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Botulinum Toxin in Primary Care Medicine

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***Clostridium botulinum*, a gram-positive anaerobic bacterium, produces a potent neurotoxin that causes muscle paralysis. The therapeutic use of botulinum toxin was discovered in the 1970s and has since been used to treat patients with a broad range of medical complaints. Botulinum toxin (BTX) is used in the primary care setting to treat conditions such as allergic rhinitis, hyperhidrosis, lichen simplex chronicus, migraine, myofascial pain syndrome, and certain task-specific idiopathic focal dystonias (eg, writer's cramp)—in addition to its more publicized use for cosmetic enhancement of the face. The expanding range of therapeutic applications for BTX make it necessary for primary care physicians to understand the biochemistry, preparation, indications, and interactions of BTX.**

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Clostridium botulinum was discovered more than 100 years ago as a food-poisoning agent that causes muscle paralysis when ingested. This gram-positive anaerobic bacterium produces a very potent neurotoxin. In 1980, after a series of animal experiments, Alan B. Scott, MD, published the first report on the therapeutic efficacy of botulinum toxin (BTX) in humans; BTX was injected into the extraocular muscles of 67 patients with strabismus.[1] In 4 to 5 days, the toxin caused weakness that produced a correction in strabismus of up to 40 prism diopters, which then gradually diminished—all without producing systemic complications.[1] Successful correction of strabismus with BTX opened a wide array of potential therapeutic targets.

Since then, BTX has been used by many physicians for a broad range of medical conditions involving many parts of the human body. To relax the muscles responsible for malignant curvature of the spine, orthopedists have injected BTX into the hyperactive paravertebral muscles of patients with spastic scoliosis.[2] Otolaryngologists have used BTX to manage spastic vocal dysphonias in which adductor muscles around the vocal cord contract too tightly.[3] Neurologists have injected BTX into pericranial muscles to safely reduce the incidence, severity, and nausea associated with migraine.[4] This report reviews the therapeutic use of BTX for allergic rhinitis, hyperhidrosis, lichen simplex chronicus, migraine, myofascial pain syndrome, focal dystonia of the hand, and cosmetic facial enhancement.

Biochemistry and Mechanism of Action

Botulinum toxin is a single-chain protein that is inactive until cleaved by its own proteases into one heavy and one light chain. The active heavy chain mediates the binding to the presynaptic cholinergic neuromuscular end plate. Membrane-embedded proteins called synaptosomal-associated proteins (SNAPs) are responsible for the release of acetylcholine (ACh). The light chain of BTX type A (BTX-A) cleaves SNAP-25 and consequently prevents the release of ACh into the neuromuscular junction. Reenervation restores muscle activity in approximately 3 months.

Preparation and Interactions

Botulinum toxin type A is supplied in a single-use vial containing 100 U of vacuum-dried purified *Clostridium botulinum* toxin type A neurotoxin complex. The vial must be stored in a freezer until ready for use. Shaking the vial can destroy its ingredients. After the contents are gently mixed with sterile or bacteriostatic saline, the vial can be used for up to 2 weeks if kept refrigerated.[5] The diluent can be adjusted to achieve the desired concentration. For example, if 1.0 mL of diluent is added, the resulting dose is 10 U per 0.1 mL.

Botulinum toxin must be administered with caution in patients who are taking aminoglycosides, which increase the half-life of BTX-A, or other neuromuscular depolarizing blockers, and in patients with a history of neuromuscular deficiency. There are no conclusive studies on the effects of BTX in pregnant patients; thus, BTX is not recommended in this group. To prevent the production of antibodies to BTX-A, it is advised to apply a maximum of 400 U per visit, a maximum of 50 U per site, and a maximum volume of 0.5 mL per site.[5] Most patients notice a gradually increasing repsonse in 3 to 7 days that plateaus and lasts for 2 to 11 months, with gradual redevelopment of wrinkles, sweating, or pain.[6*]

This review focuses on BTX-A, but there are seven antigenic forms of BTX (A, B, C, D, E, F, and G) that cleave

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SNAPs at different sites. The lethal dose of BTX for humans is estimated at 3000 U for a 70-kg person.[7] One unit of BTX is the amount of toxin needed to kill 50% of Swiss-Webster mice weighing 18 to 20 g. In humans, the lethal dose of BTX causes flaccid paralysis due to the inability of muscles to receive ACh from the motor end plate. The 100-U vial standard dose is significantly below the lethal dose, and the dose used in cosmetic procedures is less than 30 U per session.

