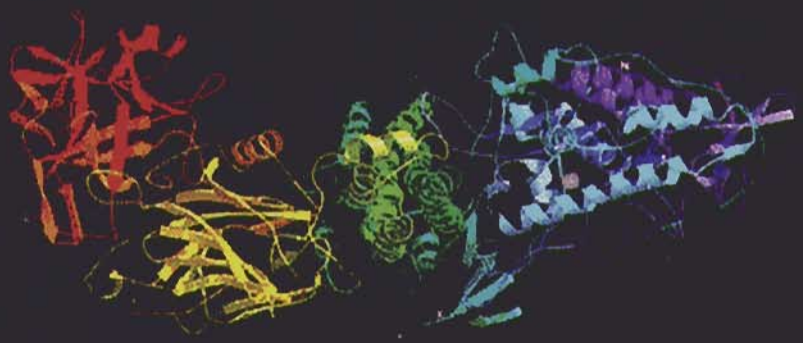
Scientific and Therapeutic Aspects of Botulinum Toxin



EDITORS

Mitchell F. Brin, MD

Mark Hallett, MD

Joseph Jankovic, MD

LIPPINCOTT WILLIAMS & WILKINS

Scientific and Therapeutic Aspects of Botulinum Toxin
edited by M.F. Brin, J. Jankovic, and M. Hallett
Lippincott Williams & Wilkins, Philadelphia, © 2002.

23

Botulinum Toxin Type A BOTOX® for Pain and Headache

Mitchell F. Brin, William Binder, Andrew Blitzer, Lawrence Schenrock, and Janice M. Pogoda

INITIAL OBSERVATIONS OF THE ANALGESIC EFFECTS OF BOTULINUM TOXIN A

Botulinum toxin type A (BTX-A; commercial preparations BOTOX®, manufactured by Allergan Inc., Irvine, California, USA; and DYSPORT, manufactured by Ipsen Pharmaceuticals, France) is one of seven distinct serotypes (A to G) of neurotoxin produced by the bacterium *Clostridium botulinum.* When injected directly into contracting muscles, BTX-A binds to the presynaptic nerve terminal, becomes internalized, and interferes with the docking of the neurotransmitter acetylcholine (ACh) with the presynaptic membrane at the neuromuscular juncture by cleaving the synaptosomal-associated protein of 25 kDa (SNAP-25) protein. This action creates chemical denervation so that muscle contraction is inhibited, thereby producing muscle weakness or relaxation. The effects of BTX-A are dose dependent. In addition, the effects are temporary because the presynaptic terminal sprouts new accessory terminals and the main terminal recovers its ability to release ACh. The recovery process takes about 3 months (1).

Therapeutic use of BTX-A in humans was first reported in 1980 for pediatric strabismus (2), and later for other ophthalmologic disorders (3,4), blepharospasm (5), and other dystonias, such as hemifacial spasm (6). Its analgesic effects were first reported in 1985 in a pilot study of BTX-A treatment for cervical dystonia, characterized by abnormal, involuntary neck and shoulder muscle contractions and often resulting in significant, disabling musculoskeletal pain. Tsui et al. described that the most marked benefit of BTX-A injections was pain relief in all six patients who reported severe neck pain caused by muscle spasm (7). In a small, double-blind, placebo-controlled extension of this pilot study, 16 patients treated with BTX-A experienced significantly reduced pain compared to placebo (8). In subsequent open-label, prospective studies involving larger numbers of patients, we reported pain relief in 74% to 84% of cervical dystonia patients following BTX-A injections (9–12). Additional double-blind, placebo-controlled studies confirmed the observed effects on pain of BTX-A in cervical dystonia patients (13–16).

In 1992, Memin et al. reported results from a pilot study conducted in Paris, France, of BTX-A as treatment for spasticity following upper motor neuron lesion; five of six patients with pain experienced significant pain relief (17). Also in 1992, Dengler et al. reported analgesic effects of BTX-A among 10 patients treated for spastic drop foot (18). Later, a larger prospective study of patients with chronic limb spasticity as a result of various causes observed that 28 (90%) of 31 patients with painful flexor spasm or passive stretching experienced at least moderate pain relief and 8 (26%) patients experienced complete pain resolution after BTX-A injections (19). Another prospective study in Thailand observed joint pain relief in 22 poststroke spasticity patients (20). Double-blind, placebo-controlled

Mitchell F. Brin became an employee of Allergan, Inc. in January 2001, subsequent to the international meeting in 1999.

studies provided further support for the effect of BTX-A on pain relief in spasticity patients (21,22).

Early in its use as a therapeutic agent, BTX-A was observed to provide pain relief in disorders other than dystonia and spasticity. Published case reports detail analgesic effects of BTX-A injections for muscle hypertrophy associated with complex repetitive discharges (23) and for stiff-person syndrome (24). In a prospective study of 60 achalasia patients, BTX-A improved chest pain associated with this disease of the esophagus (25). Among 100 patients treated for anal fissure, 78 (78%) reported pain resolution within 3 days after initial injection (26).

USES OF BTX-A SPECIFICALLY FOR PAIN RELIEF

The earliest published reports of therapeutic uses of BTX-A focused primarily on relief of muscle spasm and secondarily on pain relief. By the mid-1990s, BTX-A was recognized as a viable therapeutic approach specifically for pain-associated disorders that were otherwise difficult to treat. Acquadro and Borodic reported the successful treatment of chronic myofascial pain in two patients who had been nonresponsive to conventional therapies (27). Girdler presented a case report of a patient with a 6-year history of temporomandibular joint dysfunction in whom BTX-A injections produced functional denervation of specific masticatory muscles that led to temporary weakness but ongoing pain relief (28). Polo and Jabbari successfully used BTX-A injections in a case of painful limb myoclonus that had been nonresponsive to a wide range of therapies (29). Diaz and Gould reported the successful treatment of a case with a 10-year history of postthoracotomy myofascial pain in the left upper-thorax and arm (30). In a double-blind, placebo-controlled study, cerebral palsy patients given BTX-A for postoperative pain following adductor-release surgery had significantly reduced pain scores, analgesic requirements, and hospital stays as compared to placebo (31). In a prospective study of 11 patients with severe, chronic prostatic pain, 9 (82%) patients experienced pain relief after BTX-A injections (32). A double-blind, placebo-controlled study of patients suffering from chronic low-back pain showed statistically and clinically significant pain reduction in BTX-A treated subjects, as compared to placebo (33).

Johnstone and Adler reported on an unusual case of blepharospasm that presented with severe headaches and periorbital pain (34). After treatment with BTX-A injections, blepharospasm improved and complete pain resolution was achieved. They noted that blepharospasm usually does not present with pain as the primary complaint, and thus speculated whether this patient's pain was blepharospasm-induced or whether her blepharospasm was pain-induced. Therefore, this case offered possible evidence that not only muscle relaxation but also sympathetic mechanisms may be involved in pain relief as a result of BTX-A treatment.

STUDIES OF BTX-A FOR BRUXISM AND TEMPOROMANDIBULAR DISORDER

Historically, bruxism has had various definitions but it is generally characterized as grinding, clenching, or gnashing of the teeth. If left untreated, it results in masseter hypertrophy, headache, temporomandibular joint destruction, and complete edentulousness. There are two distinct manifestations of bruxism: that which occurs, usually diurnally, in patients with idiopathic, tardive, and/or posttraumatic cranial dystonia; and that which occurs nocturnally and is commonly seen in dental practice. Population prevalence of the latter, more common form has been estimated at 21% (35). The etiology is unclear and is somewhat controversial. At one time, it was thought that occlusal disorders and/or orofacial anatomy might be contributory, but more recently, the focus has been on pathophysiologic and psychological factors, such as sleep arousal response, disturbances in the central dopaminergic system, and stress (36). There is no consensus as to the best treatment; treatments typically prescribed include occlusal appliance, medication, counseling (37) and, for symptom relief, massage and stretching exercises (38).

In 1990, Van Zandijcke and Marchau presented a case report of successful treatment of

bruxism with BTX-A injections in a patient who was comatose as a consequence of a car accident (39). In 1997, Ivanhoe et al. similarly reported cessation of bruxism after BTX-A injections in a patient who sustained an anoxic brain injury secondary to cardiac arrest (35). In 1998, a report from the Netherlands reported successful treatment of masseteric hypertrophy in two bruxism patients using BTX-A; pain relief was also achieved in one of the patients (40).

While pain relief was addressed and/or achieved in only one of the above cases, these reports provided evidence that bruxism, which often results in orofacial muscle pain, was responsive to BTX-A. It has been hypothesized that pain results when bruxism intensity exceeds the adaptation capacity of the musculoskeletal structures (38).

A relationship between bruxism and temporomandibular disorder (TMD) exists, but the nature of the relationship is not entirely clear. One line of thought is that bruxism predisposes to, and in fact plays a role in, the initiation of TMD (41). However, another belief is that bruxism itself should be classified as TMD (42).

TMD is defined as a group of conditions affecting the temporomandibular joint, masticatory muscles, and related structures that typically presents as jaw pain; other symptoms can include earache, headache, neck pain, and facial swelling (43). TMD-related pain is usually articular, from inflammation of associated tissues, as well as myofacial (43). The source of myofacial pain is unclear, although it has been suggested that both peripheral and central mechanisms are involved (44).

