

**TITLE: Botulinum Toxin for Cosmetic Use**

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## **Introduction**

Surgical procedures continue to trend towards minimally invasive techniques. Cosmetic alterations to combat the effects of aging are no exception to this trend. Patients, more and more, are demanding cosmetic procedures that leave no scar and allow them to return to normal activity quicker. Though traditional rhytidoplasty and brow lift remain in the armamentarium of the facial cosmetic surgeon, minimally invasive procedures such as botox treatment and injection tissue contouring can often achieve satisfactory results for patients.

## **History**

Botox, or botulinum toxin is well known in modern popular culture. However, its rise to fame began almost 200 years ago. In the 1820s, the biological basis for food poisoning was not understood. Dr. Justinus Kerner began to study a batch of improperly prepared blood sausages responsible for the death of several dozen Germans. Kerner posited that there was something in the spoiled sausages that brought on the disease- something he called "wurstgift" (German for sausage poison). Ever the dedicated scientist, Kerner even went so far as to inject himself with material from the sausage. His experiments and case studies led to a better understanding of the neurological symptoms of food-borne botulism (ptosis, dysphagia, muscle weakness, and, if left untreated, paralysis and respiratory failure). He also offered up suggestions for treatment and prevention of food poisoning, and paved the way for today's therapeutic use of the toxin.

More than 70 years after Kerner conducted his experiments, Dr. Emile Pierre van Ermengem of Belgium was asked to investigate an outbreak of botulism following a funeral dinner where three people died and 23 were paralyzed. Van Ermengem was able to make a connection between botulism and a spore-forming bacterium he named *Bacillus botulinus* (now known as *Clostridium botulinum*). Many scientific studies followed, and seven strains of botulinum toxin were eventually identified (A through G).

In the early 1950s, Dr. Edward J. Schantz and his colleagues were able to purify botulinum toxin type A into crystalline form. In 1953, physiologist Dr. Vernon Brooks

discovered that injecting small amounts into a hyperactive muscle blocked the release of acetylcholine from motor nerve endings, causing temporary “relaxation.” In the 1960s, ophthalmologist Dr. Alan B. Scott began injecting botulinum toxin type A into monkeys, theorizing its muscle-relaxing effects might help in the treatment of strabismus. Before long, botulinum toxin type A became the go-to toxin in research labs around the world

In 1978, Scott received FDA approval to inject tiny amounts of botulinum toxin into human volunteers. In the early 1980s, he published a number of studies including a 1981 paper in the Transactions of the American Ophthalmological Society that asserted botulinum toxin “appears to be a safe and useful therapy for strabismus.” Additional research showed the drug’s benefits went beyond ophthalmology, providing patients with temporary relief from facial spasms, neck and shoulder spasms, even vocal cord spasms. In 1988, drugmaker Allergan acquired the rights to distribute Scott’s batch of botulinum toxin type A (or Oculinum, as it was then known) and a year later, the FDA approved botulinum toxin type A for the treatment of both strabismus and blepharospasm. Shortly thereafter, Allergan acquired Scott’s company and changed the drug’s name to the compact, catchy “Botox.”

As research continued, other potential uses came to light. Bladder spasms, writer’s cramp, excessive sweating, even cerebral palsy in kids all were alleviated — at least for a short time — by injections of the neurotoxin. But by far the most earth-shattering discovery came about by accident when Canadian ophthalmologist Dr. Jean Carruthers noticed her blepharospasm patients were starting to lose their frown lines. In 1992, she and her dermatologist husband published a study in the Journal of Dermatologic Surgery and Oncology stating that though temporary, “treatment with C. botulinum-A exotoxin is a simple, safe procedure” for the treatment of brow wrinkles. Dermatologists from immediately took note (and took advantage of this “off-label” use) and by 1997, Botox use spiked so high the country’s supply temporarily ran out.

With the new millennium, FDA approvals continued to roll in. In 2000, Botox got the FDA’s nod for the treatment of cervical dystonia. In 2002, Botox Cosmetic (the frown-line fixer) got its official government go-ahead, greenlighting Allergan to begin a multi-million-dollar marketing campaign to boost its already healthy Botox sales, which had reached \$310 million by the end of 2001. Today, botulinum neurotoxin injection is the most commonly performed cosmetic procedure in the world.

