Views and Perspectives

Procedures for Administering Botulinum Toxin Type A for Migraine and Tension-type Headache

Andrew M. Blumenfeld, MD; William Binder, MD; Stephen D. Silberstein, MD, FACP; Andrew Blitzer, MD

Key words: botulinum toxin type A, migraine, tension-type headache

Abbreviations: BoNT-A botulinum toxin type A, TTH tension-type headache

(*Headache* 2003;43:884-891)

Headache can be debilitating, causing lost productivity at work or school, impaired quality of life, and disruptions in family and social life.[1,2] The limited clinical efficacy of current preventive therapies for headache, coupled with the substantial side effects of these treatments, indicate that headache prevention is an area of unmet medical need. Botulinum toxin type A (BoNT-A) is used to treat a variety of overactive muscle and pain disorders.[3-5] Intramuscular injections of BoNT-A may provide an effective, long-lasting, and well-tolerated new approach to headache prevention and management for selected patients.

Investigators have used injection techniques with differing anatomical injection sites, doses, and concentrations of BoNT-A. The method of administering BoNT-A for headache therapy will determine, in part, the overall clinical outcome. Optimizing the protocol for clinical use of BoNT-A is, therefore, likely to improve the outcomes of therapy. This article provides a review of current practical procedures for administering BoNT-A therapy to patients with migraine and tension-type headache (TTH).

From San Diego, Calif (Dr. Blumenfeld); the Department of Otolaryngology - Head and Neck Surgery, Cedars Sinai Medical Center, Los Angeles, Calif. (Dr. Binder); the Department of Neurology, Thomas Jefferson University Hospital, Philadelphia, Pa. (Dr. Silberstein); and the Department of Clinical Otolaryngology, College of Physicians and Surgeons, Columbia University, New York, NY (Dr. Blitzer).

Address all correspondence to Dr. Andrew M. Blumenfeld, 5032 Wellworth Point, San Diego, CA 92130.

Accepted for publication May 13, 2003.

BACKGROUND

Botulinum toxin type A is approved for the treatment of a variety of conditions and pain disorders caused by muscle overactivity.[3-6] Initial serendipitous findings of a therapeutic effect of BoNT-A on migraine when it was used to treat patients for facial wrinkles were followed by a number of clinical studies in patients with headache.[4] These studies have suggested that BoNT-A is effective at reducing both migraine and TTH.[5-11] Exactly why BoNT-A is effective in relieving headache is not clear, but mechanisms of action include direct effects at the neuromuscular junction and direct antinociceptive effects on nerves in the face, head, and neck.[12] The designs of published trials range from small case studies to larger, double-blind, placebo-controlled trials, spanning the level of evidence from A to C, according to evidence-based medical standards. These studies have recently been critically evaluated according to evidence-based criteria.[12,13] While all of these studies have shown BoNT-A therapy to be safe and well-tolerated, the efficacy outcomes within the studies have not been consistent, and the conclusions drawn from the evidence-based reviews have also differed.[12,13]

There is no established or standardized methodology for the injection of BoNT-A for migraine and TTH. Inconsistencies in the way BoNT-A was administered across studies may contribute to variations in the

clinical study outcomes. Several studies used a fixed-site approach,[8,14,15] while others reported methodologies that were dependent on the anatomical location and distribution of the pain,[16-18] or a combination of the 2 approaches.[19] Other factors such as volume per injection site, number of injection sites per area, the dilution of BoNT-A, and the injection technique vary across studies and have not been consistently reported. In their critical review of the use of BoNT-A therapy for headache, Mathew and Kaup suggest that factors such as injection procedures, selection of appropriate injection sites, and BoNT-A doses play a role in the clinical efficacy outcomes.[12] This finding is supported by the clinical experience of the authors of this article.

As more clinicians involved in the care of patients with disabling headache disorders consider BoNT-A as a potential treatment, there is an increasing need for a standardized protocol for drug administration. We present here a review of the administration of BoNT-A for the treatment of headache, based on our own extensive clinical experience and that of other investigators.

