J Headache Pain (2004) 5:15–22
DOI 10.1007/s10194-004-0063-z

REVIEW

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Botulinum toxin type A in the management of headache: a review of the literature and personal experience

Received: 1 September 2003
Accepted: 21 November 2003

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Abstract Botulinum toxin type A (BoNT-A) shows significant promise in the management of a variety of headache types including migraine, chronic daily headache, tension-type headache, and other head and neck pains. Confirmation of efficacy still awaits the report of well-controlled double-blind placebo-controlled trials; however, a mounting body of evidence suggests that BoNT-A is effective, well-tolerated and safe for the management of many headache disorders. In this paper, I review recent evidence on the efficacy of BoNT-A, and also report my personal experience with the treatment in over 600 headache patients.

Key words Botulinum toxin type A • BoNT-A • Headache • Chronic daily headache • Tension headache

Introduction

Botulinum toxin type A (BoNT-A) shows significant promise in the management of a variety of headache types. Pivotal double-blind placebo-controlled trials are currently underway to establish potential efficacy in the management of headache. This review covers recent literature and personal experience in the management of headaches with BoNT-A.

Headache is one of the most common neurological symptoms in clinical practice. It is estimated that approximately 18% of women and 6% of men suffer from migraine, with the disorder affecting roughly 28 million Americans [1]. The lifetime prevalence of headache approaches 99% in women and 93% in men [2].

Headache disorders constitute a significant public-health problem with an impact on both the individual sufferer and society. Lipton and Stewart [3] estimated that lost productivity associated with migraine cost the US economy between $1 billion and $17 billion. A pharmacoeconomic survey in the United States by Hu et al. [4] found that migraine sufferers required a total of 112 million days of bed rest costing employers about $13 billion per year because of missed workdays and impaired function.

Patients with headache unresponsive to acute medications suffer considerable disability due to the frequency and severity of attacks and should be considered for preventive therapy [5]. Current preventive treatments tend to have a modest effect along with a substantial side effect burden related to vascular or systemic distribution [5]. Loder and Biondi [6], in an excellent review of the use of botulinum toxins for chronic headache, described previous reports of the use of botulinum toxin for migraine, chronic daily headache, tension-type headache, and other headache types, concluding that the use of botulinum toxin is of great interest and "deserves accelerated study."

In the sections that follow, studies are reported in various categories, but many of them deal with different

types of headaches and have been placed in the categories, even though there may be considerable overlap when studies report results for many different types of headaches.

Migraine

William Binder and colleagues [7] noted that migraineurs who received BoNT-A injections for wrinkles reported improvement in their headaches. These results led to an open-label, multicenter trial of BoNT-A in 106 predominantly female patients with migraine. Patients were defined as having "true migraine" if they met all four diagnostic criteria for migraine as defined by the International Headache Society (IHS). Of the 77 "true migraine" sufferers treated prophylactically in this open-label trial, 89% reported a complete (51%) or partial (38%) response. As pointed out by Loder and Biondi [6], limitations of the study included the open-label design, inconsistent criteria for patient selection, and variable injection sites.

Thereafter, Silberstein et al. [8] conducted a prospective, double-blind, vehicle-controlled 3-month study of BoNT-A treatment in 123 patients with a history of 2–8 moderate-to-severe migraine attacks per month. Patients were randomized to receive single administrations of vehicle or BoNT-A, 25 or 75 U, injected into multiple sites of pericranial muscles at the same visit. Patients receiving 25 U BoNT-A showed a significantly greater reduction in mean headache severity vs. placebo at months 1 and 2 ($p<0.029$) and significantly greater reduction in moderate-to-severe migraine frequency at month 2 ($p=0.008$) and at month 3 ($p=0.04$). A significant reduction in the numbers of migraines of any severity occurred at month 3 ($p=0.01$) and the number of days using acute migraine medications was significantly reduced at month 2 ($p=0.03$). Incidence of migraine-associated vomiting was reduced at month 3 ($p=0.01$). Unusual in this report was that the 25-U group appeared to do better than the 75-U group, but on subsequent analysis ([9] and Silberstein, personal communication) it appeared that the headaches were significantly worse by chance alone in the 75-U group.

Bigal et al. [10] discussed newer therapies for migraine, including the anticonvulsants and BoNT-A. The authors indicated that BoNT-A often reduced the pain associated with conditions such as cervical dystonia, acalasia, rectal fissures, and mild facial pain, and pointed out that open-label, non-controlled studies suggested benefits with migraine.

