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Review

Treatment of headaches with botulinum toxin

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Primary headache disorders, such as migraine, chronic daily headache (CDH), and chronic tension-type headache (CTTH), are some of the most frequent disorders encountered by physicians in the outpatient setting. Chronic headache disorders cause significant morbidity and functional impairment. Despite important advances in both pharmacological and behavioral management of headache disorders, a number of patients remain treatment resistant. Botulinum toxin (BT) is emerging as a new therapeutic alternative in the preventative treatment of headaches. BT has several advantages over current prophylactic strategies, such as reduced side-effect profile and improved patient compliance. Furthermore, there have been several studies supporting the safety and tolerability of BT in the treatment of headache disorders. Although additional large-scale studies are needed to clarify clinical predictors of response as well as optimal dosing, injection sites and mechanism of action, BT has demonstrated efficacy in the treatment of migraines and CDH. The evidence for the treatment for CTTH is less compelling.

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Recurrent headache is one of the most common reasons for seeking neurological consultation [1]. The majority of headache sufferers have a primary headache syndrome, rather than a headache due to an underlying medical cause. Examples of headache syndromes are migraine, chronic tension-type headache (CTTH), cluster headache, and chronic daily headache (CDH), which has been recently reclassified as chronic migraine.

There are a variety of behavior modifications and pharmacological treatments available for headache sufferers. Behavior modifications include avoidance of potential trigger foods, regulation of sleep and eating habits, regular aerobic exercise and use of biofeedback and stress-management techniques [1]. Pharmacological treatment is classified as either abortive or prophylactic. Abortive medications include over-the-counter (OTC) analgesics, such as acetaminophen and nonsteroidal anti-inflammatory medications, and prescription medications, such as triptans [1]. Prophylactic medications include nutritional supplements, such as magnesium [2], coenzyme Q_{10} [3] and riboflavin [4], as well as anticonvulsants, antidepressants and blood pressure medications [1].

Despite the large number of available treatments, many headache sufferers do not respond to either pharmacological treatment or behavioral modifications. Some patients may have difficulty complying with lifestyle changes or daily medication use. Others have difficulty tolerating the available abortive and prophylactic medications. Furthermore, common medical conditions, such as cardiovascular disease and uncontrolled hypertension, prohibit some patients from using triptans, the most widely prescribed group of abortive medications [1]. Given the large number of headache sufferers and the disability they experience, it is essential to continue to explore new treatments that are both tolerable and effective.

Mechanism of action of botulinum toxin

Botulinum toxin (BT) was discovered serendipitously as a potential treatment for headaches by a plastic surgeon, William Binder. He

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found that, after using BT for the cosmetic treatment of forehead wrinkles, many patients reported relief of their migraine headaches [5].

The finding that BT was useful in the treatment of migraine has challenged the current wisdom regarding migraine pathophysiology. BT produces its cosmetic effects by interfering with the normal function of the neuromuscular junction, and thus preventing muscle contraction. After being injected into the muscle, BT enters the terminal part of the motor axon and interferes with the release of acetylcholine into the synaptic cleft. However, the possible mechanism of action by which BT prevents migraine headaches is unclear.

Migraine is a brain disorder, and positron emission tomography (PET) scanning has identified a 'migraine generator' in the brainstem where migraine attacks begin. BT reduces both efferent input from the nerve to the muscle, as well as afferent activity from the muscle into the CNS [6]. It is possible that relaxation of pericranial muscles reduces afferent input into the brainstem migraine generator, thus raising the threshold for a migraine attack [7,8]. This is supported by the finding that patients with migraine exhibit hypertrophy of the corrugator muscles [8]. Furthermore, it has been postulated that the trigeminal nerves are stimulated to produce a nociceptive response by strong contraction of the corrugator supercilli and the temporalis muscles [7,9].

Smuts and colleagues examined the hypothesis that muscle denervation correlates with decreased migraine frequency and pain intensity [10]. Ten patients with a migraine history were injected with 20 U of BT type A (BT-A) at predefined sites in the procerus and corrugator muscles. Compound muscle action potentials (CMAPs) were recorded over the corrugator muscle at baseline and at several time periods subsequent to the baseline injections. Of the ten patients, seven reported at least a 50% decline in migraine frequency. From the time the migraine intensity declined on day 30, there was electrophysiological evidence of denervation in the muscles tested. However, after day 60, the CMAPs indicated less denervation, although 70% of patients continued to experience a decline in migraine frequency. Therefore, comparing electrophysiological evidence of reinnervation after days 60 and 90 was not coincident with the return of migraine symptoms. The finding that the therapeutic response of BT-A is not the sole result of peripheral muscle denervation correlates with both the supporting literature and the authors' observation that tension-type headaches are less amenable to BT-A than migraine headaches.

