For the majority of patients presenting for neurological evaluation of headaches, effective headache prophylaxis is the key to improved outcomes. Preventative treatments, however, are generally underutilized. Indications for headache prophylaxis include frequent or very severe headaches, excessive acute medication use, severe disability, or patient preference. Many effective prophylactic medications are associated with significant adverse events (AEs) and often take a few months to notice clinical improvement. In addition, some patients prefer to avoid daily medication, and patient compliance can be an issue. Onabotulinumtoxin A (BoNTA) is an attractive alternative headache prophylactic treatment for patients with headache. Clinicians usually perform BoNTA injections every three months, and pain relief typically begins in less than two weeks. Recent clinical trials demonstrate that BoNTA is effective in the treatment of chronic migraine (CM), leading to an approval by the US Food and Drug administration of BoNTA (Onabotulinum toxin A, Botox, Allergan) for CM prophylaxis. There are many other reports of BoNTA and its use in other headache disorders such as tension-headache, episodic migraine, cluster headache, and nummular headache.

Mechanism of Action
BoNTA has traditionally been used for disorders such as dystonia, which relate to an increase in muscle tone. BoNTA binds to nerve terminals, is endocytosed, and cleaves SNAP-25 protein. This inhibits the release of acetylcholine from nerve terminals and blocks neuromuscular transmission. Similar phenomena occur in parasympathetic and sensory neurons. There are several large randomized controlled trials demonstrating the effectiveness of BoNTA in cervical dystonia and a few smaller studies that support its use in the treatment of neck pain. Interestingly, many patients from these trials reported pain relief well before

While BoNTA shows promise in the management of chronic migraine, optimal outcomes will be achieved when clinicians learn which patients are most likely to benefit.

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any decrease in muscle tension. Starting a few days after injection, BoNTA produces partial chemical denervation of the muscle, resulting in a localized reduction in muscle activity for months. BoNTA may have other distinct properties that lead to effectiveness in headache treatment. BoNTA administration appears to inhibit the release of glutamate and neuropeptides, such as substance P and calcitonin gene-related peptide (CGRP), from nociceptive neurons. Glutamate and CGRP appear to be especially important in migraine pathogenesis. By blocking peripheral sensitization of nociceptive fibers, BoNTA may also inhibit central sensitization and allodynia. Finally, BoNTA appears to prevent the development of central sensitization in trigeminal nucleus caudalis in animal models of CM.

BoNTA in the Prophylaxis of Episodic Migraine
Multiple studies have evaluated the effect of BoNTA for prophylaxis of episodic migraine with mixed results. In a placebo-controlled trial with 123 patients, Silberstein et al. reported that a dose of only 25 units (U) injected into fixed glabellar, frontal and temporal sites decreased the number and severity of migraine attacks compared to placebo. A 75 unit dose to the same areas resulted in improved global assessment of change compared to placebo but otherwise was not significantly more effective. In a study of 60 patients, Evers et al. found no significant difference between BoNTA 16 U, 100 U and placebo in the prevention of migraine or acute medication use. Other studies have reported decreases in migraine days and acute medication use.

In the largest study of BoNTA for the treatment of episodic migraine, 389 patients were treated with BoNTA or placebo. The dose used in this study was relatively larger with a mean of 190(5) U (range, 110 U to 260 U) injected into multiple sites including frontalis, temporalis, occipitalis, trapezius, semispinalis, and splenius capitis. Patients were allowed to remain on their current acute and preventative medications. Using a goal of 50 percent improvement in headache days from baseline, both the BoNTA and the placebo groups had a response rate greater than 50 percent, with no significant differences in the two groups. In the group with more frequent headaches (12 or more per month) BoNTA patients experienced significantly fewer headache episodes (mean of four less) over 180 days compared with 1.9 fewer days in the placebo group (P=0.048). Interestingly the placebo response rate in this study was comparable to response rates for standard migraine medications, such as topiramate or gabapentin. The rate of discontinuation was only 1.9 percent, again much lower than most migraine preventative trials.

