

# The Basics of Botulinum Toxin

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Presented here are the basics of botulinum toxin, reviewing the science, facial anatomy, and injection techniques to prepare practitioners for successful treatment of patients who are seeking nonsurgical options for a rejuvenated appearance.

Injecting botulinum toxin for active rhytides is the most common nonsurgical cosmetic procedure performed each year, with more than 2.4 million total procedures in 2008 alone.<sup>1</sup> The US aesthetic market for botulinum toxin type A (BTX-A) is estimated to be approximately \$705 million in 2004.<sup>2</sup> With approval from the US Food and Drug Administration (FDA) of Dysport for the treatment of glabellar rhytides, the cost for BTX-A will likely decrease with a proportional increase in interest by patients desiring treatment. A thorough understanding of the underlying anatomy and basic principles to injecting botulinum toxin is key to generating a symmetric, youthful appearance while avoiding complications.

## BASIC SCIENCE

Seven different serotypes of botulinum toxin exist and are known as A, B, C<sub>1</sub>, D, E, F, and G.<sup>3</sup> Serotype A is available for commercial use and FDA-approved for glabellar rhytides in the forms of Botox and, more recently, Dysport. Botulinum toxin type B is FDA-approved for the treatment of cervical dystonia and marketed as Myobloc.

Botulinum toxin exhibits a similar structure across serotypes. Toxin synthesis produces a single-chain, inactive 150-kDa protein that is bound as a complex to nontoxic proteins. The toxin is cleaved into its active form through tissue proteolysis.<sup>4</sup> It exerts its effect at the presynaptic

neuromuscular junction to prevent acetylcholine release, thereby inducing flaccid paralysis. Three principle steps are involved in the toxin-mediated paralysis: binding, endocytosis, and inhibition of neuromuscular release. Each serotype disrupts a different protein. Serotype A works by cleaving synaptosome-associated protein, a pre-synaptic membrane protein that is necessary for fusion of vesicles that contain neurotransmitter. Serotype B cleaves a vesicle-associated membrane protein, also known as synaptobrevin (Figure 1).<sup>5</sup>

Botulinum toxin induces reversible denervation at the neuromuscular junction, leading to skeletal muscle atrophy. After approximately 3 months, the neuromuscular junctions regain neural transmission and loss of activity of BTX-A is observed.<sup>6</sup>

## ANATOMY

Successful chemodenervation with botulinum toxin is directly correlated with the practitioner's knowledge of the relevant underlying facial anatomy. Horizontal forehead rhytides are created by contraction of the frontalis muscle. The muscle originates on the galea aponeurotica layer superiorly and interdigitates with the procerus, corrugator, and orbicularis oculi muscles that overlie the brow region (Figure 2).<sup>7</sup> The paired muscles have a distinct midline separation composed of fibrous tissue.

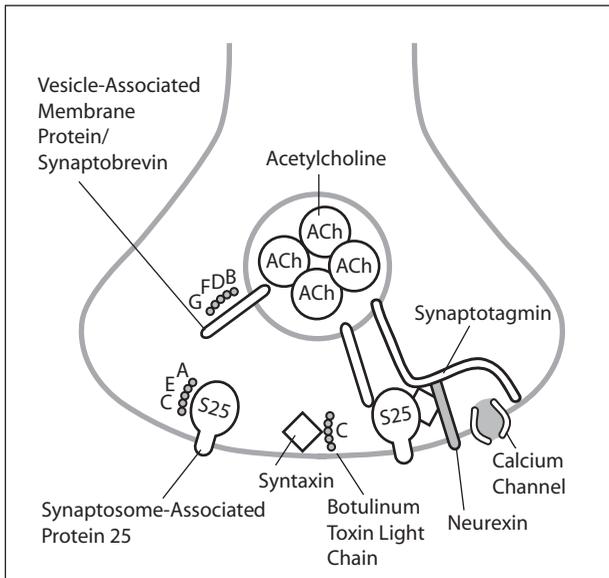
Glabellar rhytides are created by the contraction of the procerus and corrugator muscles. The procerus muscle is a thin, pyramidal muscle that is located midline of the glabella, with insertion superiorly to the frontalis muscle and inferiorly on the nasal bones.<sup>7</sup> Contraction of the procerus generates horizontal wrinkles over the glabella. The paired corrugator supercilli muscles pull the medial brows inferomedially, generating vertical wrinkles over the glabella. The muscles insert slightly lateral to the mid-pupillary line, whereas its origin lies at the junction of the frontal and nasal bones near the superomedial orbital rim. The muscles lie below the frontalis and orbicularis oculi