Another possible explanation for the effect of BT in primary headaches is that it prevents peripheral sensitization of sensory nerves and therefore reduces central sensitization [10]. BT has been shown to inhibit the release of several neuropeptides associated with nociception, such as substance P, glutamate and calcitonin gene-related peptide [11,12]. Furthermore, it has been postulated that repeated blocks with BT could produce a long-lasting effect via chronic decreased stimulation on the peripheral nociceptors. This could result in modification of neuronal activation and central hypersensitization that may clinically produce chronic pain [13]. Although further research is necessary to elucidate the mechanism of action of BT in headache treatment, the probable explanation is that BT exerts its effects both centrally as well as through its effect on pericranial muscle spasm.

Product variation

Different commercial products of BT have distinct properties and clinical effects may differ. Data obtained with one product should not be extrapolated to another, and the units of one product are difficult to correlate with those of another product.

In 1989, the first commercial preparation of BT-A, BOTOX®, was approved by the US FDA as an orphan drug for clinical use in blepharospasm and strabismus. Type B (BT-B), MYOBLOC®, was introduced in the USA more recently, while outside the USA a second BT-A product, DYSPORT® is also available.

A minority of patients (<1%) develop antibodies to BT after repeated injections [1]. BOTOX has less protein than the other commercially available products, BT-B and Dysport, making it theoretically less likely to cause antibody formation. However, it appears that patients who stop responding to BT-A due to antibody development may respond to BT-B. This can be explained by the fact that BT-A affects the soluble attachment 25 (SNAP-25), whereas BT-B affects the vesicle-associated membrane protein, also known as synaptobrevin, rendering them antigenically distinct [14].

BOTOX is available vacuum-dried in 100-U vials, and DYSPORT is available in 500 U per vial, while BT-B is available in 0.5-, 1- and 2-ml vials containing 5000 U per ml. BOTOX and DYSPORT vary regarding the strains of toxin-producing organisms used in fermentation, methods of purification, excipients and formulation. This results in distinct properties regarding potency, diffusion and antigenicity [15]. DYSPORT and BOTOX should not be regarded as generic equivalents, although there have been no direct studies assessing the efficacy of BT-A versus BT-B in headache. Previous research suggests that BOTOX offers modest advantages over BT-B for the treatment of cervical dystonia by providing a slightly longer duration of effect in those subjects experiencing symptomatic benefit and fewer adverse effects [16].

Safety & tolerability

Before proceeding with BOTOX injections, it is necessary to provide a detailed explanation of the injection procedure and possible side effects. Patients are often relieved to learn that BT-A is a remarkably safe treatment. No serious allergic reactions have ever been reported with BT-A, although rarely rash and flu-like symptoms can occur. Injection of anterior neck muscles with BT can cause swallowing difficulties in a small number of patients; nasogastric tube feeding has been required in a few reported patients. Difficulty in holding the head erect due to neck muscle weakness is another possible, but rare, side effect.

In a randomized, double-blind comparison of BT-B with BT-A, with regards to autonomic side effects in patients with cervical dystonia, neither toxin produced serious cardiovascular side effects or other cholinergic autonomic adverse effects [17]. BT-B did cause a significant decrease in saliva production, dysphagia and constipation compared with BT-A. The differences between BT-A and BT-B with respect to the frequency and severity of autonomic side effects may be attributed to serotype-specific variations in diffusion, cell membrane affinity or systemic spread [18–23].

The most common side effects when treating facial muscles are cosmetic. These include ptosis or asymmetry of the position of the eyebrows and they usually resolve over a period of several weeks. In a rare patient they may last for up to 2–3 months. Additional BT injections can correct asymmetry and even ptosis. Headache patients occasionally develop a headache following the procedure, although in some, immediate relief of an acute attack can also occur. The latter may be caused by a potential trigger point or acupuncture point injection effect. Worsening of headaches and muscle pain can occur for several days after the injections owing to the delay in the muscle-relaxing effect of BT.

Injection technique

Although there is no universal injection technique, in the authors' experience, the sites injected depend on the distribution of headache pain and trigger points identified by palpation. Typical injection sites are the frontalis, glabellar, procerus, temporalis, masseter, splenius capiti, paraspinal, cervical and trapezius muscles. The authors' personal average dose range for the treatment of headaches is 50–100 U. Higher amounts may be needed, especially in patients with pronounced associated spasm in masticatory, neck, trapezii and other upper back muscles.