Clinical Applications

Allergic Rhinitis

Nasal symptoms of allergic rhinitis include rhinorrhea, sneezing, congestion, and obstruction. In a double-blind placebo-controlled study, 2 U of BTX-A was injected into the middle turbinate, and another 2 U was injected into the inferior turbinate in each nasal cavity.[8] With the exception of sneezing and nasal stuffiness, the severity of rhinorrhea was significantly diminished (24.1%–41.5% reduction) in the BTX-A group compared with the placebo group, and this benefit lasted for 4 weeks.[8] A small (n=34) randomized controlled trial of 8 weeks' duration suggested the efficiency of BTX-A in relieving rhinorrhea, nasal obstruction, and sneezing due to allergic rhinitis.[9] Another study found that in rats, vasoactive intestinal peptide immunoreactive fibers in the nasal mucosa were markedly decreased after BTX-A application.[9] Local BTX-A treatment was thus determined to be a selective and nontraumatic method to reduce sensitization of the nasal mucosa, to alleviate most nasal symptoms, and to reduce the sensitivity of sensory neurons in the mucosa.[10]

Hyperhidrosis

Treatment with BTX-A has been found to decrease perspiration in the axilla, on the palms, and on the soles of the feet, in patients with hyperhidrosis.[11] If a patient fails to respond to topical therapy, BTX-A may be administered by intradermal injection.[12] In a study by Hornberger et al,[12] mean sweat production at 24 weeks postinjection was still below 50% of the preinjection level. Adverse effects were minimal, and 92% of patients were satisfied or completely satisfied with the results of treatment at 4 weeks postinjection.

More studies need to be conducted to determine whether BTX-A is acting directly on the sweat glands or the associated ACh components of the condition. The effect of BTX-A on ACh in the autonomic nervous system could be more clinically meaningful than its antispasmodic properties. For example, auriculotemporal syndrome occurs when sweat gland nerves attach to the parotid gland following postsurgical denervation or injury to that gland, causing the patient to perspire during food consumption. Injections can be guided by ultrasound into the parotid gland with success.

Lichen Simplex Chronicus

Recalcitrant pruritus is a hallmark of lichen simplex chronicus, an eczematous dermatitis.[13] In a study by Heckmann et al,[13] 20 to 80 U of Dysport (3-5 U of Dysport = 1 U of Botox) was injected intradermally into five circumscribed lichenoid lesions in three patients with lichen simplex chronicus–associated pruritus. The pruritus subsided within 3 to 7 days in all three patients; within 2 to 4 weeks, all lesions cleared completely. No recurrences were noted during a 4-month follow-up examination. This study concluded that lichen simplex chronicus–associated pruritus can be successfully treated with BTX-A.[13]

Pruritus has been shown to be related to ACh-sensitive C-fibers.[14] Heckmann et al[13] showed that the action of Ach on the fibers was abated by BTX-A. Perhaps it can be inferred from this study[13] that other dermatologic conditions involving pruritus may be relieved by BTX-A injections. One study[15] showed success with BTX-A for dishidrotic hand dermatitis, a recurrent eczematous condition. After saline dilution (100 U/1 mL of saline), 2 U of BTX-A was injected intradermally every 15 mm on the volar aspects of the palms and fingers, for a total dose of 162 U of BTX-A. Seven of the 10 patients in the study experienced improvement in symptoms. The role of hand perspiration in this condition is unclear. More studies are needed to determine whether the BTX-A directly affects neurotransmitters causing pruritic sensation or indirectly decreases that sensation by reducing localized perspiration.

Migraine

Seventeen percent of women and 6% of men in the United States have migraines.[16] Current prophylactic antivasospastic therapy with beta-blockers and symptomatic therapy with selective serotonin receptor agonists (eg, sumatriptan succinate, zolmitriptan, naratriptan hydrochloride) have shown limited benefit.[16] In a double-blind study by Silberstein and Lipton,[17] 123 patients with two to eight moderate to severe migraines per month received BTX-A injections of 25 U or 75 U into the glabellar, frontalis, and temporalis muscles. Results showed that 25 U—but not 75 U—of BTX-A was superior to the control treatment (saline) in reducing the frequency and severity of migraines, the need for migraine medications, and associated vomiting (*Table*). In a double-blind study by Brin et al,[18] 53 patients with two to six migraines per month received BTX-A injections into the frontal and temporal musculature (*Table*). The results of this study[18] showed that BTX-A was superior to placebo in reducing migraine severity at 12 weeks postinjection. The effect of BTX lasts much longer (3 months) than traditional treatments, is generally well tolerated, and has fewer systemic adverse effects.