METHODS

Considerations for Preventive Headache Therapy.—Selection of appropriate candidates for preventive therapy begins with accurate diagnosis and classification. This is based on a comprehensive headache history to rule out secondary headaches resulting from other causes such as tumor, infection, metabolic disorders, or other systemic illness. A medical history, including information on medications used and any prior plastic surgery, must be obtained before treatment. The overall goal of headache prevention is to help the patient to achieve the goals set forth by the US Headache Consortium; namely, to reduce headache frequency, severity, and disability, and improve the quality of life by reducing headache-related distress and symptoms.[20] Specifically, physicians can assess the success of preventive therapy based on the decreased frequency and intensity of headache, improved functioning and decreased disability, reduced use of other headache medications, as well as the increased efficacy of acute headache medications. Nonpharmacologic approaches for managing headache disorders, including exercise and dietary adjustment, continue to play an important role in headache management.[21]

Patients who are most likely to benefit from preventive therapy include those with recurring migraines that, in the patient's opinion, significantly interfere with their daily routine despite acute treatment; with frequent headaches; concerned about the high cost of acute therapies; with extant uncommon migraine conditions including hemiplegic migraine, basilar migraine, migraine with prolonged aura, or migrainous infarction; and who overuse, cannot tolerate, or poorly comply with acute treatment.

Specifically, BoNT-A therapy may be appropriate for patients with disabling primary headaches for whom other preventive medications are poorly tolerated or contraindicated, for those with compliance problems, for those refractory to other treatments, for special patient populations, as well as for those who simply prefer this treatment (Table 1). In addition, patients with headache and jaw, neck, or head muscle spasms should be considered candidates for treatment with BoNT-A.[22]

Contraindications to the use of BoNT-A include sensitivity to toxin or neuromuscular disorders such as myasthenia gravis or Eaton-Lambert syndrome.

Pretreatment Considerations.—Physicians should review the known side effects of BoNT-A treatment, including possible headache, rash, bruising, or

Table 1.—Candidates for Botulinum Toxin Type A Therapy for Headache

- Patients with disabling primary headaches
- Patients who have failed to respond adequately to conventional treatments
- Patients with unacceptable side effects (from existing treatment)
- Patients in whom standard preventive treatments are contraindicated
- Patients in special populations or situations (the elderly, those at risk of unacceptable side effects from trial drugs or traditional treatments, airplane pilots, students studying and preparing for examinations)
- Patients misusing or abusing or overusing medications
- Patients with coexistent jaw, head, or neck muscle spasm
- Patients who prefer this treatment
- Patients with disabling primary headaches
- Patients who have failed to respond adequately to conventional treatments

eyebrow and eyelid ptosis, with the patient and obtain informed consent. Patients should also be told that multiple treatment cycles may be needed to achieve an optimal therapeutic effect.[19] Have patients indicate the principal sites of their head pain, pointing to the anatomical locations most frequently affected. Examine the face and neck to assess muscle tone, asymmetry, and brow position. Palpate the frontalis, temporalis, and posterolateral neck and shoulder regions to identify areas of tenderness and anatomical sites that produce pain on palpation. Patients can be placed either in a sitting or supine position for injection of the frontal and temporal regions and in a sitting position for injection of the posterior neck region and trapezius.

The total dose of BoNT-A to be administered should be individualized by taking into account the specific features of each patient, including type of headache, severity of symptoms, and body size. One study demonstrated clinical efficacy with a total dose of 25 units (U);[8] however, studies that are more recent suggest that higher doses are needed to secure more consistent efficacy.[13]

Dilution and Reconstitution Procedures.—Two BoNT-A complexes (Botox and Dysport) and one type B complex (Myobloc) are approved for clinical use. These 3 products have different dosing, safety, and efficacy characteristics. There are no established methodologies to calculate equivalent doses.[3]

Only one type A toxin is available in the United States. Lyophilized BoNT-A (Botox, Allergan, Inc, Irvine, CA) is available in vials containing 100 U of BoNT-A. One vial is diluted with 2 or 4 mL of preservative-free 0.9% saline, which yields a preparation of 5.0 or 2.5 U per 0.1 mL, respectively.