The usual dilution is 100 U of BOTOX in 4 ml of preservative-free saline, although some physicians dilute a vial in half that volume. Preservative-free saline is recommended by the manufacturer of BOTOX and is the only FDA-approved diluent. Although diluting with a local anesthetic, such as lidocaine, might provide immediate relief of injection site pain, more adverse events have been reported to the FDA when departing from the standard recommended dilution with preservative-free saline [24].

Furthermore, although saline with preservatives may lessen the pain of injection, it anecdotally decreases the duration of BT injections compared with preservative-free saline. The 100-U vial of BOTOX is vacuum-dried and the absence of a vacuum during reconstitution suggests that the contents of the vial may be ineffective. This is a very rare occurrence; the vial should be exchanged for another.

MYOBLOC is available only in a diluted form and only in a concentration of 5000 U/ml. When used for the management of headaches and pain, rather than movement disorders, further dilution is often required. BT-B solution has a very acidic pH, which makes injections, especially in the forehead, significantly more painful.

More concentrated solutions and electromyogram (EMG) guidance are used for movement disorders because of the need for precise localization and paralysis of specific muscles. However, in the treatment of headache, EMG is not necessary, and only increases the cost and discomfort of treatment.

The use of a 30-gauge, 1-inch needle is recommended. The incidence of cosmetic and other side effects usually declines with the increase in the experience of the injector. An additional small injection of BT easily corrects any visible eyebrow asymmetry, brow ptosis or pronounced unilateral wrinkling or exaggerated elevation of the lateral aspect of an eyebrow. Ptosis can sometimes be relieved by instilling 0.5% apraclonidine (Iopidine), α-adrenergic agonist eye drops three-times a day. On rare occasions, a patient will complain of the cosmetic effects of temporalis muscle wasting. If this is of significant concern to the patient, injections of the anterior temporalis muscle can be avoided on subsequent treatments.

The first effects of BT are experienced within 2–10 days. Typical duration of action is 3 months, but there is considerable variation in individual response [1]. Remarkably, even after years of repeated injections of BT into the same muscle, recovery of muscle function is always complete.

The development of antibodies to BT is a rare phenomenon that renders treatment ineffective. People immunized against BT in the military or at toxin-manufacturing plants, also do not develop muscle paralysis. If a patient fails to develop visible paralysis of the frontalis muscles, a brow furrow test can help differentiate antibody formation from a defective product. This test consists of injecting approximately 2 U of BT into the glabellar area. If the injection again fails to produce paralysis, the patient has developed antibodies. As stated above, patients who develop antibodies to BT-A may respond to BT-B.

Botulinum toxin in the management of headaches

Several studies have examined the efficacy of BT in the treatment of migraine [5,25–36], CDH [36–40] and CTTH [41–46]. A discussion of the most salient trials follows. Unless noted, BT-A refers to BOTOX, rather than DYSPORT.

Published studies of botulinum toxin-A in migraine headache

Silberstein and colleagues assessed the safety and efficacy of BT-A in the prevention of migraine in a double-blind, vehicle-controlled study with outcomes that included changes in the frequency and severity of migraines, migraine-associated symptoms and days of medication use for acute migraine [25]. The 25- and 75-U doses were studied. Compared with patients in the vehicle placebo group, those in the 25-U group had significantly fewer migraine attacks per month, less severe migraines, fewer days when they needed acute migraine medication and less migraine-associated vomiting. Global assessments were significantly better in the 25- and 75-U groups than in the placebo group, but the 75-U group experienced more treatment-related adverse events. The investigators concluded that 25 U BT-A, was safe and reduced migraine frequency, severity, acute medication use and migraine-associated vomiting. The 25-U

dose, but not the 75-U dose, was found to be more effective than placebo. The trial design did not take into account the great variability of migraine pain distribution. The injections were given only into the forehead and temples, while many migraine patients report predominantly occipital or temporoparietal distribution of pain. It can be speculated that patients in the 25-U group had predominantly frontal pain, while those in the 75-U group did not. A therapeutic window effect, where a higher dose is less effective, is a less plausible explanation.

A second placebo-controlled trial was preformed by Evers and colleagues [26]. A total of 60 patients with migraine were randomly assigned to receive placebo injections in the frontal and neck muscles; or 16 U of BT-A in the frontal muscles and placebo in the neck muscles; or a total of 100 U of BT-A in the frontal and neck muscles. In both treatment groups, 30% of patients showed a reduction in migraine frequency at 3 months by at least 50% compared with baseline; in the placebo group 25% of patients showed such a reduction. These results were not significant and therefore do not support the use of BT-A in the preventative treatment of migraines. Nevertheless, *post hoc* analyses demonstrated that accompanying migraine symptoms were significantly reduced in the 16-U group, but not the 100 U group. The authors note that perhaps higher dosages injected only in frontal muscles as in Silberstein and colleagues [25] might have been more effective.