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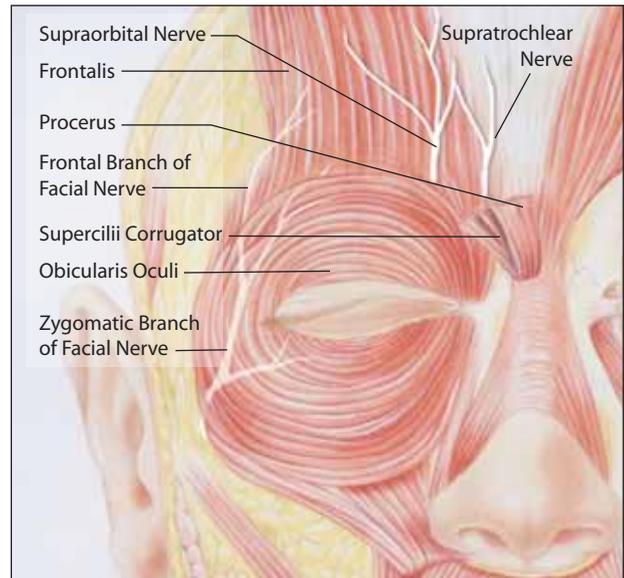
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## BOTULINUM TOXIN



**Figure 1.** Neuromuscular junction.



**Figure 2.** Facial anatomy.

muscles at its medial origin and travels through the palpebral and orbital fibers of the orbicularis oculi muscles as it inserts in the skin over the brow.<sup>7,8</sup> The majority of the corrugator muscles lie along the medial eyebrow.<sup>8</sup> Superolateral injection of botulinum toxin, rather than inferomedial, decreases the incidence of undesired brow ptosis.<sup>9</sup>

Lateral orbital rhytides, known as crow's-feet, result from the contraction of the orbicularis oculi muscle. The muscle is a circumferential orbital muscle divided into 3 parts called orbital, preseptal, and pretarsal (Figure 3). The orbital portion forms an ellipse around the orbital rim, combining with frontalis and corrugator supercillii superiorly, and zygomaticus muscles and levator labii superioris alaeque nasi inferiorly. The transverse facial vein courses on top of the lateral orbicularis oculi muscle (Figure 3).<sup>10</sup>

Bunny lines are created by contraction of the transverse nasalis muscle. The fibers course superomedial from its origin on the maxilla over the nasal bridge to fuse with its contralateral muscle and the aponeurosis of the procerus muscle. Marionette lines are created by the contraction of the depressor angularis oris. The muscle has its origin on the line of the mandible with insertion on the modeolus as it fuses with fibers from the risorius and orbicularis oris muscle.<sup>7,8</sup>

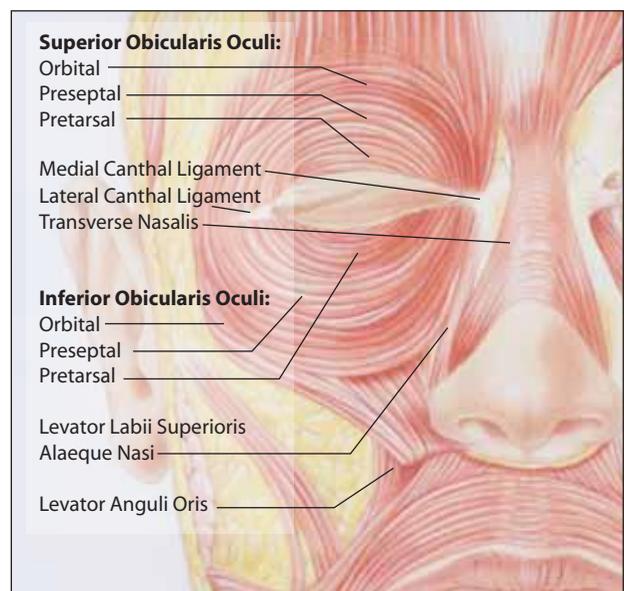
### PREPARATION OF BOTULINUM TOXIN

Botox is distributed as a vacuum-dried powder with 100 U per vial, whereas Dysport is supplied as a 300-U vial for reconstitution with 2.5 or 1.5 mL sodium chloride 0.9%. A study evaluating dilutions of Botox with 1, 3, 5, or 10 mL showed no significant differences in

outcome.<sup>11</sup> An average volume dilution for Botox is 2.5 mL, whereas 1 mL may be used when low-volume injections are desired.

### CONTRAINDICATIONS

The primary contraindication for botulinum toxin is neuromuscular disease, such as myasthenia gravis or amyotrophic lateral sclerosis, which could be exacerbated with treatment. Medications that can interfere with neuromuscular transmission, such as aminoglycosides and quinine, require additional consideration of dosage adjustment.<sup>12</sup> The treated area should be free of infection.