BoNTA in the Prophylaxis of Chronic Daily Headache and Chronic Migraine
CM is a highly disabling form of chronic daily headache and the most common disorder seen in tertiary headache centers. Patients with CM have headache at least 15 headache days per month and have headaches that meet criteria for migraine on at least eight of those days. Most preventive medications for migraine, such as many beta-adrenergic blockers, antidepressants, and anticonvulsants, have not been rigorously studied for the treatment of CM.

Several preliminary studies have evaluated the efficacy of BoNTA in the prophylaxis of chronic daily headache, which includes CM. In a randomized, placebo-controlled study, Silberstein studied the efficacy and tolerability of BoNTA for the prevention of CDH in 702 patients using a "fixed-site" protocol using doses of 75 U, 150 U, or 225 U with three BoNTA treatments over a nine-month period. Patients receiving the higher doses (150 U and 225 U) had had significantly fewer headache days.

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**Table 1. Indications for Headache Prophylaxis**

- Frequent or very severe headaches
- Excessive acute medication use
- Severe disability
- Patient preference
days compared with those who received placebo. Despite the fact that 42 percent of patients met criteria for medication-overuse, these patients improved at a similar rate to the non-overusers. Mathew et al.\textsuperscript{19} evaluated the effect of BoNT-A on 355 patients with chronic daily headache (CDH) in a randomized, placebo-controlled study using the "follow-the-pain" approach. Patients were injected three times at three-month intervals. Injections of BoNT-A were associated with a significant increase in headache-free days compared with placebo at day 180. Patients not taking other migraine preventatives actually had a greater decrease in headache frequency (7.8 vs 4.5 days/month) than those on preventatives. Injections of BoNTA non-significantly increased the number of headache-free days from baseline and decreased the use of acute pain medications more than placebo. The patients with chronic daily headache in these studies were often highly refractory to treatment as reflected by elevated disability scores and health-related quality of life indices.\textsuperscript{20}

Two recent, large, phase three multicenter studies, the PREEMPT 1 and 2 trials, have shown that BoNTA is an effective treatment for adults with CM.\textsuperscript{21,22} These studies enrolled 1,384 subjects with CM in trials consisting of a 24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week open-label phase. All subjects received at least a minimum dose of 155 units of BoNTA administered at 31 injection sites across seven head and neck muscles using a fixed-site, fixed-dose injection paradigm and up to extra 40 units into the temporalis, occipitalis, and/or trapezius using a modified follow-the-pain approach. (Table 2) The clinician performing the injections selected additional sites for injection based on pain location, muscle tenderness, and their personal judgment. Subjects receiving BoNTA in the double-blind phase had statistically significant improvement from baseline after injection compared with placebo treatment in multiple clinical domains, including mean frequency of headache days and headache episodes. BoNTA-treated subjects also had fewer migraine episodes, fewer moderate or severe headache days than the placebo group. BoNTA subjects took similar amounts of acute medication but fewer triptans than controls. BoNTA treatment also significantly improved measures of disability and health-related quality of life. Based on the results of these two large randomized placebo-controls trials, the US Food and Drug Administration recently approved BoNTA for the treatment of CM.

**BoNTA in the Treatment of Other Headache Disorders**

BoNTA does not appear to be effective in the treatment of chronic tension-type headache (CTTH). Padeberg et al. injected 40 CTTH subjects demonstrating muscle tenderness using placebo or BoNTA with individualized sites and dosing in a double-masked design.\textsuperscript{23} There were no significant differences between groups. A larger multicenter double-blind, placebo-controlled randomized study of BoNTA for the treatment of CTTH used doses of 50 U, 86 U, 100 U, or 150 U into multiple muscle groups including frontalis, sternocleidomastoid, upper trapezius, splenius capitis, and anterior temporalis.\textsuperscript{24} BoNTA was not more effective in the primary outcome: number of tension-headache free days.