The prevalence of TMD in adults has been estimated at 10% (45). Typical treatments include analgesics, antiinflammatory medications, muscle relaxants, massage, acupuncture, and orthotic devices, none of which are known to be unusually effective (43).

Open-Label, Prospective Study of BTX-A for Severe Bruxism

An open-label, prospective study of BTX-A injections for the treatment of severe bruxism was conducted with patients from the Baylor College of Medicine Parkinson's Disease Center and Movement Disorders Clinic in Houston, Texas (46). Over an 8-year period, patients who satisfied the following diagnostic criteria were recruited and followed: tooth-grinding sounds that could be corroborated by family members or caregivers; impaired chewing, swallowing, or speech; tooth wear; nonresponsiveness to conventional therapies; and tender or hypertrophied masseter muscles. Eighteen patients (17 female) participated; mean duration of bruxism was 15 years. Most had predominantly diurnal symptoms and nine (50%) had associated dystonia. At each treatment visit, masseter muscles were injected with 25 to 100 U of BTX-A (BOTOX) per side. The primary outcome was "peak effect," defined as the maximum benefit observed after treatment and scored as follows: 0, no effect; 1, mild improvement; 2, moderate improvement but no change in function; 3, moderate improvement in severity and function; and 4, marked improvement in severity and function. Peak effect was determined by personal diaries and perception as well as interviews with family and friends. Two measures of duration of response were obtained: (a) maximum, defined as the duration of peak effect, and (b) total, defined as the duration of observance of any improvement.

The study included 123 treatment visits, or an average of 6.8 treatment visits per patient. Time between treatment visits ranged from 3.2 to 9.7 months (mean, 5.0 $\pm$ 1.8 months). Mean peak effect was 3.4 $\pm$ 0.9 (range, 0 to 4), which equates to moderate improvement in severity and function. Sixteen patients (89%) reported marked improvement after at least one treatment visit. Time to response ranged from 12 hours to 5 days (mean, 2.7 $\pm$ 1.7 days). Maximum duration ranged from 2.5 to 17 weeks (mean, 11.7 $\pm$ 4.1 weeks), and total duration ranged from 6 to 78 weeks (mean, 19.1 $\pm$ 17 weeks). One subject reported dysphagia at six treatment visits with duration ranging from 21 to 40 days (mean, 34.7 $\pm$ 7 days).

Based on the theory of a "central bruxism generator," defined as phasic jaw activity that is dependent on interaction among motor, limbic, and autonomic systems (47), the authors

speculated that jaw muscle relaxation induced by BTX-A disrupts the feedback loop from the trigeminal motor nucleus and inhibits the central bruxism generator. They also proposed that BTX-A may deactivate periodontal mechanoreceptors that are thought to facilitate jaw closure motoneurons (48).

Open-Label, Prospective Study of BTX-A for TMD

An open-label, prospective Canadian study of BTX-A injections for the treatment of TMD was conducted with patients with one of three diagnoses: myofascial symptoms alone, myofascial symptoms with internal joint derangement or arthralgia, or myofascial symptoms with internal joint derangement and arthralgia (43). Patients who had never failed to respond to conventional treatment were excluded. Forty-six patients, predominantly female, participated; median duration of TMD was 8 years. Both masseter and temporalis muscles of each patient were injected with BTX-A (BOTOX): masseter with 50 U and temporalis with 25 U, each divided evenly over five sites. Five outcome measures were used: subjective facial pain measured by a visual analog scale (VAS); VAS-measured orofacial function (a series of ten different functions); interincisal opening; bite force; and objective masticatory muscle tenderness (scored by a clinician). Assessments were made before treatment and every other week after treatment for 8 weeks. Table 23.1 shows the results.

Reduction of both subjective and objective pain occurred in most patients (87% and 96%, respectively). In all cases, pain reduction coincided with muscle weakening. For all outcomes except bite force, baseline measurements were significantly different from all posttreatment measurements. For bite force, posttreatment measurements returned to baseline values by week 8. Age was inversely correlated with improvement. Median time to subjective bite weakness was 9 days. No adverse events were reported.

The authors postulated that pain relief occurred because of reduction of mechanical stimulation of sensitized peripheral nociceptive afferent pathways via one or both of the following events, based on experimental evidence (49): BTX-A inhibition of α motor neurons resulting in reduced maximum contractile force of the injected muscles, or BTX-A inhibition of γ efferents resulting in reduced resting muscle tone. They further speculated that the reduction in muscle activity indirectly altered the release of neuropeptides and modulators of local inflammation peripherally such that stimulation of central wide dynamic range neurons and nociceptive specific neurons was reduced.

STUDIES OF BTX-A FOR MYOFASCIAL PAIN SYNDROME

Myofascial pain syndrome (MPS) is a very common pain disorder. It is estimated that 14% of the US population suffers from chronic musculoskeletal pain and that 21% to 93% of patients with regional pain complaints have MPS (50).

TABLE 23.1. *Median (range) outcome measurements by time posttreatment in a prospective, open-label study of BTX-A for temporomandibular disorder, Ontario, Canada, 2000 (43)*

Outcome	Baseline	2 weeks	4 weeks	6 weeks	8 weeks
Pain[a]	8.0 (3–10)	6.0 (1–9)	5.0 (0–9)	5.0 (0–10)	5.0 (0–9)
Function[b]	5.3 (1–9)	4.4 (0.6–9)	4.1 (1–9)	4.1 (0.5–9)	3.9 (0.6–9.5)
Jaw opening (mm)	29.5 (12–54)	33.5 (12–55)	33.0 (14–50)	33.0 (16–50)	34.5 (18–53)
Bite force (lb)	12.0 (1–37)	9.0 (1–27)	11.0 (1–28)	11.0 (0–30)	14.0 (1–37)
Tenderness[c]	15.0 (5–30)	8.0 (1–30)	6.0 (0–24)	4.5 (0–26)	6.0 (0–30)

[a] Measured by VAS on a 0 to 10 scale (0, no pain).
[b] Median score of ten functions, each measured by VAS on a 0 to 10 scale (0, no limitation).
[c] Sum of scores from five muscles measured bilaterally by a clinician on a 0 to 3 scale (0, no discomfort upon palpation).

Unfortunately, MPS does not have a uniformly accepted definition or a well-understood pathology; it is underdiagnosed and lacks a satisfactory treatment regimen (51). The clinical hallmark of MPS is the "trigger point," a region of focal tenderness in a taut band of muscle fibers (52) that, upon compression, produces referred pain in characteristic areas for specific muscles. Current research supports a relationship between trigger points and integrative mechanisms in the spinal cord in response to sensitized nerve fibers associated with abnormal endplates (53). Most conventional treatments emphasize muscle relaxation; e.g., massage, heat application, therapeutic stretching, relaxant medications, and biofeedback.

Double-Blind, Placebo-Controlled Crossover Study of BTX-A for MPS

A double-blind, placebo-controlled crossover study of BTX-A injections for the treatment of MPS was conducted in 1994 with patients from the University of North Carolina Pain Clinic (54). Six subjects (four female, two male) with chronic myofascial pain (mean duration, 3 years) were injected with BTX-A (BOTOX) and placebo, in random order, 8 weeks apart. Trigger points were injected with a total of 50 U of BTX-A. At weekly intervals during the first 4 weeks after each injection and at 8 weeks after the final injection, four pain outcome measurements were obtained: (a) VAS for pain; (b) muscle tenderness; (c) patient verbal descriptions of current pain intensity (from a predetermined list of terms); and (d) patient verbal descriptions of current pain unpleasantness. For the latter two, numerical values were assigned to correspond to the verbal descriptions. Positive response was defined as a reduction from baseline of more than 30% on at least two occasions. Table 23.2 summarizes the results.

Numbers of subjects who responded positively after BTX-A but not placebo per VAS, tenderness, pain intensity, and pain unpleasantness were 4, 5, 3, and 2, respectively. Onset of benefit occurred within the first week of injection but not within 30 minutes. Mean duration of benefit was 5 to 6 weeks, with a significant difference between BTX-A and placebo from 2 to 4 weeks per VAS, tenderness, and pain intensity. BTX-A had no effect on trigger point locations or their ability to produce radiating pain. No adverse events were reported. The authors concluded that BTX-A exerts its effect on MPS by interrupting sustained muscle contraction of intrafusal muscle fibers surrounding the trigger point.