## **Mechanism of Action**

*For a graphic presentation by Allergan, see:*  
<http://www.botoxmedical.com/HowBotoxWorks.aspx>

Botulinum toxin exerts its effects by paralyzing skeletal muscle. The pharmacological site of action is at the neuromuscular synapse. The presynaptic neuromuscular nerve ending contains membranous vesicles prepared to release its stored neurotransmitter, acetylcholine. Neuronal stimulation initiates a cascade of events that leads to the fusion of the neurotransmitter-containing vesicle with the nerve membrane. This process is facilitated by a group of proteins comprising the SNARE complex. The membrane fusion results in the release of acetylcholine into the synaptic cleft by a process of exocytosis. The acetylcholine diffuses and eventually binds to receptors on the muscle, leading to muscle contraction.

Botulinumtoxin A (BOTOX) consists of a heavy chain of 100-kilodalton and a light chain of 50-kilodalton making up the 150-kilodalton core type A molecule. The toxin is protected by accessory hemagglutinin and nontoxic nonhemagglutinin proteins, yielding a uniform 900-kilodalton complex. The BOTOX core molecule enters the nerve cell by a process of receptor-mediated endocytosis.

It is the heavy chain that contains the binding domain. The toxin is now contained in a membranous vesicle inside the cell. Soon after, the light chain is released into the cytoplasm of the nerve terminal where it begins to cleave one of the SNARE proteins.

In motor neurons, the light chain of the BOTOX core molecule blocks the release of acetylcholine by cleaving SNAP-25, which is an essential component of the SNARE complex. When acetylcholine cannot be released, muscle contraction cannot occur.

The toxin does not appear to affect the conduction of electrical signals along the nerve fiber or the synthesis or storage of acetylcholine.

## **Applications**

### **Glabellar Frown Lines**

Glabellar frown lines are the most common reason for cosmetic injection of BOTOX®.

#### *Anatomy*

Facial rhytides and folds in this area result from action of the depressor muscles. The corrugator superciliaris, medial orbital portion of the orbicularis oculi, and more horizontally oriented fibers of the depressor supercillii produce the vertical lines of the glabella.

The corrugator muscle is a brow adductor moving the eyebrow downward and medially. It arises from the nasal bone just above the rim of the orbit medially and extends laterally and upward, inserting in the skin above the middle of the eyebrow. It lies deep to the frontalis, procerus, and orbicularis oculi muscles.

The medial fibers of the orbicularis oculi originate from the medial orbital rim anterior to the origin of the corrugator. The fibers interdigitate with fibers of the frontalis, procerus, and corrugator muscles.

The depressor supercillii originates from the nasal process of the frontal bone and inserts into the skin at the medial aspect of the eyebrow.

The vertically oriented procerus muscle, which originates from the upper nasal cartilage and the lower nasal bone, produces the horizontal lines of the glabella and nasal root. It inserts into the skin between the brows and the frontal belly of the occipitofrontalis. Its fibers interdigitate with those of the orbicularis, frontalis, and corrugator muscles.

A glabellar "spread test" may be performed prior to injection by spreading the glabellar wrinkles apart with the thumb and index fingers. This may allow an estimate of the expected benefit from BOTOX® injection. Patients with thick sebaceous skin and deep dermal scarring

that are not improved with manual spreading usually respond poorly to botulinum toxin injections.

### ***Technique***

Usually, 5 sites are injected with 4-6 units each for an average total dose of approximately 25 units. A 1998 dose/response study of 46 women receiving botulinum toxin for glabellar wrinkles found an effective starting dose from 2.5-4 units per injection site (12.5-20 U total).

In a 2007 double-blinded study, 70 patients were randomly assigned to treatment with 20 U botulinum toxin type A (BOTOX Cosmetic) or placebo, median glabellar line severity was significantly lower after botulinum toxin treatment than after placebo. Compared with placebo, botulinum toxin also resulted in significantly superior patient assessments and a greater proportion of patients considering they looked younger than their current age.