Barrientos and Chana also conducted a randomized, placebo-controlled trial, examining the efficacy and tolerability of BT-A in the treatment of migraine headaches [27]. A total of 30 patients with a history of migraine attacks were enrolled to receive placebo or 50 U of BT-A injected in 15 pericardial muscle sites. Patients treated with BT-A experienced fewer migraine attacks at days 30, 60 and 90. No reduction in migraine headaches was noted in the placebo group. In addition, both migraine severity and duration were significantly decreased in the treatment group compared with placebo. Furthermore, at the end of the 3-month study period, the BT-A-treated group reported a significant decrease in abortive headaches (triptans and nonsteroidal inflammatory medications) compared with placebo. Although these findings support the use of BT-A for migraine treatment, the results should be interpreted cautiously due to a complete lack of placebo response.

Brin and colleagues conducted an additional double-blind, placebo-controlled study of BT-A in the prophylactic treatment of migraine [28]. A total of 56 patients with migraine were randomized into four treatment groups: BT-A in frontal–temporal regions; BT-A in frontal and placebo in temporal; placebo in frontal and BT-A in temporal; and placebo in frontal–temporal regions. Migraine frequency was reduced by a median of 1.8 headaches per month in BT-A-treated groups and mixed BT-A-placebo groups, whereas the group that received only placebo injections experienced a median reduction of only 0.2 headaches per month. Although limited by small sample size, this study further supports the use of BT-A in the preventative treatment of migraine headaches.

The impact of BT-A on quality of life and triptan use was assessed by Relja in 32 patients enrolled in a double-blind, randomized, placebo-controlled trial [29]. All patients were determined to have moderate or severe migraine-related disability according to the Migraine Disability Assessment (MIDAS). Treatments included BT-A, 100 U, or placebo. BT-A reduced the impact of migraine on normal daily activities, reduced requirements for additional medication, reduced total triptan dosage and use and reduced pain characteristics. No change in the number of total headache-free days was noted. The change in pain characteristics was described as a shift from migraine-type pain to the pain typically associated with easier-to-tolerate tension-type headaches.

In addition to the placebo-controlled studies, there have been several open-label studies examining the efficacy of BT-A in the treatment of migraine headaches. For example, Conway and colleagues examined the efficacy of BT in 59 patients who had failed at least three adequate trials of prophylactic medications known to be effective in the treatment of episodic migraine [30]. Patients received 25 U of BT-A administration per the fixed frontal–temporal site protocol published by Silberstein and colleagues [25]. A total of 23 (41%) patients reported a 50% or greater reduction in headache days per month, 30 days after BT-A treatment. In addition, in responders, the mean number of headache days decreased from 15 to 2 and the mean days of abortive therapy during the month decreased from 21 to 4.

Eros and colleagues conducted an open-label study on 61 patients from their migraine clinic receiving BT-A treatment of either episodic or chronic migraine [31]. The treatment protocol used a fixed dose, 25 U of BT among the frontalis, temporailis, procerus and corrugator muscles. In addition, at the discretion of the treating clinician, toxins were injected into areas of spasm, including the cervical paraspinal, trapezius and/or the splenius capitis in a 'follow-the-pain' approach. Overall, the mean MIDAS score significantly decreased from 102 at baseline to 49 at the 3-month follow-up. Further examination of responders revealed an average of 80% improvement in migraine disability, a 63% improvement in headache frequency and a 24% improvement in headache intensity. Of note, subjects who responded to BT-A were younger and had migraines for less than 30 years. The authors suggest that early and more aggressive prophylactic therapy with BT-A may alter the natural history and decrease the likelihood of treatment-resistant migraine.

In a nonrandomized, open-label trial conducted in 106 patients, Binder and colleagues tested the ability of BT-A to alleviate migraine headache frequency and severity [5]. Of the group, 77 participants were judged to have true migraine and 51% of these reported complete response with a mean duration of response of 4.1 months. Of the ten patients with true migraine who were treated during the acute phase of an attack, 70% reported a complete response within 1–2 h.