Randomized, Comparative Study of BTX-A Versus Methylprednisolone for MPS

A randomized study to compare BTX-A to methylprednisolone for the treatment of MPS was conducted in Italy (51). Forty MPS patients (predominantly female) with chronic muscle spasm in the piriformis, iliopsoas, or scalenus anterior muscles of duration greater than 6

TABLE 23.2. *Positive response[a] by outcome measurement in a double-blind, placebo-controlled study of BTX-A for myofascial pain syndrome, University of North Carolina Pain Clinic, 1994 (54)*

Patient	Visual analog scale	Pain tenderness	Pain intensity	Pain unpleasantness	Spasm
1	B	B	B	B/P	B
2	N	N	N	N	N
3	B/P	B	B/P	B/P	B/P
4	B	B	N	B	B
5	B	B	B	B/P	N
6	B	B	B	B	B

[a] Positive response means greater than 30% reduction from baseline on at least two occasions.
B, responded after botulinum injection; N, responded after neither botulinum nor placebo injection; P, responded after placebo injection.

months but less than 2 years were injected with either BTX-A (BOTOX) or methylprednisolone (20 patients each) into the affected muscle(s). BTX-A dose was muscle-dependent: 100 U for piriformis, 150 U for iliopsoas, and 80 U for scalenus anterior. The pain outcome measurement, VAS, was obtained at baseline and at 30 and 60 days postinjection. Patients were given a stringent program of physiotherapy to follow over the course of the study.

Table 23.3 shows the changes from baseline VAS. BTX-A patients had significantly higher VAS at baseline than did methylprednisolone patients; however, no adjustments were made for this in the analyses. Nonetheless, BTX-A patients experienced significantly greater reductions in pain at 60 days postinjection as compared to methylprednisolone patients and, unlike methylprednisolone patients, experienced further pain reduction between 30 and 60 days postinjection. Also, at 60 days postinjection, VAS was significantly lower in BTX-A patients as compared to VAS in methylprednisolone patients ($p < 0.0001$). Seven patients were noncompliant with the physiotherapy program, all of whom were in the methylprednisolone group. The author surmised that noncompliance was because of more painful stretching in methylprednisolone patients as compared to BTX-A patients. Data on time to benefit, duration of benefit, and adverse events were not provided. The author suggested that, in addition to inducing muscle relaxation, BTX-A might also provide pain relief by affecting afferent pathways that relate to pain perception and posture.

STUDIES OF BTX-A FOR HEADACHE

Three types of headache—tension, cluster, and migraine—account for 80% of all headaches (55). Another type, cervicogenic headache, similar to migraine, was defined in 1983 by Sjaastad et al. (56) as unilateral headache triggered by forceful neck movement and/or sustained awkward position. Because of the inconsistency of headache definitions and the resulting difficulty in epidemiologic and pathophysiologic study of headache, the International Headache Society (IHS) published guidelines, in 1988, for discriminating among 13 major types (57). Although the pathophysiology of headache is not entirely clear, there is evidence that BTX-A has potential as an effective treatment for this debilitating and often underdiagnosed disease.

Cervicogenic Headache

Cervicogenic headache is characterized by unilateral pain originating in the neck and shoulders and radiating to the occiput and frontal regions. It is associated with decreased range of motion (ROM), tenderness, and abnormal neck muscle tone. Some theories of pathophysiology suggest involvement of myofascial pain (58,59) or muscular activity (60,61). Very few epidemiologic studies of cervicogenic headache exist. There are reports suggesting that it comprises 15% of headache patients visiting a headache clinic and has a population prevalence of less than 1% to 18%, depending on the criteria used to define it (62). In 1997, Hobson and Gladish reported successful treatment with BTX-A of cervicogenic headache resulting from a whiplash injury

TABLE 23.3. *Mean (standard deviation) change from baseline in pain score[a] in a randomized, placebo-controlled comparative study of BTX-A and methylprednisolone for myofascial pain syndrome, Policinico San Marco Pain Center, Zingonia/Bergamo, Italy, 2000 (51)*

Time postinjection	BTX-A ($n = 20$)	Methylprednisolone ($n = 20$)	p value[b]
30 days	−3.9 (0.2)	−3.5 (0.9)	0.06
60 days	−5.5 (0.3)	−2.5 (0.7)	<0.0001

[a] Visual analog scale from 0 (no pain) to 9 (unbearable pain).
[b] Two-tailed t-test.

from a car accident (63). A double-blind, placebo-controlled pilot study of BTX-A for cervicogenic headache is detailed below.

Double-Blind, Placebo-Controlled Pilot Study of BTX-A for Chronic Cervical-Associated Headache

A double-blind, placebo-controlled pilot study of BTX-A treatment for chronic cervical-associated headache was conducted in Canada (64). Twenty-six subjects with chronic headache secondary to cervical whiplash injury at least 2 years prior to study entry participated. Confirmation by anesthetic block, one of the IHS criteria for cervicogenic headache, was not done because it was felt that this would unacceptably confound the study results. Therefore, the term "cervical-associated headache" was chosen to describe the condition of the study subjects. Patients were injected with either 100 U of BTX-A (BOTOX) (14 patients) or placebo (saline; 12 patients) into the patient-specific five most tender cervical muscle trigger points. Muscles treated included the splenius capitis, rectus capitis, semispinalis capitis, and trapezius. Outcome measurements were pain, self-measured by VAS, and clinician-rated ROM based on rotation, flexion, extension, and lateral bending. Measurements were made at baseline and at 2 and 4 weeks postinjection. Table 23.4 shows the results.

BTX-A patients had significantly higher pain at baseline than placebo; however, no adjustments were made for this in the analyses. Nonetheless, BTX-A patients experienced improving pain and ROM scores over the course of the study and, at 4 weeks postinjection, had significantly improved scores compared to baseline. No such trends were observed for placebo. No adverse events were reported. The authors suggested that the effect of BTX-A on cervicogenic headache may result from mechanisms similar to those that produce BTX-A effects in disorders such as temporomandibular dysfunction and dystonias.

Tension Headache

Tension headache is the most common headache type and can be either episodic or chronic. It is the least distinctive type of headache, but is generally characterized by aching, tenderness, or sensations of pressure or constriction. The role of pericranial muscles or whether they are even a factor in the pathophysiology of tension headache has been debated. Other theories postulate that pain originates from myofascial tissue or from central mechanisms in the brain (65). One hypothesis of pathophysiology proposes vascular, myofascial, and supraspinal involvement (66). It suggests that minor myofascial stimuli trigger tension headache as a result of increased sensitization of the trigeminal nuclear complex and possibly the dorsolateral C2 segment of the spinal cord and thalamus. Stress is considered the most common precipitating factor in episodic tension headache (67), while depression, anxiety, and possibly heredity are associated with the chronic form (68–71).

One-year population prevalence of tension headache is estimated at 38%, with higher preva-

TABLE 23.4. *Median (range) outcome measurements by time posttreatment in a double-blind, placebo-controlled study of BTX-A for chronic cervical-associated headache, Ontario, Canada, 2000 (64)*

	Baseline		2 Weeks		4 Weeks	
Outcome	BTX-A	Placebo	BTX-A	Placebo	BTX-A	Placebo
Pain[a]	6.5 (2–9)	3.0 (0–8)	5.0 (1–10)	3.0 (0–6)	3.5 (1–8)	4.5 (1–9)
Range of motion[b]	312 (80–400)	337 (225–380)	317 (145–435)	347 (250–395)	343 (285–420)	325 (225–370)

[a] Measured by VAS on a 0 to 10 scale (0, no pain).
[b] Measured by rotation, flexion, extension, and lateral bending; increasing scores indicate improvement.

lence among women, and racially among whites (72). By age, prevalence peaks in 30- to 39-year olds and declines thereafter. It is estimated that an average of 9 work days per year per patient are lost because of tension headache and that half of all sufferers experience reduced effectiveness an average of 5 work days per year (72). Treatments for acute episodes include simple analgesics, nonsteroidal anti-inflammatories, and muscle relaxants. About 2% of tension headache patients suffer from chronic tension headache, which is defined as at least 15 attacks per month (72); 12% of these patients miss an average of 27 work days per year and 47% suffer reduced effectiveness an average of 20 days per year. Females are twice as likely as males to have chronic tension headache. Successful treatment usually depends on treating underlying depression or chronic states of anxiety (73).

The earliest reported study of BTX-A treatment for tension headache, specifically for chronic tension headache, was in 1994, by Zwart et al. (73a). In an open-label study of six patients, they observed no effect of BTX-A on either pain or pressure pain threshold, and concluded that temporal muscle tension is not a major direct factor in the pathophysiology of the chronic stage of chronic tension headache. Subsequent studies followed with mixed results. In Relja's open-label study of ten patients with individualized treatment regimens, BTX-A was associated with reduced headache duration, pain intensity, and pain sensitivity (74). Using the same methods, the same investigator observed similar effects in a second, larger open-label study (75). In a pilot study of eight patients injected with BTX-A into frontal, temporal, occipital, and sternocleidomastoid muscles, 25 U per injection, mean area-under-the-curve was significantly reduced at 4 weeks postinjection as compared to baseline (76). A study comparing BTX-A to methylprednisolone injections into the tender points of cranial muscles of tension headache patients observed significantly decreased VAS pain scores at 60 days postinjection (77). In an open-label, individualized-treatment study of 50 patients, 30 (60%) responded positively to BTX-A (78). None of three double-blind, placebo-controlled studies, two from Germany and one from Switzerland, found a BTX-A effect on tension headache, although quality of life improvement was demonstrated in some (79–81). However, Carruthers et al. found efficacy in cosmetic patients who also suffered from tension headache, as detailed below (82).