In a 2005 study, 80 men were randomized to receive a total dose of either 20, 40, 60, or 80 U of botulinum toxin type A. The 40, 60, and 80 U doses of botulinum toxin type A were consistently more effective in reducing glabellar lines than the 20 U dose (duration, peak response rate, improvement from baseline). In addition, the participants reported a dose-dependent reduction in the ability to frown, improvement in their global assessment, and increased feelings of attractiveness, self-confidence, and satisfaction. The incidence of adverse events was not increased with higher doses. The authors concluded that male participants with glabellar rhytids benefit from starting doses of at least 40 units.

One site on each side is used to inject the corrugator, one site on each side is used to inject the orbicularis oculi and depressor supercilii, and one site is used to inject the procerus in the mid line.

The patient is asked initially to frown and scowl, and the target muscles are palpated. The first injection is placed into the belly of the corrugator muscle. The needle is inserted at the origin of the corrugator fibers just above the medial canthus and superciliary arch until bone is felt, and then withdraw it slightly. The needle is then advanced within the belly of the muscle upward and lateral as far as the medial third of the eyebrow, 1 cm superior to the orbital rim. 4-6 units are injected as the needle is withdrawn.

The next site is approximately 1 cm above the upper medial aspect of the supraorbital ridge. The needle is advanced slightly in a vertical direction toward the hairline. 4-6 units are injected into the orbicularis oculi and depressor supercilii as the needle is withdrawn.

The last injection is central into the belly of the procerus to eliminate the horizontal lines at the root of the nose. 4-6 units are injected at a point where 2 lines drawn at 45° from the medial aspect of the eyebrows converge in the center of the nasal root, just superior to the horizontal plane of the medial canthi.

To avoid resultant accentuation of eyebrow arching in men, an additional 4-6 units are injected 1 cm above the supraorbital prominence vertical to the mid point of the eyebrow.

## **Horizontal Forehead Lines**

Performing BOTOX® injections to treat horizontal forehead lines is relatively easy, and the result usually is quite satisfying. Treatment can be combined with injections for glabellar frown lines when appropriate.

### ***Anatomy***

The frontalis muscle elevates the eyebrows and the skin of the forehead. The fibers of the frontalis are oriented vertically, and wrinkles of the forehead are oriented horizontally. The frontalis muscle originates on the galea aponeurotica near the coronal suture and inserts on the superciliary ridge of the frontal bone and skin of the brow, interdigitating with fibers of the brow depressors.

The medial fibers usually are more fibrous than the lateral fibers, thus requiring less toxin for paralysis. Total paralysis of the frontalis should be avoided, since this is likely to cause brow ptosis and loss of expression. Injection too close to the lateral eyebrow can cause lateral eyebrow ptosis.

### ***Technique***

Multiple injections of small amounts of toxin create weakness without total paralysis. 3-5 sites on each side of the mid line are injected, usually using 2 units (1-3 U) per site. Sites are separated by 1-2 cm. The initial injection site is approximately 1 cm above the eyebrow directly above the medial canthus. Additional sites diverge laterally and upward to the hairline in a "V" configuration, often for a total of 3 sites. Additional sites can be added in the mid line or more laterally depending on individual and clinical response.

Injections of the upper face and periocular region usually are performed with the patient seated, and the patient is asked to remain upright for 2-3 hours to prevent spread of toxin through the orbital septum.

## **Lateral Canthal Lines (crow's feet)**

Aging and photodamage cause much of the wrinkling in this area. However, the component of hyperfunctional contraction of the lateral aspect of the orbicularis oculi is targeted for improvement with BOTOX® injections.

### ***Anatomy***

The lateral fibers of the orbicularis oculi are arranged in a circular pattern around the eye. Contraction of these fibers produces wrinkles that extend radially from the region of the lateral canthus.

### ***Technique***

3 or 4 subcutaneous injections are applied approximately 1 cm lateral to the lateral orbital rim using 2-3 units per injection site (for a total of 6-12 U per side). Sites are spaced 0.5-1 cm apart in a vertical line or slightly curving arch. Doses that are too high or injections that are too medial can lead to eyelid ptosis or diplopia.

A 2002 study showed doses of 6, 12 or 18 units of botulinum toxin delivered to the lateral orbicularis were significantly superior to placebo, but with no clear dose-response relationship.