Evers et al. [11] reviewed a limited number of studies and concluded that there was not yet sufficient scientific evidence for a treatment recommendation with botulinum toxin. However, there is mounting clinical evidence, given the absence of a pivotal trial, that the majority of migraine, chronic migraine, and episodic tension-type headache patients treated with BoNT-A improve noticeably [12, 13]. Frietag [14] evaluated the efficacy of muscle relaxants in the treatment of migraine and tension-type headache, and noted that equivocal results were often present in early reports. Studies of BoNT-A use in migraine headache often suggest efficacy, whereas some studies of tension-type headache have not shown clinical evidence of efficacy. Frietag also indicated that the mechanism by which BoNT-A works to prevent headaches was unclear and that, although changes in muscle tone might play a role, additional mechanisms such as inhibitory effects on neuropeptides may also be relevant [14].

Guyuron et al. [15], in an evaluation of potential surgical treatments of migraine, found many patients in whom the injection of BoNT-A into the corregator ocular muscles resulted in complete elimination of migraine headaches. Eross and Dodick [16] reported a significant reduction in disability in both episodic and chronic migraine patients as a result of BoNT-A treatment in a prospective open-label study. Mauskop [17] reported (in abstract form) the results of 400 headache patients treated with BoNT-A, identifying 57 who received injections four or more times. This author indicated that many patients reported improved efficacy of abortive drugs or reduced need for triptans, and concluded that BoNT-A is effective for the long-term prophylactic treatment of intermittent and chronic migraines and possibly chronic tension-type headache. Relja and Klepac [18] similarly reported in preliminary form that in 32 patients with moderate or severe migraine-related disability randomized to BoNT-A or placebo had a reduction ($p<0.01$) in disability and also had a highly significant reduction in the need for acute medications such as triptans. Blumenfeld [19] reported a retrospective open-label study measuring the effect of BoNT-A in 271 patients with migraine and tension-type headache. Response to treatment was defined as a reduction in headache frequency or intensity. This abstract reported that 80% of patients responded to BoNT-A treatment and 60.5% had a good or excellent response. The author concluded that BoNT-A is an efficacious and safe preventive headache treatment in a variety of patients with primary headache disorder, including those previously refractory to oral preventive medications [20, 21].

Blumenfeld also commented that several open-label trials have suggested that administration through multiple injection cycles can enhance the benefits of BoNT-A. For example, Mathew and colleagues [22] indicated that there

was a dramatic decrease in MIDAS (migraine disability assessment scale) scores following one set of injections, with further significant improvement in MIDAS scores after additional cycles of injections.

Evans and Blumenfeld [21, 23] suggested that a patient with IHS-defined migraine should be treated with a fixed-site approach consisting of bilateral injections, even if the patient has strictly unilateral headaches. In their experience, using this fixed-site approach and resolving medication overuse issues, subjective improvement can be reported in more than 80% of patients [20].

Dodick [24] reviewed the treatment of migraine and other primary headache disorders, and concluded that clinical data and experience to date have demonstrated that BoNT-A is an effective and well-tolerated therapy for migraine prevention and other headache disorders. He suggested that the data from the ongoing well-designed, double-blind placebo-controlled trials may confirm a role for BoNT-A as a "first-line agent for migraine prevention."

Chronic daily headache

A subgroup of headache sufferers is afflicted with chronic daily headache (CDH), a headache that presents for more than 15 days per month and lasts 4 or more hours per day [25]. CDH is thought to derive from various types of headache including episodic migraine and chronic tension-type headache (CTTH), in which the frequency of attacks increases until a pattern of daily or near daily headache evolves [25]. Within the CDH population, Silberstein et al. [26] noted that roughly 78% have chronic migraine, 15% have CTTH, and 7% have other chronic headache disorders. Almost 5% of the general population (9% of women) suffer from CDH, and some 80% of these overuse symptomatic medications [27]. My personal experience, discussed later, and that of others [23] suggests that BoNT-A may be one of the most effective therapies for chronic daily headache, along with analgesic reduction.

Klapper and Klapper [28] reported a small study in which four out of five patients treated with botulinum toxin showed marked benefit for both chronic daily headache and migraine. Later, Klapper et al. [29] reported the results of a double-blind trial of 56 patients suggesting a significant reduction with BoNT-A compared to placebo. However, as pointed out by Loder and Biondi [6], "Although these results are promising, no conclusions regarding the efficacy of BoNT-A in CDH can be drawn until the investigators publish the full text of a larger study."