Retrospective, Open-Label Study of BTX-A for Tension Headache

Patients who experienced tension headache relief as an unexpected consequence of BTX-A treatment for hyperfunctional facial lines were studied retrospectively at the Vancouver Hospital and Health Sciences Center in Canada (82). The study included eight patients (seven female, one male) treated over 39 sessions with 10 to 40 U of BTX-A (BOTOX) injected into the glabella and adjacent forehead areas. Table 23.5 summarizes the findings. Responses ranged from "mildly better" to "cleared." No adverse events were reported. The authors suggested as possible mechanisms of BTX-A effect on tension headache a direct effect on paralyzed muscles reducing nociceptive stimulation, loss of biofeedback as a result of paralyzed muscles, and perhaps a secondary central effect.

In view of the efficacy observed in some of the above studies, additional investigation is warranted to assess the key patient population characteristics and treatment paradigm for these chronic tension-type headache patients.

Cluster Headache

Arguably, the most painful type of headache is the cluster headache, which is characterized by recurrent unilateral attacks occurring over a "cluster period" (usually weeks) of severe pain lasting 15 minutes to 3 hours untreated. Cluster headache can be chronic, but usually is episodic, with attacks occurring once per day with an average cluster period of 6 to 12 weeks and a remission period of 1 year (83,84). It is not uncommon for individual attacks to occur at the same time each day and for the cluster of attacks to occur at the same time each year (85).

Some conclusions about the pathophysiology of cluster headache can be drawn from its clini-

TABLE 23.5. *Characteristics of patients who experienced tension headache relief after BTX-A treatment for hyperfunctional facial lines, Vancouver Hospital and Health Sciences Center, Vancouver, Canada, 1999 (82)*

Patient	Headache severity	No. treatments	BOTOX units per treatment	Subjective postinjection response	Time to response	Response duration
1	mild	21	10–37	mildly better	3 days	2 months
2	moderate	4	25–28	much better	4 days	2 months
3	moderate	4	20–21	cleared	2 weeks	4 months
4	severe	2	35–40	much better	few minutes	2 months
5	mild	2	23–26	much better	2 weeks	several months
6	moderate	2	14–35	much better	3 weeks	4 months
7	moderate	2	12–15	cleared	1 week	3 months
8	moderate	2	23–26	mildly better	2 days	2 weeks

cal presentation: (a) ipsilateral trigeminal nociceptive pathways are likely involved because of pain centered around the eye and forehead; (b) activation of the cranial parasympathetic system and dysfunction of the ipsilateral sympathetic nerves probably occur because of the ipsilateral autonomic features; and (c) consistency in timing of attacks and clusters suggests the involvement of a central pacemaker or biologic clock, i.e., the suprachiasmatic nucleus (85).

Cluster headache is strongly associated with heavy smoking and drinking (85); there may also be a heredity factor (86–91). Very few epidemiologic studies have been performed to estimate cluster headache prevalence, but it is extremely rare; in large male cohort studies, rates ranged from 0.13% to 0.45% (84,92–94). Cluster headache is about three times more prevalent in males than in females; however, the gender ratio appears to be decreasing over time, possibly because of the association with certain lifestyle factors that are not as gender-discrepant as they once were. In men, peak age of onset is in the third decade. In women, there are two peak ages of onset: the second and sixth decades (85).

Treatment of cluster headache often begins with patient education as to their personal etiologic factors so that future attacks can be reduced or altogether prevented. Treatments aimed at quick relief of symptoms include oxygen inhalation, triptans such as sumatriptan and zolmitriptan, dihydroergotamine, and lidocaine. Short-term or "transitional" prophylactic agents to be used during cluster periods to rapidly suppress attacks include ergot derivatives and corticosteroids. Maintenance prophylactics that can be used throughout the cluster period include verapamil, lithium carbonate, methysergide, valproic acid, topiramate, and melatonin. Surgery, typically directed toward the sensory trigeminal nerve, is an option for patients unresponsive to other treatments (85).

Probably because of the rarity of the disease, no formal studies of effects of BTX-A on cluster headache have been published. Ginies et al. were the first to provide case reports detailing the use of BTX-A in cluster headache patients; they found that BTX-A ended current cluster periods in three of five patients (95). Subsequently, Freund and Schwartz reported that BTX-A ended current cluster periods in two of two patients treated (96), and Smuts and Barnard reported positive response in two of four cluster headache patients treated (78).

Migraine

Migraine is characterized by unilateral, pulsating pain associated with nausea, vomiting, photophobia, and phonophobia (97). An IHS diagnosis of migraine without aura requires at least five attacks over a lifetime of duration 4 to 72 hours. About 15% of migraine cases include a visual or sensory phenomenon called "aura" (98). IHS diagnosis of migraine with aura requires two lifetime attacks of migraine headache, either with or following aura of duration 4 to 60 minutes. Time between aura and headache is less than 1 hour.

Many models of migraine pathophysiology

have been proposed (99). The earliest modern theory on the pathophysiology of migraine was the "vascular" theory, conceived by H. Wolff in the 1940s and 1950s, which proposes that migraine aura is caused by cerebral vasoconstriction and that migraine pain is caused by subsequent vasodilation. However, current opinion on the pathophysiology of migraine is that it involves more than what the vascular theory alone proposes. The "spreading depression" theory hypothesizes that migraine results from vasodilation but that vasodilation is caused by a prolonged period of neuronal depression that follows a brief wave of excitation. The "neurovascular" theory proposes that either spreading depression or other migraine triggers (e.g., stress, glare, noise, carotid artery dilation) activate trigeminal nerve axons which results in a series of pain-inducing events: (a) vasodilation and inflammation of areas surrounding innervated vessels through the release of neuropeptides (e.g., substance P); (b) sensitization of nerve endings, also through the release of neuropeptides; and (c) transmission of pain impulses to the trigeminal nucleus caudalis and, in turn, to higher brain centers. According to the "serotonin abnormalities" theory, a surge in plasma serotonin levels causes vasoconstriction and reduced blood flow, leading to migraine aura and to a subsequent drop in serotonin levels, which, in turn, leads to vasodilation and migraine pain. The "integrated" theory attempts to combine all of these theories into a complex mechanism by which migraine occurs and is sustained.

Several migraine etiologic factors have been proposed and studied. Heredity appears to play a role in 70% to 80% of all migraine cases (100). In females, migraine has been correlated with events that produce cyclical changes in hormone levels, such as use of oral contraception, pregnancy, menopause, and estrogen replacement therapy (101). Various lifestyle and dietary factors have also been implicated: physical activity; smoking; caffeine; alcohol; chocolate; food additives; and sleep pattern, quality, and duration (67,102–104). Psychosocial factors are also believed to play an important role in migraine etiology. It has been reported that up to 54% of all migraine attacks are stress-related (104). Major depression is also a correlate of migraine (105). Certain medications are hypothesized to initiate or increase the frequency of migraine attacks: nitroglycerin, certain calcium channel-blockers, tetracycline, and sildenafil citrate (104).

Worldwide prevalence of migraine is estimated to be 13% to 17% in women and 8% to 14% in men, based on meta-analyses of international data collected from 1962 to 1992 (106–108). In the United States, prevalence is estimated at 18% in women, 7% in men, and 13% overall, with higher prevalence among 35- to 45-year olds, lower-income populations, and whites (109). The gender ratio is equal before puberty, then increases in favor of women until 40 to 45 years of age (103,110,111). Overall, migraine is twice as prevalent in women as in men. Among female migraineurs, 60% experience at least one severe attack per month; 42% of this subgroup experience at least four severe attacks per month (112).

The effect of migraine on quality of life is profound. Nearly all migraine patients experience functional impairment as a result of their condition, and more than half report severe impairment or required bedrest (109). It is estimated that migraine results in 112 million bedridden days in the United States per year, and results in an annual cost to employers of $13 billion (113). Given the prevalence pattern by age, most of these days occur during the most productive employment and most important childrearing years (114). The effect of migraine extends beyond the attacks themselves in terms of quality of life, productivity, and comorbidities such as depression, anxiety disorders, epilepsy, and stroke (115). Direct costs of migraine—i.e., medical costs—are estimated at $1 billion per year, far less than the indirect costs; about 60% of direct costs are from physician visits and 30% from prescription medications (113). Most migraineurs do not seek medical treatment; instead, they rely on over-the-counter medications (109) because they believe that effective prescribed treatments do not exist (114).

As with cluster headache, treatment of migraine often begins with patient education so that future attacks can be reduced or prevented. Pharmacologic therapy falls into two categories:

acute and prophylactic (116). Acute medication typically consists of simple analgesics for mild to moderate attacks. For moderate to severe attacks, medication used to be prescribed in the form of ergot derivatives. However, the advent of triptans, with greater receptor specificity than ergot derivatives, revolutionized acute migraine therapy for more severe attacks. Opioids are reserved for rescue therapy when other medications cannot be used. Prophylactic medications commonly prescribed include propranolol, timolol, sodium divalproex, and amitriptyline.

William Binder, an otolaryngologist and facial plastic surgeon, observed that BTX-A provided relief to migraine sufferers whom he was treating for hyperfunctional facial lines (117). Subsequently, Binder et al. conducted an open-label study to further investigate the possibility of a BTX-A effect on migraine (detailed below). Various open-label (78,118) as well as double-blind studies followed and reported promising results. Representative studies are detailed below.