But, the same researchers, in 2005, showed a dose-dependent treatment effect for efficacy, with higher doses having an increased magnitude and duration of effect. However, a clear differentiation between the 18 U and 12 U doses was not apparent. Few adverse events were reported, with no statistically significant differences between BTX-A and placebo in the incidence of subjects experiencing adverse events. They suggested 12 U per side as the most appropriate dose.

In a recent 2009 placebo-controlled study, 15, 30, or 45 U of botulinum toxin or placebo were injected unilaterally. Independent panel assessments at week 4 showed that all doses resulted in significant improvements in crow's feet severity at maximum smile. In addition, though, a clear dose-response effect was seen with 30 and 45 U delivering a more durable benefit at 12 weeks. These results suggest that higher doses than previously used are optimal for lateral canthal lines.

## **Contraindications**

Exclusion criteria for Botox® use include pregnancy or active nursing and preexisting neuromuscular conditions, such as myasthenia gravis or Eaton-Lambert syndrome, are not suitable candidates for Botox®. Some medications such as aminoglycosides, penicillamine, quinine, and calcium channel blockers can potentiate the effects of Botox and should not be used concomitantly with Botox®. Women who have inadvertently been treated with Botox® during pregnancy have had uneventful deliveries, and thus far no teratogenicity has been attributed to Botox®. Nevertheless, Botox® is classified as a pregnancy category C drug because it is not firmly established whether it can cause fetal harm when administered to pregnant women. Furthermore, it is not known whether Botox® is excreted in human milk as are many drugs. Therefore, delay of injection of Botox® until pregnancy is complete and lactation has ended is advisable.

## **Adverse Effects**

The use of botulinum toxin for treatment of facial rhytids is not without complications. Klein et al reviewed these in 2004. The complications seen with botulinum toxin are usually temporary.

Generalized reactions that have idiosyncratically occurred from Botox® injections include nausea, fatigue, malaise, flulike symptoms, and rashes at sites distant from the injection. However, a 2009 meta-analysis of 5 placebo-controlled studies showed that acne, injection site pruritus, oral herpes, rash, lower respiratory tract infection, dental caries, and eye pain were significantly more common in placebo-treated patients compared with botulinum toxin-treated participants. In addition, there were no symptoms of weakness remote to the injection site or related to the central nervous system.

Untoward sequelae that can occur at any site due to percutaneous injection of Botox® include pain, edema, erythema, ecchymosis, headache and short-term hypesthesia. Discomfort can be decreased by use of topical anesthetics such as EMLA cream before injection, and the use

of smaller-gauge needles. A 2005 single-center, double-blind, randomized study demonstrated a statistically significant reduction in subject-reported procedural pain in participants pretreated with lidocaine 4%. However, a 2006 study showed that pretreatment with topical *betacaine* followed by skin cooling seems to have a deleterious impact on botulinum toxin effect without a significantly beneficial patient-perceived reduction in injection discomfort. Techniques similar to injecting local anesthesia are also helpful in reducing pain. Pinching the skin and the underlying muscle, slowly inserting the needle bevel up through the opening of a pilosebaceous unit, and slowly injecting the solution will also help to diminish discomfort. Ice applied immediately after injection will further reduce the pain as well as the edema and erythema associated with an IM injection. Ecchymosis can be minimized by avoiding aspirin, aspirin-containing products, and NSAIDs for 7 to 10 days before injection. Bruising occurs most frequently in older patients taking aspirin and in middle-aged persons taking vitamin E. Limiting the number of injections and applying postinjection digital pressure without manipulation will also assist in reducing bruising. While the onset of headaches has been initiated with Botox® injections, they are alleviated with standard over-the-counter analgesics. It is, however, more common for patients to report that chronic tension headaches have improved following injections of Botox®.