Tension-type headache

There is a relatively inconclusive body of literature which has shown mixed results for BoNT-A in different headache types. For example, Smuts et al. [30] reported the efficacy of BoNT-A in the treatment of CTTH in a controlled trial, while in a later trial conducted by Schmitt and colleagues [31], BoNT-A treatment was not different from placebo. The differences in the injection protocols between these two studies include the BoNT-A dose, the choice or lack of a cervical muscle injection site, and the duration of follow-up. Such differences in protocol may have resulted in the distinctly different treatment outcomes observed for the treatment of CTTH. Evans and Blumenfeld recommended a combination of both fixed-site and follow-the-pain injection in patients with chronic daily headache [23].

Evans and Blumenfeld [23] reviewed the data on tension-type headache and indicated that there was significant improvement of this headache form when wrinkles were treated with BoNT-A [32]. As they pointed out, results of earlier research have not been consistent because they were open-label studies involving small numbers of patients [33, 34]. Another study of 6 patients reported a negative outcome with regard to pain intensity [34], however other brief reports showed improvement of headaches [35]. On the basis of some studies [31, 36] that found no significant difference between placebo and BoNT-A treatment in tension-type headache patients, it may be concluded that increased muscle tension does not have an acute role in this headache form. However, in a double-blind placebo-controlled study [30], 13 of 22 patients experienced improvement in headache severity with BoNT-A compared to 2 of 15 patients in the placebo group. Porta [37] reported that BoNT-A was superior for the treatment of myofacial pain compared to methoprednisolone. Moreover, BoNT-A has shown promise in several clinical trials in patients with CTTH and migraine [7, 8, 30], although the precise mechanism by which the headache pain is reduced is unclear.

Other conditions

Freund and Schwartz [38] evaluated whiplash-associated disorders resulting from trauma and reported that BoNT-A had relieved pain and improved range of movement in some small trials. They noted that botulinum toxin could be used as a diagnostic tool to identify situations in which whiplash disorder was primary or secondary to muscle causes. They had previously conducted a pilot study [39] exploring potential beneficial effects of relaxing certain

neck muscles with BoNT-A, and noted that four weeks after injection the treatment group had significantly improved from pre-injection levels. The placebo group did not demonstrate any significant change at any time during the treatment [39].

Wheeler et al. [40] evaluated a small number of patients with chronic non-whiplash neck pain and found that pain reduction with BoNT-A was similar to that with placebo. However, the total dose of BoNT-A, administered in the neck, ranged from 50 to 100 U, a dosage believed by Freund and Schwartz [38] to be insufficient to relieve neck pain. Wheeler et al. [40] indicated that some patients were retreated with larger doses with symptomatic improvement. Once again, it was concluded that additional research was necessary to determine whether high doses and sequential injections would improve the results. Freund and Schwartz [38] believe that headache is one symptom of chronic whiplash-associated disorder that does respond well to BoNT-A injections, even if neck pain persists.

Temporomandibular disorder (TMD) is a term used to characterize a variety of conditions that involve the temporomandibular joint and surrounding musculature. Freund and Schwartz [41] performed an open-labeled study of BoNT-A reatment in 60 patients with clinical temporomandibular dysfunction, of whom 46 patients met the diagnostic criteria for chronic tension-type headache. They injected the temporalis, masseter, and medial and lateral pterygoid muscles, and observed a significant improvement when BoNT-A was used for temporomandibular disorders including bruxism, oral mandibular dystonia, and tension headache. Thirty-eight of 60 subjects (63%) reported a 50% improvement in facial pain at the follow-up examination. The subset of 46 subjects with chronic tension-type headache and TMD symptoms reported a 50% or greater improvement of headache pain. These authors concluded that masticatory muscles, specifically the temporalis, may be involved in the pathogenesis of this specific type of chronic tension-type headache.

Personal experience

My colleagues and I performed a retrospective analysis of an open-label, single-center study of 600 patients with intractable headache, treated with BoNT-A, between April 2000 and September 2003. This study was conducted in compliance with the Declaration of Helsinki, followed IHS guidelines and received approval from an institutional review board. The study enrolled patients diagnosed with migraine, episodic tension-type headache (ETTH), or chronic daily headache (CDH) according to IHS criteria. The treatment protocol was tailored according to individual patient's need, with intramuscular injections administered at a fixed site, according to a "follow the pain" protocol, or with a combination of both approaches depending on the location of pain and the presence of muscle spasm or tenderness.