The origin of migraine cephalgia remains unknown, but it has been hypothesized that vascular, neuronal, and musculoskeletal components exist. The injection of BTX-A acts on the myofascial component by inhibiting contraction of the respective cranial muscles, but it also acts on the vascular component by inhibiting the release of ACh. Thus, the parasympathetic vasodilatory response is inhibited. It is also possible that BTX-A blocks neurotransmitters other than ACh that are involved in the cascade of events leading to a migraine.[19] Vasoac-

Table
Details of 1 Open-Label and 2 Double-Blind Studies of BTX-A Treatment for Migraine

Study	Population	Sample	Treatment Protocol	Injection Sites	Follow-up	Main Results
Open-label, Binder et al	Patients seeking BTX-A treatment for hyperfunctional facial lines and/or dystonias with concomitant headache or specifically for headache	106 patients, mostly women, 30-60 years old	Prophylactic or acute injections per standards for hyperfunctional facial lines	Glabellar frontal temporal, suboccipital as indicated by headache characteristics	Varied; ranged from 3 weeks to 6 months postinjections	51% true migraine subjects treated prophylactically reported complete response with mean benefit duration=4.1 months. Glabellar injections superior
Double-blind, Silberstein et al	Headache patients with histories of 2-8 moderate to severe migraines per month	123 patients, mostly women, 22-63 years old	Randomization to: 1) vehicle 2) 25 U BTX-A 3) 75 U BTX-A	Glabellar, frontal, temporal	Monthly for 3 mo postinjection	25 U bot not 75 U BTX-A superior to vehicle in reducing migraine frequency and severity, use of migraine medications, and vomiting.
Double-blind, Brin et al	Headache patients with histories of 2-6 migraines per month	53 patients, mostly women, 21-75 years old	Randomization to: 1) frontal + temporal BTX-A 2) frontal BTX-A + temporal placebo 3) temporal BTX-A + frontal placebo 4) frontal + temporal placebo 45 U to frontal 30 U to temporal	Frontal, temporal	2, 4, 8, 12, and 16 weeks postinjection	Frontal + temporal BTX-A superior to placebo in reducing migraine severity at week 12 postinjection

Source: Silberstein SD, Lipton RB. Overview of diagnosis and treatment of migraine [review]. *Neurology*.1994;44:S6-S16. Reprinted with the permission of Lippincott Williams & Wilkins.

tive intestinal peptide and vasoconstrictor neuropeptide Y have been found with ACh in parasympathetic nerves originating in internal carotid ganglia innervating cerebral arteries.[20] Another mechanism by which BTX-A may relieve migraines is in its action on pericranial muscle spasms that pull on the skull bones and their respective sutures, causing a change in intracranial pressure and pressure on the cerebral vasculature.

Myofascial Pain Syndrome

This condition is often encountered in pain clinic patients, with an indication varying between 30% and 85%.[21] The syndrome manifests as regional pain, precipitated by deep palpation of localized hyperirritable spots called trigger points. A trigger point appears as a nodular mass, approximately 2 to 3 mm in diameter, on a taut band of skeletal muscle and may be painful on palpation. Trigger points cause referred pain patterns—unlike tender points, which produce local pain when palpated. In the 1920s, Frank Chapman, DO, discovered that "ganglioform contractions" were trigger points associated with visceral dysfunction.[22] He named these trigger points Chapman's reflex. For example, a trigger point on the anterior tip of the right twelfth rib can be palpated to determine if tenderness signals visceral disease in the appendix.[22]

In a small double-blind study of six patients with myofascial pain syndrome, injections of BTX-A showed a clear improvement in their symptoms.[23] Patients were injected with either 50 U of BTX-A (in 4 mL of saline) or normal saline alone on two occasions at least 2 months apart.[23] Patients' responses occurred within the first week after injection, and the mean duration of effects was 5 to 6 weeks.[23] Similarly, in patients with tension-type headaches, experimenters "chased" the tenderness by injecting the posterior neck muscles (upper trapezius, levator scapulae, and suboccipitals) and, if still tender, injecting the temporalis and frontalis.[23]

Focal Dystonia of the Hand

The most common form of occupational dystonia is that of the hand, often called "writer's cramp."[24] The syndrome begins