Injection Technique.—Sterile injection technique should be observed for the entire procedure. Injections should be intramuscular; avoid injecting the periosteum and injecting intradermally in order to minimize discomfort and the risk of intra-arterial injection. Inject symmetrically in the frontalis region to avoid facial asymmetry. Visualization and avoidance of the superficial blood vessels helps to minimize risk of bruising. If pain is not present in the inferolateral frontalis regions (lateral suprabrow areas), avoid injection there to reduce the risk of brow ptosis.

Injection Sites and Procedures.—The entire anatomical area affected by pain should be injected with sufficient amounts of toxin in adequate volume to maximize clinical effect (unpublished observations). The injection sites commonly used for BoNT-A treatment of headache are the glabellar and frontal regions, the temporalis muscle, the occipitalis muscle, and the cervical paraspinal region.[4,5,7-10,16,17,23]

Protocols for Injection.—There are 3 injection protocols commonly used. The overall objective is to inject toxin at multiple sites to ensure complete dispersal of toxin through the target regions. These protocols can be described as a "fixed-site" approach, a "follow-the-pain" approach, and a "combination" approach.

The fixed-site method is often used for patients with migraine or migrainous headache. This approach is based on clinical experience and uses fixed symmetrical injection sites and a range of predetermined doses. Patients treated for unilateral headaches with a unilateral injection may develop headaches on the opposite, untreated side. In 2 studies that utilized a fixed-site approach, one in patients with chronic TTH and the other in patients with migraine, headache symptoms improved significantly more in patients receiving injections of BoNT-A than in patients receiving placebo.[8,23] Using a modification of the fixed-site approach (Table 2), we recently obtained a marked reduction in the use of additional oral headache medications in 37 of 50 patients with migraine.[24]

The follow-the-pain approach is most often used to treat TTH. The sites and doses are adjusted depending on the patient's symptom profile and the location of pain and tenderness. Assess head and neck position, muscle bulk, tender spots, and temporomandibular joint function. The muscles selected for injection in the posterior neck are similar to those injected in patients experiencing pain associated with cervical dystonia. The injection sites are determined by where the patient feels pain and where the examiner can elicit pain and tenderness on palpation of the muscle. A follow-the-pain approach is suitable where torticollis is not present. Subtle torticollis can be a cause of head and neck pain, particularly anterocollis with posterior neck pain (often caused by overactive sternocleidomastoid muscles) or lateral collis (often caused by overactive splenius capitis, sternocleidomastoid, levator scapulae,

Table 2.—Variations of the Fixed-Site Approach to Botulinum Toxin Type A Injection*

Muscle	Source, No. of Botulinum Toxin Type A Units Injected, No. of Sites Injected		
	Blumenfeld, 2002[14]	Silberstein et al, 2000[8]	Smuts et al, 1999[23]
Procerus	5	3 or 9, 1 site	—
Medial corrugator	2.5-4	1.5 or 4.5, 4 sites of medial and lateral muscles	—
Lateral corrugator	2.5	1.5 or 4.5, 4 sites of medial and lateral muscles	—
Frontalis	2.5 per site, 4-6 sites per side	2.5 or 7.5 per site, 4 sites	—
Temporalis	2.5-5, 4 sites	3 or 9, 2 sites	9, 2 sites
Suboccipital area	5 (optional)	—	7, 2 sites
Trapezius	15-25, 3 sites	—	9, 2 sites
Botulinum toxin type A concentration	100 U/4 mL	Not reported	100 U/2 mL
Total injection sites	25	11	12

