus are
customized to each patient’s individual situation. Some
issues that are still unresolved include questions of most
appropriate dosage and determining which sites to
inject. Figure 3 illustrates commonly injected sites for
the treatment of headache.

CLINICAL TRIAL DATA:
ESTABLISHING PARADIGMS FOR TREATMENT

The double-blinded placebo-controlled data regarding
the use of botulinum toxin type A for CDH are sum-
marized in Tables 1-13 and 2.9,10,18 Most of the earlier
studies were conducted on relatively small numbers of
patients (ie, 30-60 subjects) and were mainly patients
with CTTH. Doses ranging from 20 U to 200 U were
administered, although the majority of trials used 100 U
of botulinum toxin type A in a fixed-site regimen.
Positive outcomes included significant decreases in
headache severity and headache intensity,13,15-17 in addi-
tion to increases in headache-free days.10 In addition, sec-

Table 1. CDH Early Studies of BoNTA

<table>
<thead>
<tr>
<th>Study</th>
<th>LOE/Study Design</th>
<th>CDH Subtype</th>
<th>Dose/Injection Site</th>
<th>Outcomes Measures/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smuts et al13</td>
<td>DB, RCT, PBO</td>
<td>(n = 41) CTTH failed prophylaxis</td>
<td>100 U FS</td>
<td>(+) Severity (+) Headache scores (+) Headache-free days (+) Quality of life No adverse events</td>
</tr>
<tr>
<td>Schmitt et al14</td>
<td>DB, RCT, PBO</td>
<td>(n = 60) CTTH</td>
<td>20 U FS</td>
<td>(+) Pain intensity (-) Headache-free days (-) Acute medications No adverse events</td>
</tr>
<tr>
<td>Relja15</td>
<td>DB, RCT, PBO</td>
<td>(n = 30) CTTH</td>
<td>100 U or PBO, FS</td>
<td>(+) ↓ Pericranial tenderness vs PBO All showed: (+) ↓ Severity (+) ↓ Headache-free days vs PBO No adverse events</td>
</tr>
<tr>
<td>Padberg et al16</td>
<td>DB, RCT, PBO</td>
<td>(n = 40) CTTH</td>
<td>100 U or PBO, FS</td>
<td>(+) ↓ Intensity (VAS scale) (+) ↑ Headache-free days vs PBO (+) ↓ Frequency vs PBO (+) ↓ Medication days vs PBO No adverse events</td>
</tr>
<tr>
<td>Ondo et al17</td>
<td>DB, RCT, PBO</td>
<td>(n = 60) CTTH and TM</td>
<td>200 U FTP</td>
<td>(+) Headache-free days (+) Global impressions (+) Abortive medications Mild adverse events (NS)</td>
</tr>
</tbody>
</table>

BoNTA = botulinum toxin type A; CDH = chronic daily headache; CTTH = chronic tension-type headache; DB = double-blind; FS = fixed site; FTP = follow-the-pain; LOE = level of evidence; NS = not significant; OL = open-label; PBO = placebo; RCT = randomized controlled trial; TM = transformed migraine; VAS = visual analog scale.

Data from Smuts et al13; Schmitt et al14; Relja15; Padberg et al16; and Ondo et al17.
ondary positive outcomes included improved quality of life and a reduction in the use of abortive medications. Adverse events were mild or absent.

These studies paved the way for the late phase II studies (Table 2)\(^9,10,18\) and the phase III investigations currently under way. Phase II investigations by Mathew et al\(^9\) and Silberstein et al\(^18\) were randomized, double-blind, placebo-controlled trials. The 2 trials differed in that Mathew et al used a modified follow-the-pain approach, injecting between 105 U and 260 U of botulinum toxin type A, whereas the Silberstein et al paradigm included 3 fixed-site doses of 75 U, 150 U, or 225 U versus placebo. The Silberstein et al study did not meet the primary or secondary endpoints even though improvements were seen in the botulinum toxin type A and placebo groups.\(^18\) Although the primary endpoint for the Mathew et al study of headache-free days was not met, the secondary endpoint of responder rate was met, with more than 50% of patients experiencing a decrease in headache frequency.\(^9\) In addition, data from an earlier investigation (but not supported by this study) suggest that the effect of botulinum toxin type A may be enhanced over time. The earlier study was a retrospective, open-label design involving 112 patients with CM who had 1 or more of the following inclusion criteria: high disability scores (>30 on the Migraine Assessment Disability scale [range, 30–180]), failure to improve with prophylactic pharmacotherapy, failure to tolerate prophylactic pharmacotherapy, unable or unwilling to use a serotonin agonist, and/or being of advanced age. Injection doses ranged from 50 U to 100 U in a fixed-site or follow-the-pain regimen. These individuals had a significant decrease in the mean number of headache