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**Table 2. Injection Sites for PREEMPT Study**

<table>
<thead>
<tr>
<th>Muscle Injected</th>
<th>Standard Dose</th>
<th>Optional Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procerus</td>
<td>5 U (one site)</td>
<td>n/a</td>
</tr>
<tr>
<td>Corrugator</td>
<td>5 U each side (10 U)</td>
<td>n/a</td>
</tr>
<tr>
<td>Frontalis</td>
<td>10 U each side (20 U)</td>
<td>n/a</td>
</tr>
<tr>
<td>Temporalis</td>
<td>10 U each side (20 U)</td>
<td>Up to 2 sites (10 U)</td>
</tr>
<tr>
<td>Cervical Paraspinals</td>
<td>10 U each side (20 U)</td>
<td>n/a</td>
</tr>
<tr>
<td>Occipitalis</td>
<td>15 U each side (30 U)</td>
<td>Up to 2 sites (10 U)</td>
</tr>
<tr>
<td>Trapezius</td>
<td>15 U each side (30 U)</td>
<td>Up to 4 sites (20 U)</td>
</tr>
<tr>
<td>Total</td>
<td>155 U</td>
<td>Up to 40 U</td>
</tr>
</tbody>
</table>
BoNTA may also be effective in less common headache disorders, but has not been established in controlled trials, mainly due to the fact that many of these disorders are rare. Nummular headache, a constant or remitting headache in a small circumscribed area such as an oval or elliptical shape, is often refractory to oral medications. A small case series of four patients with nummular headache reported significant improvement, lasting about 14 weeks, in all with a small dose of BoNTA (25 U).25

Chronic cluster headache is another headache disorder that is often refractory to treatment. A recent open-label study of cluster headache used 50 units of BoNTA injected into the ipsilateral pericranial muscles of 12 patients.26 Of the nine patients with chronic cluster headache, one had a cessation of attacks and two improved significantly. The other patients, including the three with episodic cluster headache, did not notice improvement.

Other examples of using BoNTA for the treatment of headache include: occipital neuralgia improved with an injection of 50 units into the affected side at the site of the greater and lesser occipital nerves,27 a case series of 24 patients with primary stabbing headache which improved with 5 U injections into each area of pain,28 hemicrania continua,29 and new daily persistent headache.

Conclusions

Injections using BoNTA appear to be a safe and effective treatment for the prophylaxis of chronic migraine and may be effective in other headache disorders as well. BoNTA offers a different approach to therapy for patients suffering from chronic migraine, including those in whom multiple oral preventative therapies have failed due to ineffectiveness or poor tolerability or in those with contraindications to other effective therapies. BoNTA also appears effective in CM patients with medication overuse. Despite achieving response rates equal to or greater than those of other migraine preventative agents, studies of BoNTA for the treatment of episodic migraine have been largely negative, probably due to a higher placebo response. Although the two recent CM trials used relatively higher doses, it is uncertain which dosing strategy and location of injections (fixed doses or follow-the-pain) is most effective. Based on earlier studies, it seems likely that smaller doses may be adequate for many patients. It is also worth noting that patients in clinical trials often remained on other preventative medications and continued to take acute medications.

Finally, BoNTA is a fairly expensive treatment which requires special training to administer which may limit its use, so several studies have attempted to find factors that predict outcomes. Preliminary studies suggest women and those with unilateral headaches or allodynia are more likely to respond to BoNTA. In one sample of 63 patients, BoNTA responders were more likely to describe their headaches as pressure from the outside (imploding) or ocular pain, while non-responders were more likely to report exploding headache which builds up from the inside.31 A relatively shorter duration of disease (less than 30 years)32 and occasional headache free days before treatment33 also appeared to predict improvement. Determining potential best responders before initiating treatment may lead to better outcomes.

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