*All injections were performed bilaterally, with the exception of those in the procerus muscle. —Indicates site was not injected.

or trapezius muscles with pain on the contralateral side). For patients with torticollis, injections must be into overactive muscles, since weakening contralateral muscle groups with botulinum toxin injections could worsen the pain. Botulinum toxin type A injection protocols for patients with torticollis have been reviewed elsewhere.[25]

Bilateral symmetrical frontalis injections help to maintain visible facial symmetry. Elsewhere, injections, when bilateral, need not be symmetrical. The total dose of BoNT-A ranges from 100 to 150 U. Muscles typically injected for TTH include the frontalis, temporalis, occipitalis, splenius capitis, trapezius, and cervical paraspinal muscles, although the use of a range of muscle sites and doses has been reported in the literature.[7,14,16-18] Table 3 summarizes reported variations in this technique. The patient's clinical response to treatment is used to adjust subsequent doses.

Table 3.—Variations of the Follow-the-Pain Approach to Botulinum Toxin Type A Injection in Patients With Tension-type Headache*

Muscle	Blumenfeld, 2002[14]	Relja, 1997[16]	Wheeler, 1998[18]	Relja and Korsic, 1999[17]	Freund and Schwartz, 2000[7]
Trapezius	2-3 sites	—	X	—	X
Splenius capitis	1 site	—	X	—	X
Semispinalis capitis	1 site	—	—	—	X
Occipitalis	1-2 sites	—	—	—	—
Sternocleidomastoid	2 sites	X	—	X	—
Temporalis	4 sites	X	X	X	—
Frontalis	4-5 sites	X	X	X	—
Corrugators	—	—	X	—	—
Rectus capitis	—	—	—	—	X
Botulinum toxin type A concentration	100 U/4 mL	NR	NR	NR	100 U/1 mL
Dose at each site or	5-10 per site	NR	NR	NR	NR
Total dose, U	65-100	15-35	197	35-80	100

*—Indicates site not injected; X, muscle injected but number of sites not provided; NR, not reported.

Patients often have coexisting migraine and TTH. In these cases, a combination of the fixed-site and follow-the-pain approaches is used. These patients generally receive higher doses of BoNT-A. The fixed-site approach is supplemented with additional injections of BoNT-A in areas that are tender or consistently symptomatic (or a combination of both).

Anatomical Considerations.—GLABELLAR AREA.—This area consists of the procerus (a midline muscle) and the corrugator muscles. In the glabellar area, smaller fluid volumes (ie, 0.1 mL) per injection will minimize spread to adjacent muscles. In addition, precise placement of small volumes with slow injection of the toxin is important to prevent dispersion of the toxin. Approximately 12.5 to 20 U are given in the glabellar area at 5 injection sites, 1 in the procerus and 2 in each corrugator (Figure 1).

PROCERUS MUSCLE.—The procerus is a triangular muscle between the frontalis muscles. Its apex extends to the bridge of the nose, while its base sits above the brows. Injections of approximately 2.5 to 5 U should be made in the base of this muscle (Figure 1).