Open-Label, Prospective Study of BTX-A for Migraine

We conducted an open-label study of BTX-A for migraine that included a sample of 106 patients (95 female, 11 male) recruited from private practice cosmetic surgery clinics in Los Angeles and San Francisco, and from otolaryngology and neurology clinics in New York City (119). Patients either sought BTX-A (BOTOX) treatment for hyperfunctional facial lines or other dystonias with concomitant headache disorders, or were candidates for BTX-A treatment specifically for headaches. Based on IHS criteria, patients were classified as true migraineurs (75%), possible migraineurs (17%), or nonmigraineurs (9%), and received prospective BTX-A treatments either prophylactically (93 patients) or for acute migraine episodes (4 patients); a small subgroup (9 patients) received both types of treatments. Injections were administered to the glabellar, temporal, frontal, and, in two subjects, the suboccipital regions of the head and neck. Average dose per injection was 31 U. True migraineurs received higher doses, and patients treated specifically for headache tended to receive larger doses as the study progressed. Length of follow-up ranged from 3 weeks to 6 months. Treatment benefit was evaluated by self-reported degree and duration of response. Degree of response was defined as (a) complete response (elimination of headache symptoms), (b) partial response (at least 50% reduction in frequency or severity of headaches), and (c) nonresponse (less than 50% reduction in frequency or severity of headaches). Patients lost to follow-up were considered nonresponders.

Among true migraineurs treated prophylactically, 51% (95% CI = 39% to 62%) were complete responders with mean (SD) duration of benefit of 4.1 (2.6) months. Complete response was related to lower baseline migraine frequency ($p = 0.06$) and severity ($p = 0.07$). Figure 23.1 shows the response by baseline severity. "Improvement," defined as complete or partial response, was unrelated to baseline frequency and severity. Mean (SD) duration of benefit among improvers was 3.2 (2.3) months. Complete responders with severe baseline headaches had somewhat longer duration of benefit [mean (SD), 4.6 (3.1) months] compared to those with less severe headaches at baseline [mean (SD) 3.7 (2.3) months]. Although there was no evidence of dose-response, injection site appeared to be related to response; 87% of complete responders received glabellar injections versus 66% of non- or partial responders ($p = 0.01$). Of 13 subjects treated for acute migraine, 10 were complete responders, and all responded within 1 to 2 hours postinjection. Two patients reported transient brow ptosis; other adverse effects were limited to transient local pain and ecchymosis at the injection site.

Based on observations from this study, we proposed that the effect of BTX-A on migraine may not be limited to muscle relaxation. Among these patients, dose-duration curve did not necessarily directly correlate with the duration of action associated with muscle relaxation. Also, in some patients, relief of migraine symptoms persisted beyond the time that muscle function returned (after 3 months). We suggested that BTX-A for migraine acts by inhibiting the sensory trigeminal nerve endings, the vesicular re-

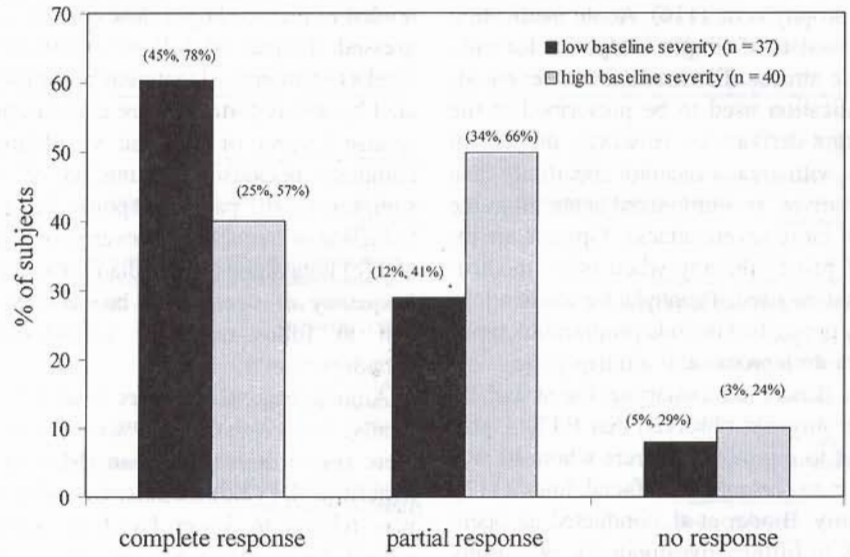


FIG. 23.1. Proportion (95% confidence intervals) of self-reported complete, partial, and nonresponders among 77 true migraineurs treated prophylactically by baseline headache frequency (high frequency, at least three times per month) and severity (high severity, "severe"); open-label, prospective study of BTX-A for migraine (119).

lease of pain-associated neurotransmitters, or the vasculature and extracranial inflammatory process believed to be involved in the vicious trigeminal-neurovascular cycle of migraine pathophysiology. Specifically, we hypothesized that (a) BTX-A injected into the temple or forehead muscles recognizes the parasympathetic neurons innervating the extracranial vasculature and causes a disruptive effect on the vesicular release of ACh as well as other ACh-like neuropeptides; (b) blockade of these neuropeptides may also inhibit neurogenic inflammation, thought to play a role in migraine, that may result from the release of neuropeptides from trigeminal nerves innervating both the intracranial and extracranial vasculature; and (c) parasympathetic neurons may be a likely site of action for BTX-A because of their known cholinergic component and possible colocalization of the other vasodilatory neuropeptides within these nerves.

Double-Blind, Placebo-Controlled Study of BTX-A for Migraine

A double-blind, placebo-controlled study of BTX-A (BOTOX) for migraine was conducted with 123 (105 female, 18 male) patients from 12 headache centers across the United States (120). Patients were randomized to one of three groups: (a) placebo (41 patients); (b) 25 U BTX-A (42 patients); or (c) 75 U BTX-A (40 patients). Symmetrical injections were administered to the frontal, temporal, and glabellar regions of the head. The primary outcome in intent-to-treat analysis was change from baseline in number of moderate-to-severe migraines per month. Other outcome measurements were the occurrence of migraines, severity of migraines, migraine-associated symptoms, use of acute migraine medications, and Subject Global Assessment. Outcome data were collected at three monthly postinjection visits.

Twenty-five units BTX-A resulted in significantly greater reduction in moderate-to-severe migraine frequency than did placebo at month 2 (−1.57 vs −0.37, $p = 0.008$) and at month 3 (−1.88 vs −0.98, $p = 0.04$) postinjection. Twenty-five units BTX-A also resulted in a significantly greater reduction in frequency of migraines of any severity than did placebo at month 3 (−2.12 vs −0.90, $p = 0.01$) and a tendency toward fewer migraines at month 2 (−1.55 vs

−0.37, $p = 0.07$). At month 3, when compared to placebo, significantly more subjects who received 25 U BTX-A reported at least two fewer migraines of any severity ($p = 0.01$) and a decrease in migraine frequency of at least 50% ($p = 0.046$). When compared to placebo, 25 U BTX-A resulted in a significantly greater reduction in migraine severity at months 1 and 2 ($p < 0.03$) and in use of migraine medications at month 2 ($p = 0.03$). At month 3, significantly fewer subjects who received 25 U BTX-A experienced migraine-associated vomiting compared to placebo ($p = 0.01$). Regardless of dose, BTX-A-treated patients had significantly better Subject Global Assessment scores than did placebo-treated patients at month 2 (75 U BTX-A = 1.25, 25 U BTX-A = 1.19, vehicle = 0.46; $p = 0.041$).

Seventy-five units BTX-A resulted in higher incidence of treatment-related adverse events as compared to placebo (50% vs 24%, $p = 0.02$), whereas 25 U BTX-A and placebo were similar in adverse event incidence. All adverse events were transient and included blepharoptosis, diplopia, and injection-site weakness.

The authors surmised that 75 U BTX-A did not perform as well as 25 U because patients randomized to the higher-dose group had lower baseline migraine frequency than did the lower-dose group. However, they reported adjusting for this in the analyses. Their explanation of BTX-A effect on migraine was that pericranial muscle contractions are part of the trigger process for migraine and that BTX-A reduces such contractions. They also acknowledged the possibility of a central secondary effect through inhibition of pain pathways.

Double-Blind, Placebo-Controlled Study of BTX-A for Migraine

We conducted a double-blind, placebo-controlled study of BTX-A (BOTOX) for migraine with 53 patients (50 female, 3 male) recruited from three headache centers in New York City, Loma Linda, California, and Englewood, Colorado (121). Patients were randomized to one of four treatment groups: group 1, BTX-A to the frontal and temporal regions (45 and 30 U, respectively; 14 patients); group 2, BTX-A to the frontal region (45 U), placebo to the temporal region (12 patients); group 3, BTX-A to the temporal region (30 U), placebo to the frontal region (14 patients); and group 4, placebo to the frontal and temporal regions (13 patients). Primary outcome measurements in intent-to-treat analyses were change from baseline in frequency, duration, and pain intensity (0 to 10 scale) of migraine headaches. Outcome data were collected at baseline and at 2, 4, 8, 12, and 16 weeks post-injection. Group 1 versus group 4 at week 12 was defined as the key comparison.