In 2003, Blumenfeld reported on the efficacy of BT-A in reducing headache frequency and intensity in a retrospective, open-label analysis that included 271 patients. All participants

had disabling, chronic migraine [32]. BT-A was administered at an average, fixed dose of 63.2 U either at a fixed site or in a pattern that followed the pain. A response to treatment was reported by 80% of patients and significant reductions in the frequency of headache occurred (from 18.9 to 8.3 days/month). Headache intensity was diminished by 25%. The author concluded that BT-A provides 'efficacious and safe' preventive treatment for headaches.

Mathew and colleagues reported on their long-term experience with BT-A in patients with chronic headache in a retrospective, open-label trial of 208 patients [33]. All participants had disabling, chronic migraine and were treated with 50–100 U of the study medication administered at fixed sites or at sites that corresponded to the location of pain. According to the physician's global assessment, the 100-U dose was more effective than the 50-U dose. The incidence of severe, disabling migraine was greatly reduced compared with the incidence of less severe headache. Patients returned for treatment as the effects of an injection wore off and there was no evidence of tachyphylaxis. This observation also suggests that the benefits were not attributable to a placebo effect. BT-A therapy significantly reduced the disability associated with migraine, as well as migraine frequency and the need for other, acute medications. No patients dropped out of the study owing to a lack of efficacy.

The efficacy of BT-A for the treatment of patients with cervicogenic migraine was studied in a prospective, open-label study carried out by Krusz [34]. Cervicogenic headache is, by definition, a condition that is closely related to the cervical spine in both its initiation and perpetuation [35]. The study dose was 100 U administered at four to six posterior cervical injection sites. Headache frequency was reduced by more than 70% and migraine severity was judged to be diminished by 50%. The investigators concluded that BT-A was effective in reducing headache and spasm symptoms in this patient population.

Mauskop evaluated the long-term efficacy of BT-A in the treatment of episodic and chronic migraine headaches in a retrospective, open-label trial, in patients treated multiple times and over long periods of time [36]. In some, other multiple treatments had failed. Dosages of 25–200 U were administered in a follow-the-pain pattern. Among the findings were that improvements lasted up to 15 months, headaches were completely eliminated in some patients and symptom relief from abortive drugs was improved by BT-A treatment. In addition, headache frequency and intensity, as well as triptan use, were diminished. Adverse events included transient neck pain and weakness in two patients, acute headache in two patients and neck weakness and a fainting feeling in one patient each.

Published studies of BT-A in tension-type headache, chronic daily headache & other headache types

Chronic daily headache

In a randomized, double-blind controlled trial, Mathew and colleagues evaluated the safety and efficacy of BT-A treatments of CDH compared with placebo using a flexible dosing protocol [37]. The study was conducted at 13 North American study centers and followed 571 patients over 11 months. After a 30-day baseline observation period during which data regarding headache characteristics and medication overuse were collected, 350 patients meeting inclusion/exclusion criteria were treated with placebo injections (single blind) in a minimum of six areas. Next, placebo responders and nonresponders were randomized to receive either BT-A or placebo. At day 180, placebo nonresponders treated with BT-A had an improved mean change from baseline of 6.7 headache-free days per 30-day period, compared with a mean change from baseline of 5.2 headache-free days for placebo-treated patients. Although this result was not statistically significant, BT-A did meet secondary outcome measures including a statistically significant decrease compared with placebo in the percentage of placebo nonresponder patients with a 50% or more decrease in frequency of headaches at 180 days, and statistically significant decreases from baseline for the frequency of headaches per 30-day period. The authors postulated that the lack of efficacy on primary endpoints may be secondary to medication overuse and the use of adjunctive prophylactic medication in the study population.

Dodick and colleagues [38] examined a subgroup of 228 patients from the above study by Mathew and colleagues [37] who were not taking prophylactic medication. After two injection sessions, patients in the BT-A group had a significant improvement in headache-free days compared with the placebo group. Patients receiving BT-A continued to improve significantly after a third injection session. In addition, BT-A treatment at least halved the frequency of baseline headaches in more than 50% of patients after three injection sessions compared with baseline measures. The authors concluded that BT-A is an effective and well-tolerated unique prophylactic agent in patients with CDH, although the efficacy of BT-A in combination with other prophylactic agents is inconclusive.

A total of 56 patients with CDH were enrolled in Klapper's double-blind, placebo-controlled study of BT-A for the prophylaxis of CDH [39]. Treatment groups included BT-A 100 U, BT-A 27.5 U plus placebo, BT-A 72.5 U plus placebo or placebo alone. Both headache duration and frequency of moderate and severe headaches were reduced by active treatment in a subgroup of patients with two injection regions.