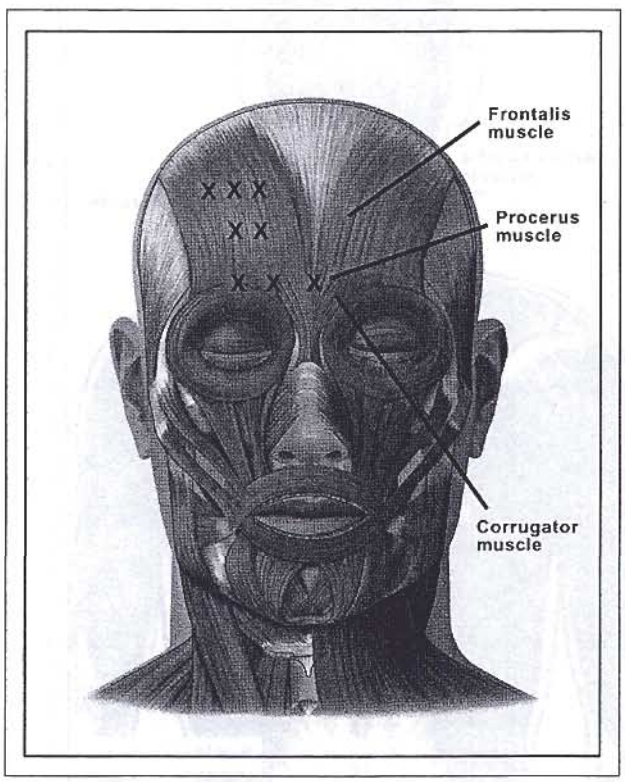

Fig 1.—Injection sites for botulinum toxin type A in the treatment of headache: glabellar and frontal regions. Copyright (c) 2003 Nucleus Medical Art, All rights reserved. www.nucleusinc.com

CORRUGATOR MUSCLE.—To identify injection sites for the corrugator muscles, have the patient frown. The medial aspect of the corrugator muscle corresponds to where the supratrochlear nerve exits from its foramen. The mid-to-lateral aspect of the corrugator muscle injection site corresponds to the supraorbital nerve course. Direct pressure at the border of the supraorbital ridge can reduce the potential for extravasation of BoNT-A downward into the eyelid and avoid inadvertent weakening of the levator muscle of the upper eyelid and ptosis. By grasping the mid-to-lateral portion of the corrugator muscle between 2 fingers, the deposition of BoNT-A into this area can be more precisely delivered. Eyelid ptosis rarely occurs when proper injection technique is used. Sites and doses are shown in Figure 1 and Table 2.

FRONTALIS MUSCLE.—In sites such as the forehead and temporal regions, greater dispersion of the toxin with larger volumes is preferred. In the area of the forehead, the dosage and number of injections may range from 20 to 30 U dispersed among 8 to 12 injection sites. Assess the location of the frontalis muscle by having the patient elevate his or her eyebrows prior to injection. This helps to identify areas where needle placement will occur. Injection of the lower third of the frontalis muscle with BoNT-A will inhibit the patient's ability to raise the brows. To avoid brow ptosis, avoid injecting the area of the forehead over the lateral aspect of the brow. This is the area between the brow and an oblique line drawn from the medial eyebrow to a point approximately 1 cm above the lateral portion of the eyebrow (Figure 1). If this area does require injection, brow ptosis can be reduced by injecting the lateral aspect of the infrabrow or eyelid area to reduce the downward pull of the lateral orbicularis oculi muscle.

The area directly lateral to the brow is the anterior temporal region or "temple" (Figure 2). If the patient has pain in this area, it can be injected with an additional 2.5 U. If pain is present over the lateral supraorbital region and injection is required, patients should be informed that brow ptosis might occur. Most patients are able to adapt well to a lowering effect of the