Maximum pain decrease for group 1 occurred by week 12 and was significantly greater than for group 4 [median (range) = −4.0 (−7.5, −0.1) for group 1 and −0.2 (−5.1, 3.5) for Group 4; p = 0.01]. At week 12, when compared to placebo (group 4), BTX-A (groups 1 to 3) produced a greater decrease in the number of migraines per month [median (range) = −1.7 (−7.2, 20.6) for BTX-A; −0.5 (−8.5, 10.7) for placebo] and had the largest difference in maximum duration (hours) decrease [least-squares mean (SE) adjusted for baseline = −19.2 (3.7) for BTX-A and −8.0 (6.5) for placebo; $p = 0.15$]. Only group 1 experienced a significant increase in proportion of participants with a two-migraine decrease in frequency since baseline ($p = 0.006$) and a significant decline in medication use ($p < 0.0001$) over the course of follow-up.

CONCLUSIONS

BTX-A has emerged as a promising option for patients suffering from chronic pain disorders. A primary benefit of BTX-A is its duration of effect, which typically begins within 1 to 14 days, peaks within 2 to 6 weeks, and may require retreatment 12 to 16 weeks subsequently. These time frames coincide with known properties of BTX-A. Another benefit is its established safety and tolerability. In headache, therapeutic doses of BTX-A range from 25 to 250 U (116). Adverse effects associated with BTX-A for pain are generally mild and reversible; the most common are excessive weakness in the treated muscle and unwanted weakness in adjacent muscles. Examples include ptosis after injection to the

levator muscle for treatment of blepharospasm, hyperfunctional facial lines, or headache, and dysphagia after treatment for cervical dystonia (122).

An uncommon complication of BTX-A therapy is the formation of neutralizing antibodies that render it ineffective (for review, see reference 123). Estimated prevalence of BTX-A resistance is less than 5% (124) and appears to be correlated with dose and frequency rather than with duration of exposure (125,126). In 1997, Allergan released the current BOTOX with a lower protein exposure per unit than the original BOTOX. Current BOTOX is thought to have a lower potential for antibody formation because of the lower protein exposure. Cervical dystonia patients who develop BTX-A immunoresistance can benefit from different preparations of BTX-A or from other botulinum toxin serotypes (127–131). However, there is laboratory evidence that cross-reactivity and cross-neutralization among different botulinum toxin serotypes may occur (132).

The association between BTX-A and pain relief was originally thought to relate only to its effect on muscle contraction. However, some studies of BTX-A for various conditions suggest that muscle relaxation may not directly coincide with pain relief, suggesting alternative mechanisms for analgesic effects of BTX-A. There is experimental evidence that BTX-A affects afferent transmission (49,133), which may be a factor in pain relief, and that BTX-A inhibits the release of substance P (134) and potentially other neuromodulators. Substance P is a neuropeptide that plays a role in pain perception, vasodilation, and neurogenic inflammation. Also, it has been shown experimentally that BTX-A relieves formalin-induced pain in laboratory animals (135). This is an important observation in understanding the action of BTX-A on pain because formalin causes pain not through muscle tension, but by first directly stimulating nociceptors and then through inflammation. It seems likely that the analgesic effects of BTX-A relate not only to its well-established effect at the neuromuscular juncture, but also to an effect on the nociceptor system (122).

Unanswered questions include optimum treatment regimen (i.e., dose and injection sites), as well as specific headache and patient characteristics that are associated with the maximum clinical response. However, it should be emphasized that an "optimum treatment regimen" for a generalized patient population may not exist; i.e., "optimum treatment" might be highly individualized for reasons such as the dose-dependency on targeted muscles and injection regions. Furthermore, pain clinical trials are challenged to manage the "placebo effect," particularly when an injectable therapy is evaluated. These factors undoubtedly contribute to the findings from some studies that failed to show a consistent BTX-A effect on pain. In medical practice, the appropriate dose for a given patient is determined through controlled and systematic observations after each treatment, beginning at low doses and adjusting dose and injection sites until maximum effect is achieved.

BTX-A as BOTOX is currently FDA-approved for use in strabismus, blepharospasm, and cervical dystonia. It is approved in other countries for hyperhidrosis, poststroke spasticity, juvenile cerebral palsy, and cosmetic conditions. It is used clinically for numerous other disorders in patients for whom conventional therapies are ineffective or poorly tolerated, and it is likely that additional applications will continue to be discovered. Further research is warranted to fully understand the potential and limitations of such a widely applicable therapeutic agent as botulinum toxin type A.

ACKNOWLEDGMENTS

This work was supported by the Bachmann-Strauss Dystonia and Parkinson Foundation.

REFERENCES

1. de Paiva A, Meunier FA, Molgo J, et al. Functional repair of motor endplates after botulinum neurotoxin type A poisoning: biphasic switch of synaptic activity between nerve sprouts and their parent terminals. *Proc Natl Acad Sci U S A* 1999;96:3200–3205.
2. Scott AB. Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. *J Pediatr Ophthalmol Strabismus* 1980;17:21–25.
3. Scott AB. Injection treatment of endocrine orbital myopathy. *Doc Ophthalmol* 1984;58:141–145.
4. Scott AB. Botulinum toxin treatment of strabismus. Am Orthopt J 1985;35:28–29.
5. Frueh BR, Felt DP, Wojno TH, et al. Treatment of

blepharospasm with botulinum toxin. A preliminary report. *Arch Ophthalmol* 1984;102:1464–1468.
6. Mauriello JA Jr. Blepharospasm, Meige syndrome, and hemifacial spasm: treatment with botulinum toxin. *Neurology* 1985;35:1499–1500.
7. Tsui JK, Eisen A, Mak E, et al. A pilot study on the use of botulinum toxin in spasmodic torticollis. *Can J Neurol Sci* 1985;12:314–316.
8. Tsui JKC, Eisen A, Stoessl AJ, et al. Double-blind study of botulinum toxin in spasmodic torticollis. *Lancet* 1986;2:245–247.
9. Brin MF, Fahn S, Moskowitz C, et al. Localized injections of botulinum toxin for the treatment of focal dystonia and hemifacial spasm. *Mov Disord* 1987;2: 237–254.
10. Tsui JKC, Fross RD, Calne S, et al. Local treatment of spasmodic torticollis with botulinum toxin. *Can J Neurol Sci* 1987;14:533–535.
11. Jankovic J, Schwartz K. Botulinum toxin injections for cervical dystonia. *Neurology* 1990;40:277–280.
12. Poewe W, Schelosky L, Kleedorfer B, et al. Treatment of spasmodic torticollis with local injections of botulinum toxin. One-year follow-up in 37 patients. *J Neurol* 1992;239:21–25.
13. Greene P, Kang U, Fahn S, et al. Double-blind, placebo-controlled trial of botulinum toxin injections for the treatment of spasmodic torticollis. *Neurology* 1990; 40:1213–1218.
14. Blackie JD, Lees AJ. Botulinum toxin treatment in spasmodic torticollis. *J Neurol Neurosurg Psychiatry* 1990;53:640–643.
15. Lorentz IT, Subramaniam SS, Yiannikas C. Treatment of idiopathic spasmodic torticollis with botulinum toxin A: a double-blind study on twenty-three patients. *Mov Disord* 1991;6:145–150.
16. Lu CS, Chen RS, Tsai CH. Double-blind, placebo-controlled study of botulinum toxin injections in the treatment of cervical dystonia. *J Formos Med Assoc* 1995; 94:189–192.
17. Memin B, Pollack P, Hommel M, et al. Effects of botulinum toxin on spasticity. *Rev Neurol (Paris)* 1992; 148:212–214.
18. Dengler R, Neyer U, Wohlfarth K, et al. Local botulinum toxin in the treatment of spastic foot drop. *J Neurol* 1992;239:375–378.
19. Dunne JW, Heye N, Dunne SL. Treatment of chronic limb spasticity with botulinum toxin A. *J Neurol Neurosurg Psychiatry* 1995;58:232–235.
20. Viriyavejakul A, Vachalathiti R, Poungvarin N. Botulinum treatment for post-stroke spasticity: low-dose regime. *J Med Assoc Thai* 1998;81:413–422.
21. Grazko MA, Polo KB, Jabbari B. Botulinum toxin A for spasticity, muscle spasms, and rigidity. *Neurology* 1995;45:712–717.
22. Hyman N, Barnes M, Bhakta B, et al. Botulinum toxin (DYSPORT) treatment of hip adductor spasticity in multiple sclerosis: a prospective, randomised, double blind, placebo controlled, dose ranging study. *J Neurol Neurosurg Psychiatry* 2000;68:707–712.
23. Nix WA, Butler IJ, Roontga S, et al. Persistent unilateral tibialis anterior muscle hypertrophy with complex repetitive discharges and myalgia: report of two unique cases and response to botulinum toxin. *Neurology* 1992;42:602–606.
24. Davis D, Jabbari B. Significant improvement of stiff-person syndrome after paraspinal injection of botulinum toxin-A. *Mov Disord* 1993;8:371–373.
25. Fishman VM, Parkman HP, Schiano TD, et al. Symptomatic improvement in achalasia after botulinum toxin injection of the lower esophageal sphincter. *Am J Gastroenterol* 1996;91:1724–1730.
26. Jost WH. One hundred cases of anal fissure treated with botulin toxin: early and long-term results. *Dis Colon Rectum* 1997;40:1029–1032.
27. Acquadro MA, Borodic GE. Treatment of myofascial pain with botulinum A toxin [Letter]. *Anesthesiology* 1994;80:705–706.
28. Girdler NM. Use of botulinum toxin to alleviate facial pain. *Br J Hosp Med* 1994;52:363
29. Polo KB, Jabbari B. Effectiveness of botulinum toxin type A against painful limb myoclonus of spinal cord origin. *Mov Disord* 1994;9:233–235.
30. Diaz JH, Gould HJ. Management of post-thoracotomy pseudoangina and myofascial pain with botulinum toxin. *Anesthesiology* 1999;91:877–879.
31. Barwood S, Baillieu C, Boyd R, et al. Analgesic effects of botulinum toxin A: a randomized, placebo-controlled clinical trial. *Dev Med Child Neurol* 2000;42: 116–121.
32. Zermann D, Ishigooka M, Schubert J, Schmidt RA. Perisphincteric injection of botulinum toxin type A. A treatment option for patients with chronic prostatic pain? *Eur Urol* 2000;38:393–399.
33. Foster L, Clapp L, Erickson M, et al. Botulinum toxin A and chronic low back pain: a randomized, double-blind study. *Neurology* 2001;56:1290–1293.
34. Johnstone SJ, Adler CH. Headache and facial pain responsive to botulinum toxin: an unusual presentation of blepharospasm. *Headache* 1998;38:366–368.
35. Ivanhoe CB, Lai JM, Francisco GE. Bruxism after brain injury: successful treatment with botulinum toxin-A. *Arch Phys Med Rehabil* 1997;78:1272–1273.
36. Lobbezoo F, Naeije M. [Etiology of bruxism: morphological, pathophysiological and psychological factors]. *Ned Tijdschr Tandheelkd* 2000;107:275–280.
37. van der Zaag J, Lobbezoo F, Naeije M. [Dental and pharmacological treatment options for bruxism]. *Ned Tijdschr Tandheelkd* 2000;107:289–292.
38. Visscher CM, Lobbezoo F, Naeije M. [Treatment of bruxism: physiotherapeutic approach]. *Ned Tijdschr Tandheelkd* 2000;107:293–296.
39. Van Zandijcke M, Marchau MM. Treatment of bruxism with botulinum toxin injections [Letter]. *J Neurol Neurosurg Psychiatry* 1990;53:530.
40. Rijsdijk BA, van ES RJ, Zonneveld FW, et al. [Botulinum toxin type A treatment of cosmetically disturbing masseteric hypertrophy]. *Ned Tijdschr Geneeskd* 1998; 142:529–532.
41. Stegenga B, Lobbezoo F. [Bruxism and temporomandibular disorders]. *Ned Tijdschr Tandheelkd* 2000;107: 285–288.
42. Lobbezoo F, Lavigne GJ. Do bruxism and temporomandibular disorders have a cause-and-effect relationship? *J Orofac Pain* 1997;11:15–23.
43. Freund B, Schwartz M, Symington JM. Botulinum toxin: new treatment for temporomandibular disorders. *Br J Oral Maxillofac Surg* 2000;38:466–471.
44. Sessle BJ. Biological and psychological aspects of orofacial pain. In: Stohler CS, Carlson DS, eds. *Craniofacial growth series 29, Center for Human Growth &*