In 2004, Tepper and colleagues preformed a retrospective review of the efficacy of BT-A in the preventative treatment of 100 patients with headaches refractory to many previous standard preventative therapies [40]. The vast majority of these patients had CDH (80%). The remaining had migraine with or without aura. Fixed-site injections were performed in the frontalis and temporalis muscles bilaterally. A follow-the-pain approach was followed in the other muscles. Results demonstrated a statistically significant reduction of the frequency of headache days 1 month after BT-A was administered, which was maintained through the 3 months of the study. In addition, there was a significant reduction in headache index, number of days with severe headache per month and MIDAS scores at 1 month and through the 3-month study duration.

An open-label study preformed by Edwards in 20 patients with CDH refractory to other treatment modalities also found positive results using BT-A in dosages of 20–100 U [41]. The mean headache frequency dropped from 7 to 3.5 days per week. No clinical weakness was observed, and the side effects were limited to injection-site discomfort. The authors considered the benefits of BT-A to be 'highly significant'. They noted that BT-A might represent an alternative treatment for patients with CDH that poses no risk of drug abuse, drug–drug interaction, sedating effects or other systemic toxicities.

Chronic tension-type headache

In 1999, Smuts and colleagues assessed the efficacy of BT-A in the prophylaxis of CTTH [42]. This double-blind, randomized, placebo-controlled study enrolled 37 patients, and outcomes included changes in headache intensity, headache-free days and chronic pain index. Patients were randomized to receive 100 U of BT-A or placebo. The number of headache-free days improved significantly in the BT-A group relative to the placebo group and patients randomized to BT-A reported improvement in quality of life after the injections. Improvements lasted for 3 months and no serious side effects were reported.

The usefulness of BT-A as prophylaxis for CTTH was also examined by Relja and colleagues in a 10-month randomized, double-blind, placebo-controlled Phase and in an 18-month, prospective, open-label Phase [43]. A total of 30 patients were enrolled. BT-A was administered at doses of 40–95 U in a follow-the-pain pattern at multiple sites. During the placebo-controlled phase, the number of headache-free days was increased, while headache severity was diminished. During the open-label period, tenderness diminished. Adverse events were rare.

By contrast, a study preformed by Sebastian and colleagues was unable to show a benefit for BT-A in their 12-week, double-blind, placebo-controlled trial in 40 patients with CTTH [44]. Subjects were treated with 100 U of BT-A or placebo. No significant difference between the groups was apparent with respect to average headache days, headache hours each day, requirements for additional symptom management or the patient global assessments.

An additional double-blind, placebo-controlled study carried out by Schulte Mattler and colleagues was also unable to find a significant effect of DYSPORT in the treatment of CTTH [45]. In this study, 112 patients received 500 mouse U of DYSPORT in a fixed scheme. Findings demonstrated a decrease in the area under the curve (the sum of headache duration multiplied by headache intensity over a 6-week period) of eight in the treatment group versus four in the placebo group. However, these results were not significant. There were also no significant differences between the placebo and treatment groups regarding number of days with headache or intake of analgesics, duration of nocturnal sleep or change in Beck Depression Inventory score. The negative results of this study could be attributed to the fact that DYSPORT was given as a standardized protocol instead of a follow-the-pain approach.

Rollnick and colleagues also failed to show significant improvement using DYSPORT in the treatment of CTTH [46]. A double-blind, placebo-controlled study with 21 patients assigned randomly to either a treatment group using DYSPORT injections in the fronto–occipital muscles and temporal muscles bilaterally or placebo injections. No significant differences were found in the treatment group versus placebo with regard to frequency and duration of headaches, analgesic consumption, pressure pain threshold, total tenderness score and quality-of-life parameters.

Padberg and DeBruijn also reported insignificant improvements in headache intensity and frequency, headache-free days and medication days among 40 patients with CTTH who were enrolled in a randomized, double-blind, placebo-controlled study [47]. The BT-A dosage was 100 U administered at multiple, individualized sites. Improvements persisted for up to 3 months.

Mixed chronic headache populations

A number of studies have examined the use of BT-A in a group consisting of patients with a variety of headache diagnoses [48–56]. A discussion of the most salient trials follows.

Ondo and colleagues examined 60 patients in a double-blind, placebo-controlled, parallel study of BT-A for CTTH and chronic migraine headaches [48]. Patients received either 200 U of BT-A or matching placebo. All patients were given the option of repeat injection of BT-A (open-label) at 12 weeks and participants were followed for an additional 12 weeks. Over a 12-week period, headache-free days significantly improved in the BT-A group from weeks 8 to 12, and strongly tended to improve, however, insignificantly, at the 12-week period. At week 24, headache-free days were more in the twice BT-A injected group compared with the once injected group, implying a cumulative effect with subsequent injections.