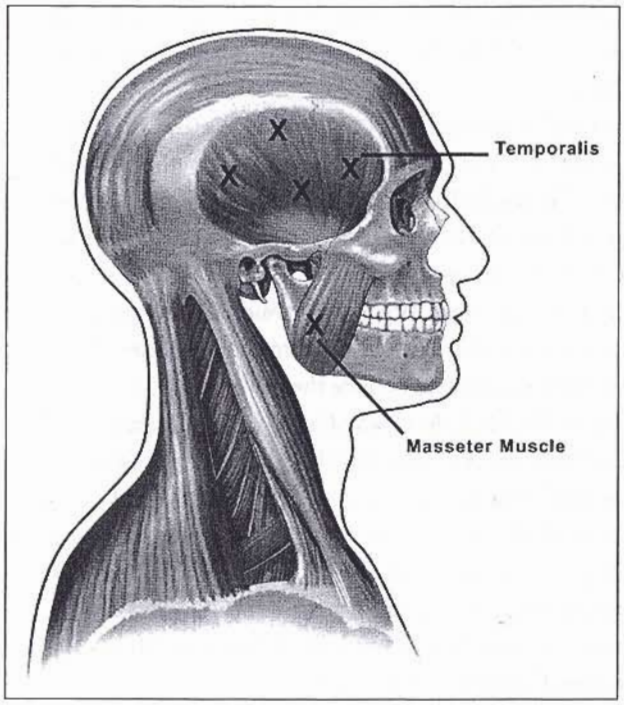

Fig 2.—Injection sites for botulinum toxin type A in the treatment of headache: temporalis, masseter, and suboccipital regions. Copyright (c) 2003 Nucleus Medical Art, All rights reserved. www.nucleusinc.com

lateral part of the brow without significant problems if this area requires injection.

TEMPORALIS MUSCLE.—The temporal area, like the frontal area of the forehead, should be injected bilaterally. Having the patients clench their teeth can identify the anterior aspect of the temporalis muscle. This produces an identifiable impulse that can be visualized or palpated. The posterior, superior, and inferior aspects of the temporalis muscle can also be injected (Figure 2). We usually inject approximately 0.2 mL per site (5 U) in 4 sites, providing an average dose of 20 U per temporalis muscle. Because of the large size of this muscle, if needed, a larger volume per site can easily be injected without affecting adjacent muscles.

OTHER MUSCLES.—If the patient has posterior neck pain, then the occipital or cervical paraspinal areas should be evaluated (Figure 3). Pain may be present in the occipital area but more typically is located in the cervical paraspinal area, below the nuchal ridge, where the trapezius, splenius capitis, and semispinalis capitis converge. It is not necessary to differentiate the specific muscles injected. Rather, the areas associated with pain and tenderness on palpation, typically in the region of the splenius capitis, should be injected. Inject 1 or 2 sites on each side with the total dose varying between 5 to 15 U per side (Figure 3). If there is involvement of the trapezius, this area should also be injected (1 to 3 sites per side; dose varying between 5 to 15 additional U). Masseter muscles should be injected in patients with features of temporomandibular disorder. These patients typically respond to 5 to 15 U per side for masseters, combined with injections to temporalis muscles as described above. In patients with torticollis, the overactive muscles should be injected (eg, sternocleidomastoid muscles in patients with anterocollis).

Side Effects.—The side effects of BoNT-A injections are minimal and have been described in detail elsewhere.[26,27-29] No systemic reactions have been noted in studies of BoNT-A therapy for headache.