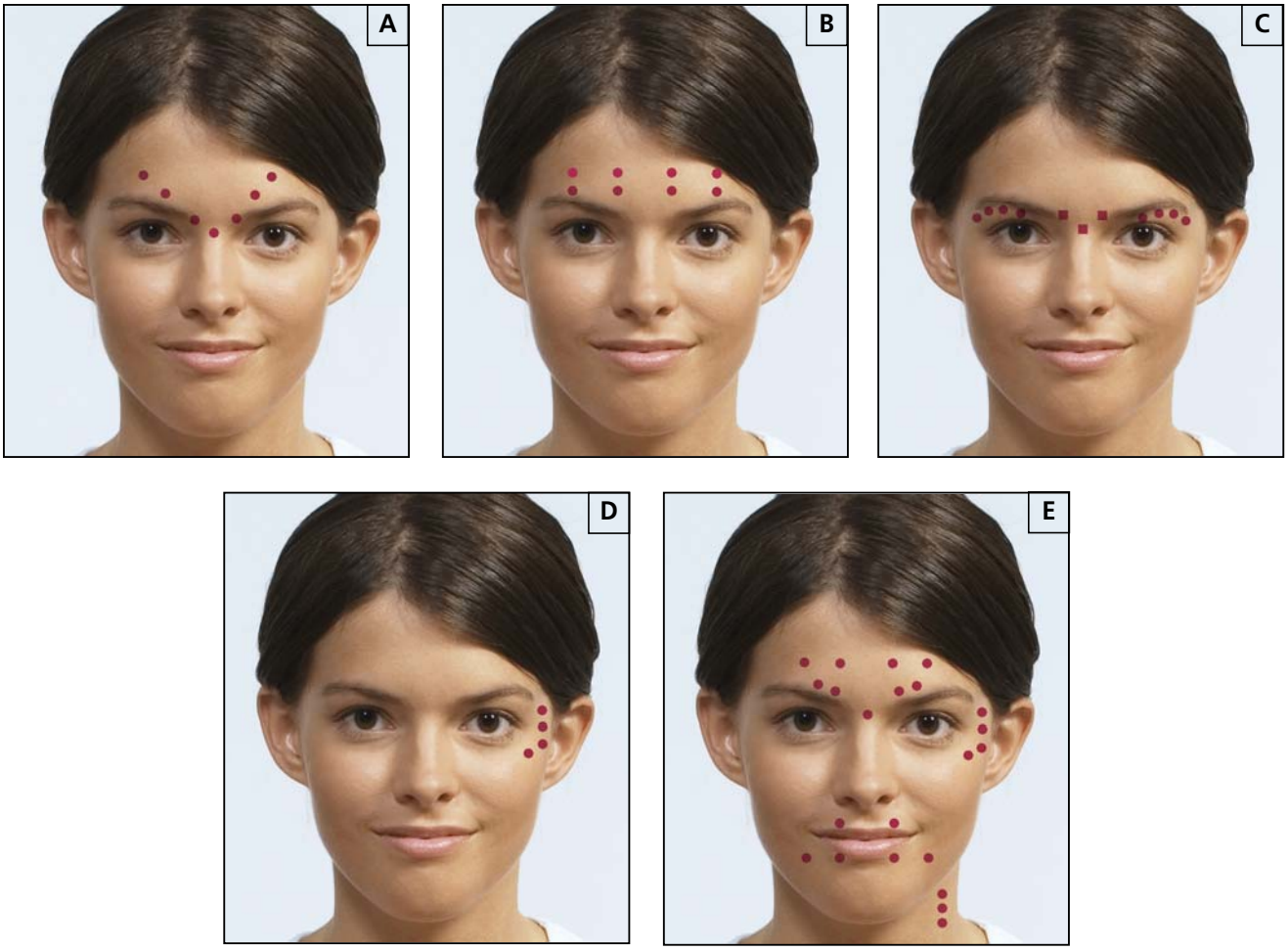

Figure 1. *Glabellar injection sites (A).[6,26] Forehead injection sites (B).[6,26] Brow lift (C). Circles, Huang injection technique[27] (each site received 0.05 mL or 2.5 U); squares, Carruthers injection technique[7]* (glabellar area, 7 to 10 U; brow, 0 to 2.5 U; dilution or 1 U/0.01 mL). Injection sites for lateral canthal lines (D).[26] *Injection summary (E).[7]*

with clumsiness during writing or other fine motor activity and progresses to tightness and aching, accompanied by a loss of speed and fluency of movement. These symptoms may extend to the forearm or shoulder. Cohen et al[25] identified the dystonic muscles in patients by clinical examination and electromyograph recordings of localized bursts of muscle activation with fine wire electrodes during the tasks that precipitated dystonia. These muscles were injected every 2 weeks in increasing doses until the symptoms improved. Patients reported improvement in cramping, pain, and/or tension.