Development. Ann Arbor, MI: University of Michigan, 1994:1–33.
45. LeResche, L. Epidemiology of temporomandibular disorders: implications for the investigation of etiologic factors. *Crit Rev Oral Biol Med* 1997;8:291–305.
46. Tan EK, Jankovic J. Treating severe bruxism with botulinum toxin. *J Am Dent Assoc* 2000;131:211–216.
47. Hartmann E. Bruxism. In: Kryger MH, Roth T, Dement WC, eds. *Principles and practice of sleep medicine, 2nd ed.* Philadelphia, PA: WB Saunders, 1994: 598–601.
48. Lavigne G, Kim JS, Valiquette C, et al. Evidence that periodontal pressoreceptors provide positive feedback to jaw closing muscles during mastication. *J Neurophysiol* 1987;58:342–358.
49. Filippi GM, Errico P, Santarelli R, et al. Botulinum A toxin effects on rat jaw muscle spindles. *Acta Otolaryngol* 1993;113:400–404.
50. Finley JE. Myofascial pain. *eMed J* 2 (Oct. 2, 2001) (http://www.emedicine.com/PMR/topic84.htm).
51. Porta M. A comparative trial of botulinum toxin type A and methylprednisolone for the treatment of myofascial pain syndrome and pain from chronic muscle spasm. *Pain* 2000;85:101–105.
52. Travell JG, Simons DG. Myofascial pain and its trigger points. In: Travell JG, Simons DG, eds. *Myofascial pain and dysfunction.* Baltimore, MD: Williams and Wilkins, 1983:5–164.
53. Hong CZ, Simons DG. Pathophysiologic and electrophysiologic mechanisms of myofascial trigger points. *Arch Phys Med Rehabil* 1998;79:863–872.
54. Cheshire WP, Abashian SW, Mann JD. Botulinum toxin in the treatment of myofascial pain syndrome. *Pain* 1994;59:65–69.
55. Winner PK. Migraine: diagnosis and rational treatment. *Int J Fertil Womens Med* 1998;43:104–110.
56. Sjaastad O, Saunte C, Hovdahl H, et al. "Cervicogenic" headache. An hypothesis. *Cephalalgia* 1983;3: 249–256.
57. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia* 1988;8:19–28.
58. Pfaffenrath V, Dandekar R, Pollmann W. Cervicogenic headache—the clinical picture, radiological findings and hypotheses on its pathophysiology. *Headache* 1987;27:495–499.
59. Jaeger B. Are "cervicogenic" headaches due to myofascial pain and cervical spine dysfunction? *Cephalalgia* 1989;9:157–164.
60. Pikoff H. Is the muscular model of headache still viable? A review of conflicting data. *Headache* 1984;24: 186–198.
61. Bansevicius D, Sjaastad O. Cervicogenic headache: the influence of mental load on pain level and EMG of shoulder-neck and facial muscles. *Headache* 1996;36: 372–378.
62. Sjaastad O, Fredriksen TA. Cervicogenic headache: criteria, classification and epidemiology. *Clin Exp Rheumatol* 2000;18:S3–S6.
63. Hobson DE, Gladish DF. Botulinum toxin injection for cervicogenic headache. *Headache* 1997;37:253–255.
64. Freund BJ, Schwartz M. Treatment of chronic cervical-associated headache with botulinum toxin A: a pilot study. *Headache* 2000;40:231–236.
65. Jensen R. Pathophysiological mechanisms of tension-type headache: a review of epidemiological and experimental studies. *Cephalalgia* 1999;19:602–621.
66. Olesen J. Clinical and pathophysiological observations in migraine and tension-type headache explained by integration of vascular, supraspinal and myofascial inputs. *Pain* 1991;46:125–132.
67. Rasmussen BK. Migraine and tension-type headache in a general population: precipitating factors, female hormones, sleep pattern and relation to lifestyle. *Pain* 1993;53:65–72.
68. Rasmussen BK. Migraine and tension-type headache in a general population: psychosocial factors. *Int J Epidemiol* 1992;21:1138–1143.
69. Holroyd KA, France JL, Nash JM, et al. Pain state as artifact in the psychological assessment of recurrent headache sufferers. *Pain* 1993;53:229–235.
70. Mitsikostas DD, Thomas AM. Comorbidity of headache and depressive disorders. *Cephalalgia* 1999;19: 211–217.
71. Russell MB, Ostergaard S, Bendtsen L, et al. Familial occurrence of chronic tension-type headache. *Cephalalgia* 1999;19:207–210.
72. Schwartz BS, Stewart WF, Simon D, et al. Epidemiology of tension-type headache. *JAMA* 1998;279: 381–383.
73. Diamond S. Tension-type headache. *Clin Cornerstone* 1999;1:33–44.
73a. Zwart JA, Bovim G, Sand T, et al. Tension headache: botulinum toxin paralysis of temporal muscles. *Headache* 1994;34:458–462.
74. Relja M. Treatment of tension-type headache by local injection of botulinum toxin. *Eur J Neurol* 1997; 4(Suppl 2):S71–S74.
75. Relja MA. Treatment of tension-type headache by local injection of botulinum toxin: 1-year followup. *Cephalalgia* 2000;20:336.
76. Schulte-Mattler WJ, Wieser T, Zierz S. Treatment of tension-type headache with botulinum toxin: a pilot study. *Eur J Med Res* 1999;4:183–186.
77. 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.
78. Smuts JA, Barnard PWA. Botulinum toxin type A in the treatment of headache syndromes: a clinical report of 79 patients. *Cephalalgia* 2000;20:332.
79. Gobel H, Lindner V, Krack P, et al. Treatment of chronic tension-type headache with botulinum toxin. *Cephalalgia* 1999;19:455.
80. Rollnik JD, Tanneberger O, Schubert M, et al. Treatment of tension-type headache with botulinum toxin type A: a double-blind, placebo-controlled study. *Headache* 2000;40:300–305.
81. Schmitt WJ, Slowey E, Fravi N, et al. Effect of botulinum toxin A injections in the treatment of chronic tension-type headache: a double-blind, placebo-controlled trial. *Headache* 2001;41:658–664.
82. Carruthers A, Langtry JA, Carruthers J, et al. Improvement of tension-type headache when treating wrinkles with botulinum toxin A injections. *Headache* 1999;39: 662–665.
83. Ekbom K. A clinical comparison of cluster headache and migraine. *Acta Neurol Scand* 1970;Suppl 41:11.
84. Kudrow L. Cluster headache mechanisms and management. New York: Oxford University Press, 1980.