### Table 2. Late Phase II Trial Data for CDH and BoNTA

<table>
<thead>
<tr>
<th>Study</th>
<th>LOE/Study Design</th>
<th>CDH Subtype</th>
<th>Dose/Injection Site</th>
<th>Outcomes Measures/Results</th>
<th>Primary</th>
<th>Secondary and Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mathew et al(^9)</td>
<td>DB, RCT, PAR, PBO</td>
<td>CM ± CTTH</td>
<td>105–260 U FTP</td>
<td>(+) Headache-free days</td>
<td>(PNR group)</td>
<td>(+) Headache-days vs PBO</td>
</tr>
<tr>
<td></td>
<td>Duration: 11 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(+) % Pts = ≥50% ↓ headache frequency (responder rate)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(+) Frequency of headache/mo (change from baseline)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4/173 BoNTA pts d/c due to AEs</td>
</tr>
<tr>
<td>Dodick et al(^10)</td>
<td>Subgroup analysis of Mathew et al</td>
<td>Pts not taking prophylactic medications</td>
<td>105–260 U FTP (from Mathew et al)</td>
<td>(+) Headache frequency (+) Headache days (+) ↓ Headache severity</td>
<td>Subgroup analyses</td>
<td>(+) % Pts = ≥30% ↓ headache frequency</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>(+) % Pts = ≥50% ↓ headache frequency</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(+) ↓ Days of acute medications</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(NS d 180, PNR, all doses)</td>
</tr>
<tr>
<td>Silberstein et al(^18)</td>
<td>DB, RCT, PAR, PBO</td>
<td>CM ± CTTH</td>
<td>75, 150, or 225 U FS</td>
<td>(+) Headache-free days</td>
<td>(NS d 180, PNR, all doses)</td>
<td>(+) % Pts = ≥50% ↓ headache frequency</td>
</tr>
<tr>
<td></td>
<td>Electronic diaries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(d 30, 240)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(+) ↓ Acute headache medication use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Transient, mild-moderate AEs (27/702 d/c due to AEs)</td>
</tr>
</tbody>
</table>

AE = adverse event; BoNTA = botulinum toxin type A; CDH = chronic daily headache; CM = chronic migraine; CTTH = chronic tension-type headache; DB = double-blind; d/c = discontinued; FS = fixed site; FTP = follow-the-pain; LOE = level of evidence; NS = not significant; PAR = population-attributable risk; PBO = placebo; PNR = placebo nonresponders; pts = patients; RCT = randomized controlled trial.

Data from Mathew et al\(^9\); Dodick et al\(^10\); and Silberstein et al\(^18\).
days (from 64.4 ± 2.2–29.3 ± 7.1) at 3 months after the initial botulinum toxin type A treatment (\(P < .001\)). Seventy-eight patients who received a second treatment cycle experienced a significant reduction in mean headache days (33.9 ± 5.7 pretreatment vs 22.7 ± 5.1 at 3 months posttreatment, respectively; \(P < .01\)). A further significant reduction in mean headache days was observed in 60 patients returning for treatment cycle 3 (21.5 ± 4.5 pretreatment vs 13.2 ± 2.7 posttreatment, respectively; \(P < .05\)). In patients returning for subsequent treatment cycles 4 to 6, the number of mean headache days remained low. Again, as with earlier studies, botulinum toxin type A was found to be safe and well tolerated.

**CURRENT TREATMENT PARADIGM**

The most commonly used current botulinum toxin type A treatment paradigm consists of using 100 U of botulinum toxin type A in a 4 to 1 dilution and distributing it to a large number of sites in a relatively fixed-site, fixed-dose pattern, with the option of following-the-pain. The current phase III study is using a fixed-site, slightly modifiable fixed-dose regimen with approximately 170 U of botulinum toxin type A. This treatment paradigm is based on the success of the late phase II study rather than the predominant treatment paradigm in the real world. Although at the present time, physicians are administering these injections, it may be within the scope of practice for well-trained registered nurses, nurse practitioners, and physician assistants to also carry out these injections.

**CONCLUSIONS**

Chronic daily headache remains relatively frequent, often very disabling, and usually difficult to treat effectively without medication side effects. An efficacious therapy without significant side effects, much less a cure, still eludes us. Clinicians and researchers continue to search for a safe and effective treatment for this disabling condition. The use of botulinum toxin type A represents a departure from traditional, systemic prophylactic therapies. It has been shown to be safe and only requires treatment approximately every 12 weeks. Although not all of the endpoints in the late phase II studies yielded significant outcomes, many headache specialists believe that botulinum toxin type A is a promising and novel treatment for the prevention of CDH. Phase III studies that are currently ongoing will hopefully answer many of the as yet unanswered questions about dosing, injection sites, and of course, efficacy. For now, botulinum toxin type A represents one more pharmacotherapeutic option for the millions of patients who are frustrated by the pain of chronic headache unrelieved by existing acute and preventive therapies.