For frontal headaches, the procerus, frontalis and temporalis muscles were injected with 30–50 U BoNT-A (Figs. 1, 2). For posterior headaches, the occipitalis (20 U) and trapezius (35 U on each side) muscles were injected (Figs. 3, 4). When muscle tenderness or spasm was present, the rhomboids were injected with 40 U BoNT-A divided between the two sides. Following the injections, patients were required to complete a full 3-month treatment period at which time treatment effects were assessed and, if required, further treatment was administered. The primary outcome measure was the self-evaluation of BoNT-A treatment effect 3 months after injection using a 5-point categorical scale (1, no change; 2, mild improvement; 3, moderate improvement; 4, good improvement; and 5, excellent improvement) developed for the purpose of this study. The scale evaluated post-treatment improvement based on the patients' subjective analyses of their symptoms before treatment. Safety was assessed from the patients' spontaneous reports of adverse events (AEs) to the investigating physician.

The initial analysis of 436 patients has been reported in abstract form [13]. As of the time of this writing, 2000

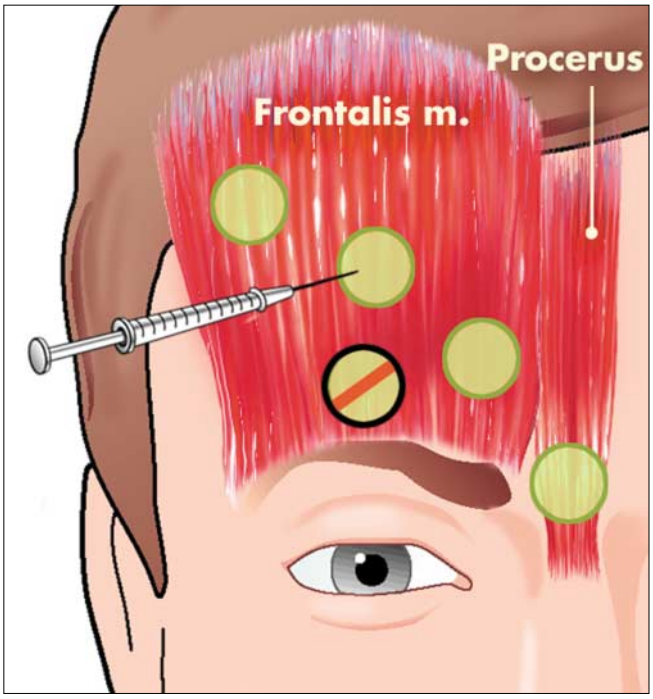

Fig. 1 Anterior injection sites in procerus and frontalis muscles. Each injection site (*green circles*) received 2.5–5.0 U of BoNT-A

injections have been performed on 600 patients. In the preliminary analysis, the 436 patients were administered at least one treatment of BoNT-A. Most of the patients (>95%) had previously failed 3 or more preventive pharmacologic therapies for migraine. The majority of patients (340 of 436, 78%) were female. The mean age of the patients was 46 years (range, 12–88 years) and four of the patients were minors (12–16 years of age).

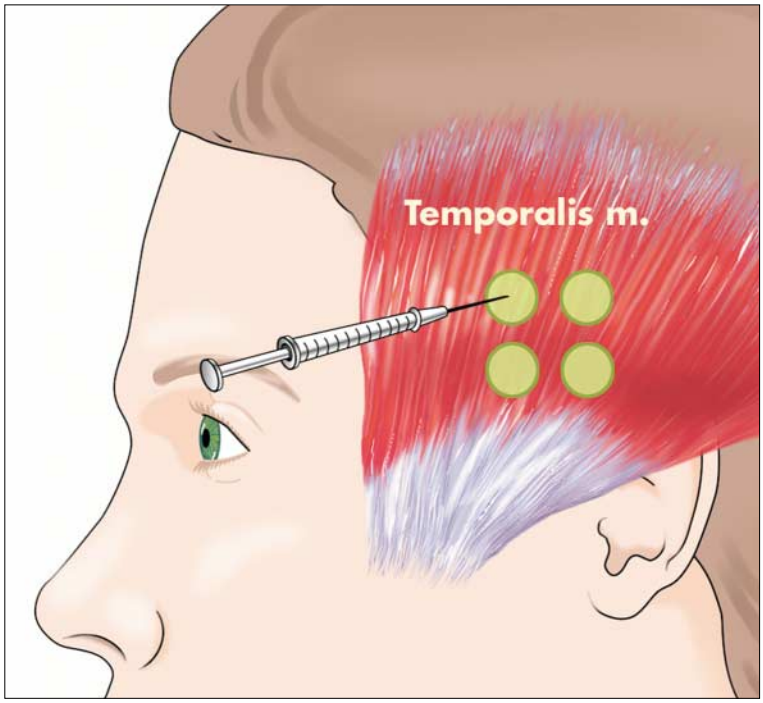

Fig. 2 Potential injection sites in temporalis muscle. Some patients received more or less depending upon pain location