**Figure 3.** Periorbital facial anatomy.

## TREATMENT

The desired end point for treatment of the forehead is to soften the horizontal creases without complete paralysis. Overtreatment can lead to lack of expressiveness, whereas treating less than 2 cm above the brow can lead to brow ptosis. Injections should be evenly spaced at least 1 cm above the brow. The authors use 16 to 20 U depending on the patient. In a study by Carruthers et al,<sup>13</sup> higher doses of BTX-A resulted in great efficacy and longer duration of effect in the reduction of forehead rhytides.<sup>13</sup>

For treatment of glabellar rhytides, injection methods vary. A study by Pribitkin et al<sup>14</sup> using a single injection into each corrugator reported that the best results were found in patients with thin skin and fine wrinkles. The authors' practice is to use 1 injection in each corrugator. Other practitioners inject at 5 sites, with 1 in the procerus and 2 in each corrugator (Figure 4).<sup>15</sup> For the injection of Botox, the recommended method is 5 injection sites as described above, each receiving 4 U of product for a total of 20 U.<sup>16</sup> For the injection of Dysport, the recommended injection is the same 5 sites, with 10 U in each site for a total of 50 U.<sup>17</sup> The size of corrugator muscles varies between patients and dosing must be adjusted accordingly. The potency of Botox and Dysport is different and not interchangeable. Injecting in a superolateral rather than inferomedial technique and staying 1 cm above the brow minimizes the risk for undesired blepharoptosis.<sup>9</sup>

Dosing for crow's-feet varies from 12 to 15 U per side for Botox. An intradermal injection at least 1 cm away from the lateral orbital rim helps to minimize bruising or migration to the lateral rectus muscles, respectively.<sup>18</sup> While 1 injection is the most desirable since it is the area most likely to bruise due to the superficial venous plexus, some individuals require more injections to achieve optimal treatment.

Bunny lines on the nose can be treated with 2 to 4 U of Botox, injecting bilaterally on the lateral nasal sidewall. Care must be taken to keep injections away from the nasofacial groove because diffusion can lead to paralysis of levator labii superioris leading to lip ptosis.<sup>8,19</sup>

Treatment of the marionette lines can be achieved with 2 to 5 U of Botox into each depressor anguli oris above its origin at the angle of the mandible and 1 cm lateral to the lateral oral commissure. Due to the risk for migration and resulting asymmetric smile, this should be considered a more advanced area for using botulinum toxin (Figure 5).<sup>8,19</sup>

## COMPLICATIONS AND MANAGEMENT

The incidence of brow ptosis for both Botox and Dysport varies among studies, typically less than 5%.<sup>20,21</sup> This can occur when there is overaggressive treatment of the forehead with unopposed brow depressors. In some



Figure 4. Injection sites for glabellar rhytides.

older individuals baseline brow ptosis is balanced by frontalis contraction. With the treatment of botulinum toxin, the frontalis is paralyzed and the true ptotic brow position becomes apparent. In individuals with hyperkinetic lateral frontalis muscle activity, paralysis of the medial forehead can lead to a jokerlike appearance.<sup>22,23</sup> This can be corrected by injecting 1 to 2 U of Botox into each of the lateral frontalis fibers along the lateral third of the eyebrow.<sup>22</sup>

The rare complication with treatment of the glabella is migration of botulinum toxin to eyelid levators and resulting upper eyelid ptosis. Ptosis becomes apparent within 2 to 10 days and can last up to 1 month. Apraclonidine 0.5% or phenylephrine 2.5% ophthalmic

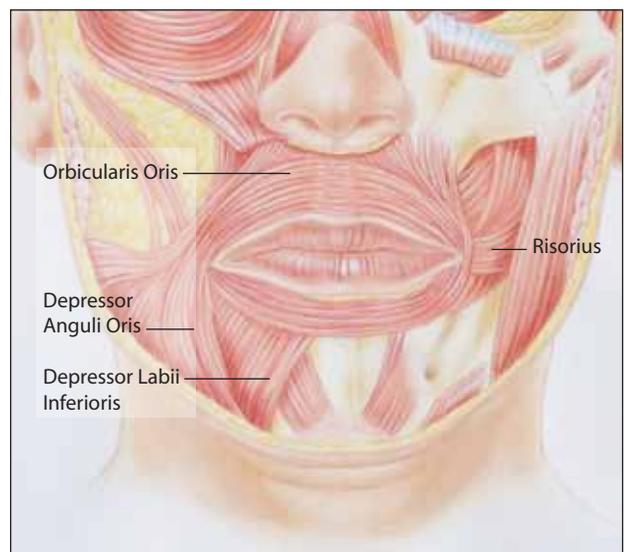


Figure 5. Perioral facial anatomy.

solution can be used 2 to 3 times daily. These medications are  $\alpha$ -adrenergic agonists that stimulate Müller muscles with resulting 1 to 2 mm of upper eyelid elevation.<sup>22,24</sup>

Complications with the treatment of crow's-feet include bruising, diplopia, and lip ptosis. Using intradermal injections staying at least 1 cm from the lateral orbital rim helps to minimize these complications. Direct pressure posttreatment can be applied to minimize the risk for bruising.

### CONCLUSION

With a proper understanding of the basic science of botulinum toxin, facial anatomy, and basic injection technique, the practitioner is prepared for successful treatment of patients to create a subtle, more refreshed appearance. Presented here are the basics of botulinum toxin and its cosmetic use. As the physician becomes more comfortable with the basics of botulinum toxin, there are more advanced treatment methods that are well documented in the literature. With the FDA-approval of a new BTX-A, Dysport, the price of the product may decrease further, opening up the market to more patients.

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