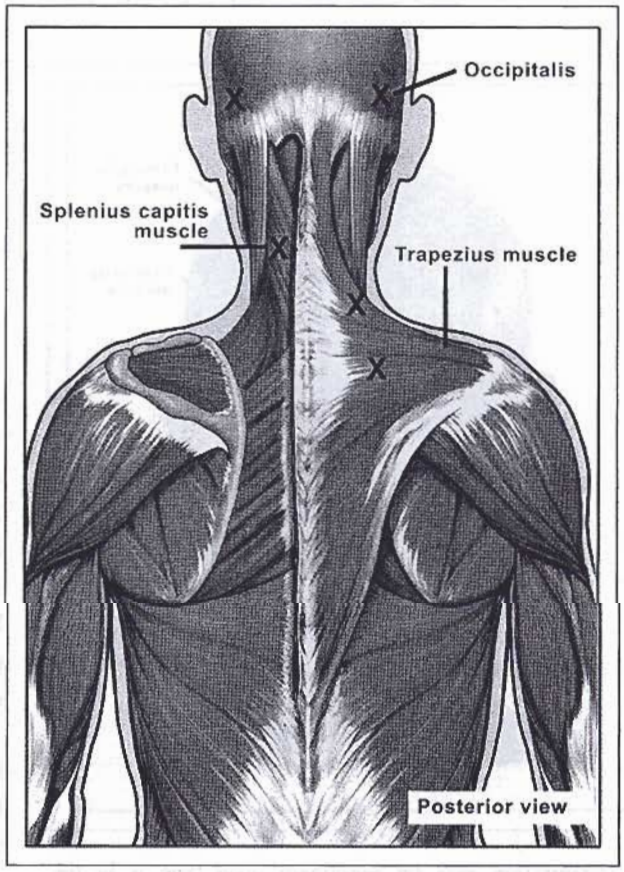

Fig 3.—Injection site for botulinum toxin type A in the treatment of headache: occipitalis muscle. Copyright (c) 2003 Nucleus Medical Art, All rights reserved. www.nucleusinc.com

Silberstein et al reported that treatment-related adverse events were transient and included blepharoptosis, diplopia, and muscle weakness at the injection sites.[8] Furthermore, as described above, minor side effects can be minimized through injection technique.

Postinjection Patient Management.—Patients should be reassured that any wheals or blebs at the injection site, particularly on the forehead, will disappear within approximately 2 hours. Patients should also be prepared for the reduction in hyperfunctional lines of the face. The effect on the dynamic, hyperfunctional lines of facial expression may take several days. The headache relief produced by BoNT-A may take several weeks to reach its maximal benefit. The response to injection may change over time; with repeated injections, some patients report a greater therapeutic effect.[12]

Patients should be evaluated 4 to 6 weeks after the first injection. Patients still need acute medications for breakthrough headaches. They should be instructed to maintain a headache diary in order to document the frequency, location, and severity of headache, and the amount of medication taken over a full 4-month period from the start of therapy. The headache diaries provide an extremely important objective measure for determining the effectiveness of treatment and directing future treatment. The need for repeat treatments varies among patients, but typically will be at 3 to 4 months.

CONCLUSION

The mechanisms by which BoNT-A relieves head pain are not fully understood. However, despite the ambiguity regarding specific mechanisms of action of BoNT-A in headache, empiric evidence and results of clinical investigations suggest that BoNT-A is a promising treatment option for selected patients with headache. Based on the collective experience of investigators, a successful paradigm for the use of botulinum toxin therapy in the treatment of headache is emerging. Preliminary clinical evidence and the aggregate experience with the application of BoNT-A therapy to a variety of disorders in the fields of neurology, facial plastic and reconstructive surgery, and otolaryngology support the idea that selected patients with migraine and TTH can achieve a sustained, well-tolerated, and effective response to BoNT-A therapy. Further clinical experience and controlled investigations will help to refine the technique for administering BoNT-A therapy for specific patient types and clinical disorders.

REFERENCES

1. Solomon GD. Treatment considerations in headache and associated medical disorders. *J Pain Symptom Manage*. 1993;8:73-80.
2. Lipton RB, Silberstein SD. The role of headache-related disability in migraine management: implications for headache treatment guidelines. *Neurology*. 2001;56:S35-S42.
3. Jankovic J, Brin MF. Botulinum toxin: historical perspective and potential new indications. *Muscle Nerve Suppl*. 1997;6:S129-S145.
4. Binder WJ, Brin MF, Blitzer A, Schoenrock LD, Pogoda JM. Botulinum toxin type A (BOTOX) for treatment of migraine headaches: an open-label study. *Otolaryngol Head Neck Surg*. 2000;123:669-676.
5. Brin M, Swope D, O'Brien C, Abbasi C, Pogoda J. Botox for migraine: double-blind, placebo-controlled, region-specific evaluation [abstract]. *Cephalalgia*. 2000;20:421-422.
6. Mauskop A, Basdeo R. Botulinum toxin A is an effective prophylactic therapy for migraines [abstract]. *Cephalalgia*. 2000;20:422.
7. Freund BJ, Schwartz M. Treatment of chronic cervical-associated headache with botulinum toxin A: a pilot study. *Headache*. 2000;40:231-236.
8. Silberstein S, Mathew N, Saper J, Jenkins S. Botulinum toxin type A as a migraine preventive treatment. For the BOTOX Migraine Clinical Research Group. *Headache*. 2000;40:445-450.
9. Porta M. A comparative trial of botulinum toxin type A and methylprednisolone for the treatment of tension-type headache. *Curr Rev Pain*. 2000;4:31-35.
10. Rollnik JD, Tanneberger O, Schubert M, Schneider U, Dengler R. Treatment of tension-type headache with botulinum toxin type A: a double-blind, placebo-controlled study. *Headache*. 2000;40:300-305.
11. Relja M, Klepac N. Botulinum toxin type A as a prophylactic treatment for chronic tension type headache: long term follow-up study [abstsract]. *Neurology*. 2001;56(suppl 3):A349-A350.
12. Mathew NT, Kaup AO. The use of botulinum toxin type A in headache treatment. *Curr Treat Options Neurol*. 2002;4:365-373.