Among the published, peer-reviewed abstracts on this subject is that of McAllister, who reported on improvements in headache and changes in headache medications among 116 patients with a variety of headache types who were treated with BT-A in a retrospective, open-label analysis [49]. Headache types included migraine with or without aura, episodic tension-type headache, cervicogenic headache and cervical myofascial pain. Injections were administered both at fixed sites and in a follow-the-pain pattern and dosages ranged from 40 to 280 U. Of note, all patients reported some degree of headache improvement, with 76% reporting an improvement of 75% or more; 9% reported a complete remission of headache. The monthly cost of headache medications decreased from US$253 to $97. The investigators called for larger trials to confirm these results.

The efficacy of BT-A in patients with chronic, intractable headache with or without concomitant neck pain was the subject of a study by Miller and Denny, who conducted a prospective, open-label study in 68 patients [50]. All subjects had unsuccessful trials with other treatment modalities. BT-A was administered at a dosage of 100 U in a follow-the-pain protocol. A total of 75% of patients reported 50–100% pain relief. A

total of 13% reported no benefit and 12% judged their improvements to be of little clinical use. Treatment efficacy was similar in patients with and without neck pain.

Troost and colleagues studied the impact of repeated BT-A treatments in 436 patients with intractable migraine or episodic tension-type headaches [51]. BT-A dosages were in the range of 25–300 U and were given at fixed and multiple sites. A total of 91% of patients reported improvements, and the more cycles of treatment a patient had, the greater the improvements. Improvements were cumulative through three cycles of treatment and sustained through eight treatments. Minor injection-site pain was the only adverse reaction reported in this series. Importantly, tachyphylaxis was not observed.

Blumenfeld assessed the efficacy of BT-A as prophylactic therapy in 271 patients with a range of headache types, including CDH, episodic tension, episodic migraine or mixed headache [52]. Mean BT-A dose was 63.2 U administered at multiple sites. Headache intensity and frequency was diminished by treatment and improvements persisted for more than 8 months. Three patients experienced transient ptosis.

To evaluate the possibility that BT-A is associated with progressive and cumulative treatment effects, Troost administered the drug in doses of 30–240 U to 134 patients enrolled in a prospective, open label study [53]. The subjects represented an array of headache types. No adverse events were reported, but pain was diminished. Headache scores improved according to both patient and clinical ratings. Improvements again persisted beyond 8 months.

Smuts and colleagues investigated the efficacy of BT-A in 79 patients with a variety of headache types enrolled in a prospective, open-label trial of 100 U, BT-A, [54]. Positive outcomes were reported in 50–68% of patients with CTTH, migraine, cluster headache and cervicogenic headaches. The authors concluded that BT-A could be considered an alternative therapy in patients with a variety of refractory headache syndromes.

Miller and Denny conducted a retrospective cohort analysis in 48 patients with chronic headache who were treated with BT-A in a combination fixed injection and follow-the-pain protocol [55]. The patients had not obtained adequate headache relief from other therapies. All received multiple treatments of 50–300 U of BT-A. The response to BT-A was rated as good, very good or full in 71% of participants; 8% reported being headache-free after treatment. These investigators concluded that BT-A therapy may be beneficial in patients who have not benefited from other headache therapies and that multiple regimens may be more effective than single treatments.

In a study of chronic cervical-associated headache associated with whiplash injuries, Freund and Schwartz conducted a randomized, double-blind, placebo-controlled trial in 26 patients who received BT-A at a dose of 100 U or placebo [56]. Pain was diminished and cervical range of motion increased, but the authors made no conclusions about efficacy owing to the short follow-up and small sample size.

Expert commentary

Aside from BT, there are a number of effective treatment options available to headache sufferers. These include abortive agents, such as triptans, and prophylactic agents, such as antidepressants (tricyclics and venlafaxine), β-adrenergic blockers (timolol and propanolol), angiotensin II receptor antagonists (candesartan) and anticonvulsants (divalproex sodium and topiramate). Despite this wide selection of therapeutic options, lack of benefit to acute and preventative strategies is not an uncommon phenomenon in clinical practice [1]. Adverse side effects also often limit effectiveness. Triptans are commonly associated with side effects, such as a flushed sensation, noncardiac chest pressure and paresthesias. In addition, they are contraindicated in patients with uncontrolled hypertension, complicated migraine and ischemic heart disease. The available prophylactic medications are associated with various side effects, such as dry mouth, constipation, gastrointestinal upset, decreased libido, fatigue, bradycardia, weight gain or loss, alopecia and cognitive deficits.