**DISCUSSION**

**Dr Frishberg:** In the treatment paradigm, we have fixed-site and follow-the-pain regimens. Each patient is separate and different, and in my opinion, one needs to look at the location of the pain, presence of trigger points, and presence of tenderness rather than doing the same thing in every patient. My question is, if a patient always has unilateral headaches, do we have to treat bilaterally? I have never not treated both sides, but I have treated people with more neurotoxin on one side than on the other. I have heard from other neurologists about patients who were only treated unilaterally, because they had headaches that were always on the same side, and then after treatment, the headache pain moved to the other side.

**Dr Dodick:** That is why I will not treat purely unilaterally. Even if someone has a very unilateral headache pattern, I will inject 10% or 20% of the medication on the other side.

**Dr Saxton:** I have seen pain migration similar to that in patients with cluster headaches, not with botulinum toxin, but with other preventive and acute treatments during a cluster, and their pain then shifts to the other side. If you are targeting a specific area in the follow-the-pain technique, does this then just become a trigger point injection?

**Dr Schim:** No, I do not go for the trigger point, but I look for postural imbalance, dystonic features, and myofascial features as an indication. It is very common to see someone come in, and you can see immediately that one shoulder is higher than the other by 1 cm. Their headaches are right-sided. You touch the neck, and you feel the levator muscle is in spasm.

**Dr Saxton:** But I think that if you want to be able to compare one study to another and analyze the data, it would be best to try to develop a standard protocol and have everyone conform to those guidelines and techniques.

**Dr Frishberg:** We are in the midst of a large phase
III study and are all following the same standard protocol—one that may be very different from our usual treatment methods; thus, we will see what comes out of this study. But different treating injectors have different experiences, and I treat very differently than what I think of as mainstream. For example, I administer approximately 30 injections per session. I like to use a dilute solution, cover more areas, and really spread the medication around. Would you all share what you are doing in terms of your treatment paradigms for CDH?

**Dr Mondell:** In terms of the number of injections I give, I find that it mirrors your protocol. As for the typical number of units used, in my patient population, my average is 150 U to 175 U. However, the range is from 100 U to 200 U administered in a fixed-site (and largely fixed-dose) regimen that permits modification to allow for following-the-pain—especially posteriorly and temporally—to meet the needs of the individual patient being treated.

**Dr Saxton:** I use 100 U in a fixed-site regimen with 2 sites in the neck.

**Dr Aurora:** I may start with 100 U, but usually go to between 150 U and 175 U. I usually will follow a fixed-site, fixed-dose regimen, and then I may customize where I think more medication is needed, such as in the trapezius, suboccipitalis, and temporalis muscles, because these are such large muscles. If a patient tells me that he or she has a particularly tender spot, I also will inject at that site.

**Dr Schim:** My approach is fixed-site, fixed-dose across the frontal areas. Even if their pain is very asymmetric, I want them to be cosmetically acceptable. The exception I will make is at the scalp line. If I am treating at a low dose—100 U to me is a low dose—I might inject 3 locations on the painful side, but only 2 on the less painful side. For example, I will treat asymmetrically at the corrugator muscle if I think I need to. I will frequently treat very asymmetrically into the temporalis muscle if necessary—sometimes 10 U or 15 U on one side versus 40 U or 50 U on the other side—especially if there are temporomandibular disorder components. Posteriorly, if patients are asymmetric in their pain patterns or if they have any subtle dystonic features, I am going to capitalize on that and use the drug asymmetrically there.

**Dr Dodick:** My treatment regimen depends on the patient’s pain pattern. If the pain is always anterior, I give 25 U to 50 U fixed-site, fixed-dose in the frontal region, including the temporalis muscle. If the pain is anterior and posterior, but does not involve the neck, I will give the patient 100 U typically, with the other 50 U divided equally between the occipitalis and suboccipitalis muscles. If patients have neck involvement, then typically I will decrease the dose in the occipitalis and suboccipitalis and administer the toxin into the splenius capitis, cervical paraspinus, and trapezius muscles. It is a rare patient in my practice that gets more than 150 U. Most patients get 100 U or less of botulinum toxin type A.

**Dr Saxton:** Have any of you changed from a 2:1 to a 4:1 dilution?

**Dr Schim:** We started off at a 2:1 dilution, and then we started managing more patients with headache who had more severe pain. After looking at some of the literature regarding the use of botulinum toxin type A for spasticity where there is a large territory that you want to infiltrate with toxin, it seemed logical to use a larger volume (4:1 dilution) and allow better infusion.

**Dr Saxton:** A patient came in the other day and told me that she had gotten botulinum toxin once or twice, and it was associated with atrophy of her temporalis muscle. How often do you see that?

**Dr Frishberg:** It is fairly well reported that this can cause temporalis muscle wasting. It depends the amount of toxin used. I personally have not had a patient with this problem, but have heard about it from other injectors. I have noticed some patients who have some thinning of the temporalis muscle. However, it is important to remember that like most of the adverse side effects, they resolve completely with time, and it should be reversible once the treatments are stopped.

**REFERENCES**