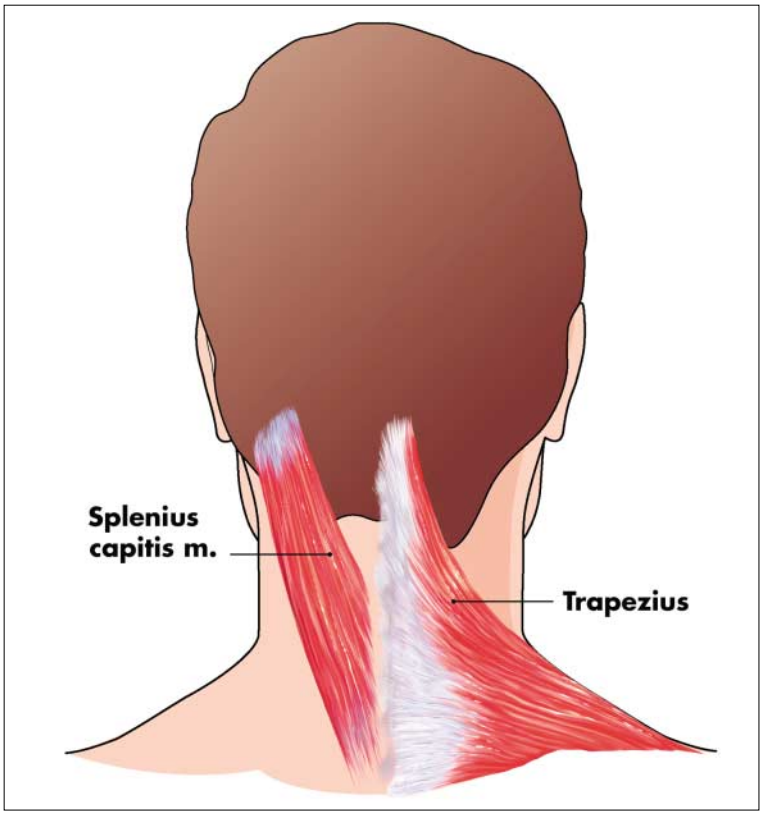

Fig. 3 Posterior view displaying splenius capitis and trapezius muscles

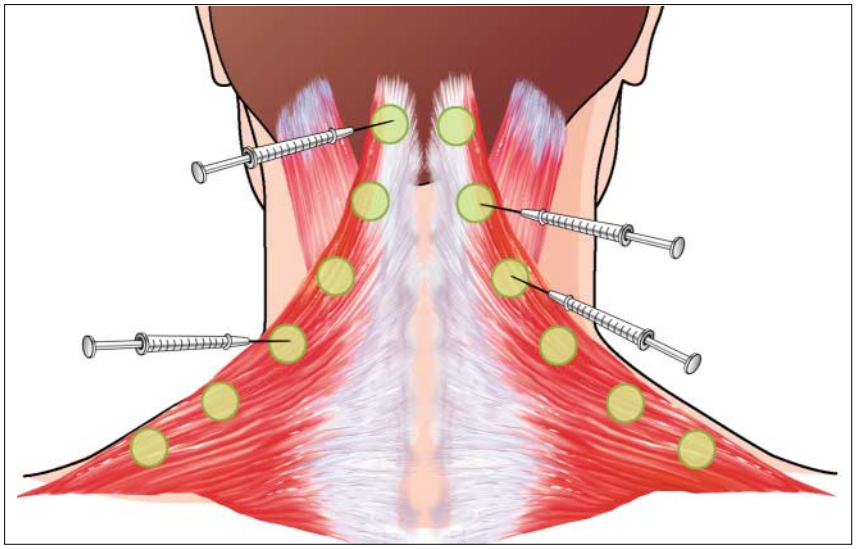

Fig. 4 Injection sites in trapezius and splenius capitis muscles. The number of injection sites and doses vary from patient to patient depending upon size, pain location, and palpable muscle spasm

After administration of BoNT-A, patients rated the level of improvement as a result of treatment. The combined mean patient-rated improvement score for all treatments across all headache types was 3.6 (moderate to good) for those receiving 1–8 treatments. This result was based on the patients who had at least 1 result recorded (n=334). Patients administered 2 treatments noted significantly greater improvement than those administered 1 treatment ($p<0.05$, paired t test). Likewise, patients administered 3 treatments noted significantly greater improvement than those administered 2 treatments ($p<0.05$, paired t test). The overall mean improvement scores for each specific type of headache were 3.5, 3.8, and 3.5 for CDH, migraine, and ETTH, respectively.