BT represents a completely new and unique form of treatment for headache sufferers. As reviewed above, several placebo-controlled trials and extensive open-label studies have confirmed the safety and tolerability of BT in the treatment of various headache disorders. Regarding the efficacy of BT-A in the treatment of headaches, the literature is most robust regarding migraine headaches. Specifically, at least three placebo-controlled studies [25,27,28] have supported the use of BT-A for the prophylactic treatment of migraines, whereas two did not show improvement at primary endpoints [26,29]. However, many aspects of BT-A for prophylactic migraine therapy still need to be elucidated. These include number and placement of injections and mechanism of action. Larger double-blind, placebo-controlled trials are needed to further delineate these aspects of treatment and support unequivocal efficacy of BT in migraine headaches.

Regarding CDH and CTTH, the literature is more contradictory. In CTTH, only two placebo-controlled trials showed benefit [42,43], whereas four did not show any significant improvement on primary endpoints [44–47]. There are at least two placebo-controlled trials for CDH. One showed no benefit [37] of BT-A over placebo except in a subgroup of patients who were not taking prophylactic medications [38], and one showed a benefit of BT-A over placebo [39]. Regarding uncontrolled studies, one retrospective review [40] and one open label study [41] showed benefit of BT-A in the treatment of CDH. Although these results are underwhelming with regard to the efficacy of BT-A in the treatment of CDH and CTTH, no studies documented any serious adverse events.

There have been several studies that have examined populations with a variety of headache types [47–55], although only one was placebo controlled [47]. All of the uncontrolled studies showed a favorable response for BT-A in the treatment of a wide spectrum of headache types. The placebo-controlled trial by Ondo and colleagues examined the efficacy of BT-A in the treatment of a mixed population of patients with either chronic

migraine or CTTM. Results showed improvement of primary endpoints only at weeks 8–12 and at 24 weeks, but not at 12–24 weeks [47].

Many of the studies reviewed here are limited by small sample size and/or study design. Furthermore, several are difficult to compare since they do not employ identical dosing and injection techniques. Despite these limitations, the literature does seem to support the treatment of migraine headaches with BT-A and is less supportive regarding the treatment of CTTH and CDH.

In the authors' extensive clinical experience using BT-A in the treatment of a variety of headache types (>1200 patients treated), we have found benefit of BT-A in many patients with migraine, CDH and CTTH using a follow-the-pain technique and using dosages from 50 to 100 U. In addition, we find that there are several other clinical benefits of using BT-A in headache patients, including the lack of compliance issues and side effects. Finally, BT treatment of headaches has the added advantage of being cost effective [52]. BT can often actually reduce medication costs by reducing the need for expensive triptans and other daily prophylactic drugs and reduce doctor and emergency room visits. However, as discussed here, additional placebo-controlled studies with large statistical power are needed to confirm whether there is scientific evidence to support our experience.

Five-year view

Given the data regarding efficacy and tolerability, it is possible that BT will emerge as a first-line treatment for the prophylaxis of migraines and CDH during the next 5 years. The literature is more contentious regarding CTTH. More large-scale, placebo-controlled studies are needed to clarify optimal dosing and injection sites and techniques, unequivocal efficacy and headache characteristics particularly amenable to improvement with BT before the treatment becomes scientifically accepted. Such large clinical trials are currently underway and they will hopefully lead to FDA approval and more widespread use of this therapy.

Key issues

- Despite the number of available treatments for primary headache disorders, many patients do not respond to therapy or cannot tolerate treatment.
- Botulinum toxin (BT) injections are a novel treatment for primary headache disorders. BT has several advantages, including beneficial side-effect profile, reduced need for patient compliance and established safety and efficacy.
- The mechanism of BT in the treatment of headache is thought to be caused by its effect on pericranial muscle spasm and inhibition of neurotransmitter release from the sensory nerves.
- Several placebo-controlled and open-label trials have established the efficacy of BT in the treatment migraines. Although there have been some trials supporting both the treatment of chronic daily headache and chronic tension type headache, there have been several negative studies for both conditions.
- Larger, placebo-controlled trials are needed to provide unequivocal proof of efficacy for BT and optimal injection techniques in migraine headaches and to establish the efficacy of BT in the treatment of chronic daily headache and chronic tension-type headache. Nevertheless, BT seems to be a simple, safe and cost-effective treatment for headaches, especially episodic and chronic migraine.

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