The most common complication in treatment of the glabellar complex is ptosis of the upper eyelid. This is caused by diffusion of the toxin through the orbital septum, where it affects the levator palpebrae muscle. Ptosis can occur as early as 48 hours or as late as 7 to 10 days following injection and can persist for up to 2 to 4 weeks. The 1 to 2 mm of ptosis is often initially only of subtle cosmetic significance, but as the day progresses, the eyelid droop becomes more exaggerated and more apparent. To avoid ptosis, injections should not cross the midpupillary line, and should be 1 cm above the eyebrow. Digital pressure at the border of the supraorbital ridge while injecting the corrugator also reduces the potential for extravasation of Botox. Patients often are instructed to remain in an upright position for 3-4 hours following injection and to avoid manual manipulation of the area. Active contraction of the muscles under treatment may increase the uptake of toxin and decrease its diffusion. Ptosis can be treated with apraclonidine 0.5% eyedrops. This is an alpha2-adrenergic agonist, which causes Müller muscles to contract. Apraclonidine is contraindicated in patients with documented hypersensitivity. Phenylephrine (Neo-Synephrine) 2.5% can be used when apraclonidine is not available. Neo-Synephrine is contraindicated in patients with narrow-angle glaucoma and in patients with aneurysms. 1-2 drops 3 times daily are used until ptosis resolves.

The most significant complication of treatment of the frontalis is brow ptosis. Injections in the forehead should always be above the lowest fold produced when the subject is asked to elevate their forehead (frontalis). If the patient has a low eyebrow, treatment of the forehead lines should be avoided, or limited to that portion of the forehead 4.0 cm or more above the brow. The lower 2.5 to 4.0 cm of the frontalis muscle moves cephalad to elevate the eyebrows. An equally esthetically unfavorable outcome is the brow that assumes a quizzical or “cockeyed” appearance.

This occurs when the lateral fibers of the frontalis muscle have not been appropriately injected. The central brow then becomes lowered and the lateral brow is still able to contract and is pulled upward. This can be either unilateral or symmetric affecting both sides of the brow. The treatment is to inject a small amount of Botox into the fibers of the lateral forehead that are pulling upward. To correct this flaw, however, only a small amount of Botox is required, as

overcompensation can quickly and irreversibly turn a lateral brow that is pulled upward into an unsightly facial palsy with a hooded brow that partially covers the eye.

The most common reported complications in the “crow’s feet” area are bruising, diplopia, ectropion and an asymmetric smile due to injection of zygomaticus major. If severe lower lid weakness occurs, an exposure keratitis may result. Treatment is symptomatic. These complications are avoided by injecting at least 1 cm outside the bony orbit or 1.5 cm lateral to the lateral canthus, not injecting medial to a vertical line through the lateral canthus and not injecting close to the inferior margin of the zygoma. Violating these boundaries has on occasion also resulted in diplopia due to medial migration of Botox and resultant paralysis of the lateral rectus muscle. Covering or patching the eye will alleviate some of the double vision.

It should be noted that, even though serious adverse events have not been seen with the use of licensed products, the same is not true with the use of unlicensed preparations. A case series of 4 patients with symptoms consistent with naturally occurring botulism was published in 2006. All case-patients had been injected with a highly concentrated, unlicensed preparation of botulinum toxin A and may have received doses 2857 times the estimated human lethal dose by injection. Pretreatment serum toxin levels in 3 of the 4 case-patients were equivalent to 21 to 43 times the estimated human lethal dose. These laboratory-confirmed cases of botulism demonstrate that clinical use of unlicensed botulinum toxin A can result in severe, life-threatening illness.

## **Antibodies**

An estimated 5-15% of patients injected serially with botulinum toxin develop secondary non-responsiveness from the production of neutralizing antibodies. Risk factors associated with the development of neutralizing antibodies include injection of more than 200 units per session and repeat or booster injections given within 1 month of treatment.

When a patient loses his or her response, serum can be tested for neutralizing antibodies, although this rarely is performed outside research settings. Alternatively, a patient's physiologic response can be evaluated with a single injection of 15 units into the frontalis on one side.

Limited information is available as to whether neutralizing antibodies resolve over time and, consequently, whether attempts at reinjection should be made after a prolonged period. Using the lowest dose of toxin necessary to achieve the desired clinical effect and avoiding reinjection within 1 month appear prudent in an effort to keep antibody formation as low and unlikely as possible.

## **Conclusion**

Botulinum injections have become widely popular for combating the effects of aging. Aging patients will continue to seek out the procedure. Knowledge of optimal treatment patterns and adverse effects will allow physicians to safely and effectively deliver this therapy.

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