Cosmetic Uses

The most popular and well-known use for BTX-A is in cosmetic enhancement of the face (*Figure 1*). The chemical brow lift, reduction in lateral canthal lines, glabellar furrows, and transverse forehead lines, as well as other cosmetic uses of BTX-A have become fashionable cosmetic trends for both sexes. A detailed understanding of the facial musculature is necessary for the cosmetic application of BTX-A. Most facial rejuvenation techniques, such as collagen and autologous fat transplantation, laser resurfacing, and surgical procedures, do not target the underlying cause of the wrinkles—the muscle (*Figure 2*).

■ **Brow Lift—**A chemical brow lift is created when BTX-A is injected into the brow depressor muscles, which include the procerus, the medial fibers of the orbicularis oculi, the corrugator supercilii, and the lateral orbicularis fibers. Huang et al[27] reported the largest brow lift of 2 to 3 cm after 5 U (in 0.1 mL of saline) of BTX-A was injected into the glabellar region of each brow, and an additional 10 U was injected at four sites along the orbital rim, starting at the midpupillary line and extending to the lateral brow. Achieving a brow lift in men is more difficult than in women due to men's larger muscle mass; 35 U or more may be required.[7] Injections below the orbital rim in the midorbital region are associated with a greater risk of upper eyelid ptosis. This technique diminishes

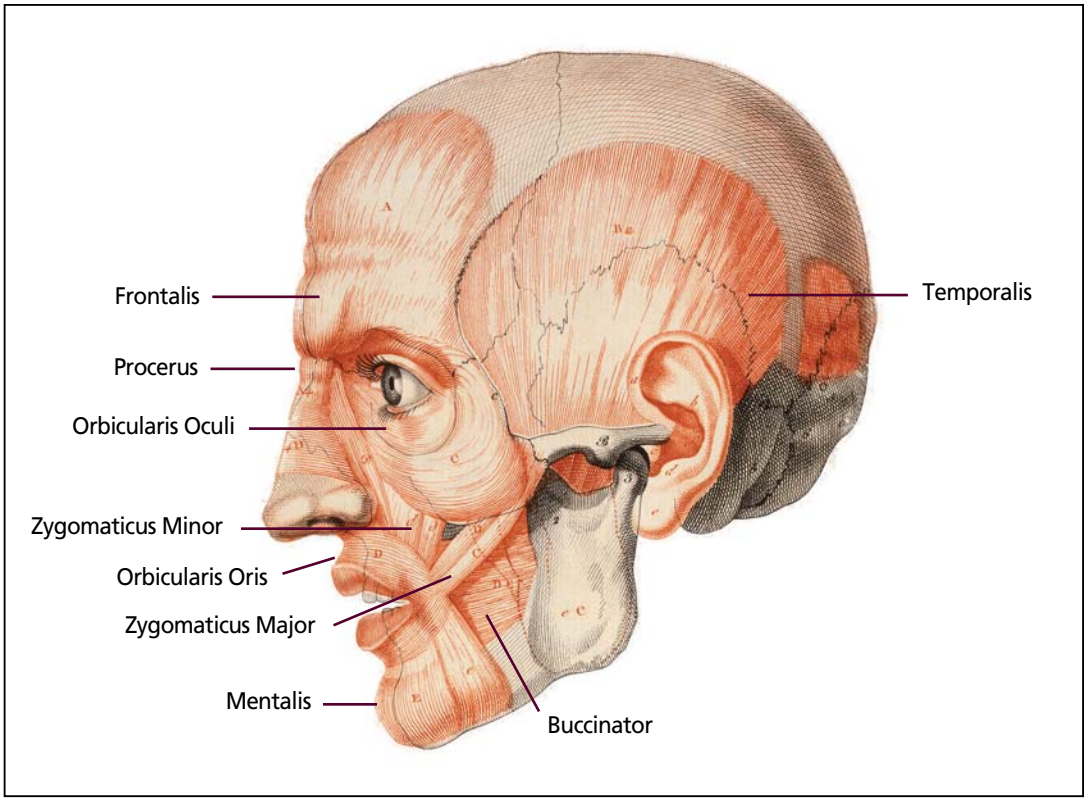

Figure 2. *Facial musculature.*

the function of the orbicularis muscle, permitting the frontalis to elevate the brow unopposed by the upper orbicularis fibers, which lower the brow. The frontalis muscle should not be injected or little effect will be achieved. To prevent brow and upper-lid ptosis, injections should not be given below or less than 1 cm above the superior orbital margin lateral to the midpupillary line.[6]