13. Evers S, Rahmann A, Vollmer-Haase J, Husstedt IW. Treatment of headache with botulinum toxin A—a review according to evidence-based medicine criteria. *Cephalalgia*. 2002;22:699-710.
14. Blumenfeld A. Botulinum toxin type A (BOTOX™) as an effective prophylactic treatment in headache [abstract]. *Cephalalgia*. 2002;22(suppl 1):20.
15. Miller T, Denny L. Retrospective cohort analysis of 48 chronic headache patients treated with botulinum toxin type A (BOTOX®) in a combination fixed injection site and follow-the-pain protocol [abstract]. *Headache*. 2002;42:389-463.
16. Relja M. Treatment of tension-type headache by local injection of botulinum toxin [abstract]. *Eur J Neurol*. 1997;4(suppl 2):71-72.
17. Relja M, Korsic M. Treatment of tension-type headache by injections of botulinum toxin type A: double-blind placebo controlled study. *Neurology*. 1999;52(suppl 2):A203.
18. Wheeler AH. Botulinum toxin A, adjunctive therapy for refractory headaches associated with pericranial muscle tension. *Headache*. 1998;38:468-471.
19. Mathew N, Kallasam K, Meadors L. Disease modification in chronic migraine with botulinum toxin type A—long-term experience. *Headache*. 2002;42:389-463.
20. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55:754-762.
21. Campbell J, Penzien D, Wall E. Evidence-based guidelines for migraine headache: behavioral and physical treatments. *Neurology* [serial on-line]. Available at: http://www.neurology.org. Accessed October 25, 2002.
22. Blitzer A, Sulica L. Botulinum toxin: basic science and clinical uses in otolaryngology. *Laryngoscope*. 2001;111:218-226.
23. Smuts J, Baker M, Smuts H, Stassen J, Rossouw E, Barnard P. Prophylactic treatment of chronic tension-type headache using botulinum toxin type A. *Eur J Neurol*. 1999;6(suppl 4):S99-S102.
24. Blumenfeld A. Decrease in headache medication use and cost after botulinum toxin type A (Botox®) treatment in a high triptan use population [abstract]. *Headache*. 2002;42:420.
25. Brashear A. The botulinum toxins in the treatment of cervical dystonia. *Semin Neurol*. 2001;21:85-90.
26. Carruthers A, Carruthers J. Update on the botulinum neurotoxins. *Skin Therapy Lett*. 2001;6:1-2.
27. Brin MF. Botulinum toxin: chemistry, pharmacology, toxicity, and immunology. *Muscle Nerve Suppl*. 1997;6:S146-S168.
28. Huang W, Foster JA, Rogachefsky AS. Pharmacology of botulinum toxin. *J Am Acad Dermatol*. 2000;43(2 pt 1):249-259.
29. BOTOX [package insert]. Irvine, Calif: Allergan, Inc; 2000.