Improvement for patients with CDH was cumulative through 3 treatments and was maintained through 12 treatments. In contrast, in patients with migraine, improvement was cumulative through 4 treatments and was maintained through 12 treatments. Overall, 91% of patients noted improvement as a result of BoNT-A treatment, and 75% of patients reported improvement as good to excellent. The percentage of patients reporting good to excellent improvement increased from 51% after 1 treatment to 85% after 6 treatments. The mean dose of BoNT-A used in this trial was 115 U for patients who received 1 treatment; for patients receiving more treatments, the average dose was 127 U. Of the initial 436 patients who were assessed after 3 months, the majority (64%) decided to proceed with a second treatment.

This study lends strong support to a global approach to headache management with BoNT-A. The use of injection protocols tailored to meet individual patient's needs and administration of sufficient doses of BoNT-A are important considerations as well as adequate follow-up intervals and repeated treatment if necessary. In summary, there is a mounting body of evidence, albeit much of it open-label, to suggest that BoNT-A has a significant role in the treatment of migraine, chronic daily headache, chronic tension-type headache, neck muscle spasm, and atypical facial pain.

Mechanism of action

Patients with intractable headache may benefit from treatment with BoNT-A, a focally acting neurotoxin that inhibits the release of acetylcholine and other neurotransmitters from presynaptic nerve endings. At the neuromuscular junction this results in reduced muscle tone, but there is speculation that BoNT-A can also affect pain signaling [42]. Botulinum toxin type A treatment has been shown to relieve pain associated with the muscle hyperactivity characteristic of cervical dystonia and spasticity [43–46] without vascular or systemic effects. There is discussion that the antinociceptive effects of BoNT-A may extend beyond its effects on muscle relaxation. Improvement in pain has been reported in cervical dystonia before the advent of muscle relaxation, with pain relief surpassing the degree of muscle spasm reduction [47, 48]. Based on limited in vitro and in vivo data, it is possible that BoNT-A treatment may reduce the local release of nociceptive neuropeptides [42, 49, 50], thereby reducing the perception of pain.

In my experience, patients with migraine with aura usually experience reductions in headache along with a reduction in aura. Menstrual migraine-associated headache is also reduced following the use of botulinum toxin, prompting investigators to consider whether there is central desensitization from the peripheral muscle and scalp injections of botulinum toxin.

Aoki [51] reviewed the evidence for antinociceptive activity of BoNT-A and pain management and suggested that BoNT-A blocks peripheral sensitization and indirectly "reduces central sensitization." This would then fit in with the hypothesis that migraine involves both peripheral and central sensitizations and that BoNT-A may inhibit migraine pain by acting on these two pathways.

Dolly [52] reviewed the molecular basis for inhibition by botulinum toxins of neuroexocytosis in subsequent functional recovery at the neuromuscular junction, resulting in muscle relaxation and contributing to pain relief. He pointed out that, additionally, BoNT-A inhibits exocytosis from sensory neurons in the dorsal root ganglia and reduces the release of other neurotransmitters, such as glutamate and peptide neurotransmitters, due to the cleaving of SNAP-25.

Loder and Biondi [6] believed that muscle tension may trigger or aggravate migraine headache. By reducing muscle hyperactivity and tension, botulinum toxin may reduce headache. Silberstein [53] reviewed the basic neurobiological mechanisms of pain sensation, focusing on migraine pain.

Conclusions

Interpretation of the high response to BoNT-A is limited by several factors including the open-label nature of the design, retrospective analysis, and the failure to quantify the patients' pretreatment pain on a validated scale such as a visual analogue scale for pain. Nevertheless, these results provide further support for the potential role of BoNT-A in headache management. At the present time, no large scale, double-blind, randomized placebo-controlled studies have been completed to validate what has been noticed in clinical practice and in smaller controlled trials. Currently, two large placebo-controlled, double-blind studies are underway to evaluate the effect of BoNT-A in episodic migraine and in chronic daily headache. The results of the studies are eagerly anticipated.

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