■ **Glabellar Furrows—**These "frown lines" between the eyebrows are formed by the actions of the procerus, corrugator supercilii, and medial fibers of the orbicularis oculi.[28] Injection of BTX-A into the corrugator supercilii causes temporary and local chemical denervation and muscle paralysis for up to 6 months, followed by full recovery.[7] Carruthers et al[7] used seven injection sites, injecting a total of 20 to 25 U of Botox (Allergan Inc, Irvine, Calif) in women and 35 U in men. A possible adverse effect of this technique is eyelid ptosis, which results when BTX-A affects the levator muscle. Ptosis may persist for 2 to 4 weeks. Ensuring that the injection site is above the orbital ridge will decrease this risk.[26]

■ **Lateral Canthal Lines—**Also referred to as "crow's feet," these lines are created mainly by contraction of the orbicularis oculi and to a much lesser extent, the zygomaticus (mouth corner elevator).[24] The lateral orbicularis is injected in one to four sites, with total doses ranging from 5 to 15 U of BTX-A followed by gentle massage for even distribution.[7] For example, two 5-U injections may be given on each side in opposite directions, tracing a 1.5-cm radius from the lateral canthus, which is 1 cm outside the orbital rim. This injection must be superficial to paralyze the superficial fibers of the orbicularis muscle where they attach to the skin.

■ **Transverse Forehead Lines—**To soften or eliminate these lines, caused by the contraction of the frontalis muscle, and to "open" the eyes, injections can be given at four sites, 2 to 3 cm above the orbital rim.[30] Carruthers et al[7] injected a total of 10 to 20 U of Botox across these four injection sites, the lateral two sites in line with the midpupillary line and the medial two sites spaced evenly between. Some authors believe that the elevations between the wrinkles contain the most frontalis muscle fibers and thus are optimal injection sites.[27] The Botox forehead injections should be administered subcutaneously into the ridge between the wrinkles formed by the patient raising his or her eyebrows.[6] Intramuscular injections can be more uncomfortable and may bleed more than subcutaneous injections, but both techniques achieve similar responses.[6]

The frontalis muscle has no bony attachments. Its actions include elevating the eyebrows and giving the face a surprised look, producing transverse wrinkles in the forehead. The cor-

rect dose of BTX-A (10–20 U) must be given to reduce the action of the frontalis but not to completely deenervate the muscle so as to cause eyebrow ptosis. Also, injecting 1.0 cm or more above the brow maintains some lower frontalis function and usually prevents eyebrow ptosis.

■ **Other Cosmetic Applications—**Neck rejuvenation has been achieved by injecting BTX-A at regular intervals within the vertical platysmal bands.[7] A total dose of 15 to 21 U per band or 2 to 3 U per injection is given in the area from 1 to 3 cm from the jaw line to the lower neck.[7] Botulinum toxin also has been used, although less commonly, to diminish nasolabial folds by injecting the zygomaticus muscles, mouth wrinkles by injecting small doses superficially between the vertical lip lines, and mentalis folds by injecting each mentalis muscle adjacent to the midline of the chin.[7] The research on these topics is minimal at this time.

Conclusion

New therapeutic applications of BTX continue to emerge. In patients with cerebral palsy[31] and multiple sclerosis,[32] BTX-A injected into spastic muscles has been shown to control their activity. One study showed a reduction of body weight and food intake in rats after injecting BTX into the gastric antrum to delay gastric emptying.[33] In this study, BTX most likely blocked the parasympathetic actions of ACh. In a case report, BTX injected into the sphincter of Oddi helped relieve biliary pain after cholecystecomy.[34]

Botulinum toxin has revolutionized the treatment of certain medical and cosmetic conditions. For the primary care physician who treats patients with refractory muscle spasticity and complaints related to ACh-mediated actions, BTX currently provides a viable and well-studied option.

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