85. Dodick DW, Rozen TD, Goadsby PJ, et al. Cluster headache. *Cephalalgia* 2000;20:787–803.
86. Kudrow L, Kudrow DB. Inheritance of cluster headache and its possible link to migraine. *Headache* 1994; 34:400–407.
87. Russell MB. Genetic epidemiology of migraine and cluster headache. *Cephalalgia* 1997;17:683–701.
88. Eadie MJ, Sutherland JM. Migrainous neuralgia. *Med J Aust* 1966;1:1053–1057.
89. Couturier EG, Hering R, Steiner TJ. The first report of cluster headache in identical twins [see Comments]. *Neurology* 1991;41:761.
90. Roberge C, Bouchard JP, Simard D, et al. Cluster headache in twins [Letter; Comment]. *Neurology* 1992;42: 1255–1256.
91. Sjaastad O, Shen JM, Stovner LJ, et al. Cluster headache in identical twins. *Headache* 1993;33:214–217.
92. Ekbom K, Ahlborg B, Schele R. Prevalence of migraine and cluster headache in Swedish men of 18. *Headache* 1978;18:9–19.
93. D'Alessandro R, Gamberini G, Benassi G, et al. Cluster headache in the Republic of San Marino. *Cephalalgia* 1986;6:159–162.
94. Swanson JW, Yanagihara T, Stang PE, et al. Incidence of cluster headaches: a population-based study in Olmsted County, Minnesota. *Neurology* 1994;44: 433–437.
95. Ginies PR, Fraimount JL, Siou DK, et al. Treatment of cluster headache by subcutaneous injection of botulinum toxin (abst). In: Jensen TS, editor. *Progress in Pain Research and Management.* Seattle: IASP Press, 1996:501.
96. Freund BJ, Schwartz M. The use of botulinum toxin A in the treatment of refractory cluster headache: case reports. *Cephalalgia* 2000;20:329–330.
97. Olesen J, Lipton RB. Migraine classification and diagnosis. International Headache Society criteria. *Neurology* 1994;44(Suppl 4):S6–S10.
98. Cady RK. Diagnosis and treatment of migraine. *Clin Cornerstone* 1999;1:21–32.
99. Silberstein SD, Lipton RB, Dalessio D, eds. *Wolff's Headache.* 7th ed. South Melbourne, NZ: Oxford University Press, 2001.
100. Hickey JV. The clinical practice of neurological and neurosurgical nursing, 4th ed. New York: Lippincott, 1997.
101. Edelson RN. Menstrual migraine and other hormonal aspects of migraine. *Headache* 1985;25:376–379.
102. Spierings EL, Sorbi M, Haimowitz BR, et al. Changes in daily hassles, mood, and sleep in the 2 days before a migraine headache. *Clin J Pain* 1996;12:38–42.
103. Stang P, Sternfeld B, Sidney S. Migraine headache in a prepaid health plan: ascertainment, demographics, physiological, and behavioral factors. *Headache* 1996; 36:69–76.
104. Rapoport AM. Pharmacological prevention of migraine. *Clin Neurosci* 1998;5:55–59.
105. Breslau N, Davis GC, Schultz LR, et al. Joint 1994 Wolff Award Presentation. Migraine and major depression: a longitudinal study. *Headache* 1994;34: 387–393.
106. Lipton RB, Silberstein SD, Stewart WF. An update on the epidemiology of migraine. *Headache* 1994;34: 319–328.
107. Stewart WF, Shechter A, Rasmussen BK. Migraine prevalence. A review of population-based studies. *Neurology* 1994;44(Suppl 4):S17–S23.
108. Stewart WF, Simon D, Shechter A, et al. Population variation in migraine prevalence: a meta-analysis. *J Clin Epidemiol* 1995;48:269–280.
109. Lipton RB, Stewart WF, Diamond S, et al. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache* 2001;41: 646–657.
110. Stewart WF, Linet MS, Celentano DD, et al. Age- and sex-specific incidence rates of migraine with and without visual aura. *Am J Epidemiol* 1991;134:1111–1120.
111. Stewart WF, Lipton RB, Celentano DD, et al. Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors. *JAMA* 1992;267:64–69.
112. Lipton RB, Stewart WF. Prevalence and impact of migraine. *Neurol Clin* 1997;15:1–13.
113. Hu XH, Markson LE, Lipton RB, et al. Burden of migraine in the United States: disability and economic costs. *Arch Intern Med* 1999;159:813–818.
114. Mannix LK. Epidemiology and impact of primary headache disorders. *Med Clin North Am* 2001;85: 887–895.
115. Lipton RB, Stewart WF, Vonkorff M. Burden of migraine: societal costs and therapeutic opportunities. *Neurology* 1997;48(Suppl 3):S4–S9.
116. Silberstein SD. Review of botulinum toxin type A and its clinical applications in migraine headache. *Expert Opin Pharmacother* 2001;2:1649–1654.
117. Binder W, Brin MF, Blitzer A, et al. Botulinum toxin type A (BOTOX) for treatment of migraine headaches: An open-label study. *Otolaryngol Head Neck Surg* 2000;123:669–676.
118. Mauskop A, Basedo R. Botulinum toxin A is an effect prophylactic therapy of migraines. *Cephalalgia* 2000; 20:422.
119. Binder WJ, Brin MF, Blitzer A, et al. Botulinum toxin type A (BOTOX) for treatment of migraine headaches: An open-label study. *Otolaryngol Head Neck Surg* 2000;123:669–676.
120. Silberstein S, Mathew N, Saper J, et al. Botulinum toxin type A as a migraine preventive treatment. *Headache* 2000;40:445–450.
121. Brin MF, Swope DM, Abassi S, et al. BOTOX for migraine: double-blind, placebo-controlled, region-specific evaluation. *Cephalalgia* 2000;20:421–422.
122. Aoki KR. Pharmacology and immunology of botulinum toxin serotypes. *J Neurol* 2001;248(Suppl 1): 3–10.
123. Brin MF. Botulinum toxin therapy: basic science and overview of other therapeutic applications. In: Blitzer A, Binder WJ, Boyd JB, et al, eds. *Management of facial lines and wrinkles.* New York: Lippincott Williams & Wilkins, 2000:279–302.
124. Jankovic J, Schwartz K. Response and immunoresistance to botulinum toxin injections. *Neurology* 1995; 45:1743–1746.
125. Gonnering RS. Negative antibody response to long-term treatment of facial spasm with botulinum toxin. *Am J Ophthalmol* 1988;105:313–315.
126. Tsui JK. Botulinum toxin as a therapeutic he agent. *Pharmacol Ther* 1996;72:13–24.
127. Ludlow CL, Hallett M, Rhew K, et al. Therapeutic use of type F botulinum toxin [Letter]. *N Engl J Med* 1992; 326:349–350.

128. Greene PE, Fahn S. Use of botulinum toxin type F injections to treat torticollis in patients with immunity to botulinum toxin type A. *Mov Disord* 1993;8: 479–483.
129. Mezaki T, Kaji R, Kohara N, et al. Comparison of therapeutic efficacies of type A and F botulinum toxins for blepharospasm: a double-blind, controlled study. *Neurology* 1995;45:506–508.
130. Sheean GL, Lees AJ. Botulinum toxin F in the treatment of torticollis clinically resistant to botulinum toxin A. *J Neurol Neurosurg Psychiatry* 1995;59: 601–607.
131. Sankhla C, Jankovic J, Duane D. Variability of the immunologic and clinical response in dystonic patients immunoresistant to botulinum toxin injections. *Mov Disord* 1998;13:150–154.
132. Halpern JL, Smith LA, Seamon KB, et al. Sequence homology between tetanus and botulinum toxins detected by an antipeptide antibody. *Infect Immun* 1989; 57:18–22.
133. Rosales RL, Arimura K, Takenaga S, et al. Extrafusal and intrafusal muscle effects in experimental botulinum toxin-a injection. *Muscle Nerve* 1996;19: 488–496.
134. Ishikawa H, Mitsui Y, Yoshitomi T, et al. Presynaptic effects of botulinum toxin type A on the neuronally evoked response of albino and pigmented rabbit iris sphincter and dilator muscles. *Jpn J Ophthalmol* 2000; 44:106–109.
135. Cui M, Aoki KR. Botulinum toxin type A (BTX-A) reduces inflammatory pain in the rat formalin model. *Cephalalgia* 2000;20:414(abstr).