# Neurotoxin Update and Review, Part 2: The Art

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By temporarily blocking muscle movement, injectable commercial neurotoxins have become a mainstay of the treatment of dynamic wrinkles; however, because results can be subtle or extreme, their use has been both celebrated and maligned. A clear understanding of the anatomy and directionality of the involved muscles is necessary to create a natural appearance, rather than one that is expressionless. Selective injection of specific muscle groups allows the clinician to control treatment results. As more botulinum toxin products become commercially available, it is clear that differences exist and the nuances of dosing and injection pattern continue to be elucidated. Part 1 of this series discussed the science of the currently available botulinum toxin products. Here we outline best practices for their use in aesthetic dermatology.

# TREATMENT PARAMETERS FOR THE AESTHETIC USE OF NEUROTOXINS

The substantial body of published data has shown that botulinum toxins are safe and effective in the treatment of facial rhytides of many locations. Most data available pertain to the use of neurotoxins in the upper face, though clinicians have expanded their use to various other locations of the head and neck. Although each neurotoxin has been shown to be safe and effective in the treatment of rhytides, each one is unique and not interchangeable for clinical use at any one fixed-dose ratio. Further, the differing physical properties dictate disparity in onset, duration, and diffusion and/or spreadability, signifying different risk-benefit profiles. Thus, different injection patterns and techniques may be needed for proper implementation to ensure natural aesthetic results.

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## **UPPER FACE**

#### Glabellar Complex

The most common and only US Food and Drug Administration-approved cosmetic indication for botulinum toxin are the frown lines created by the glabellar complex, which includes the procerus, corrugator supercilii, depressor supercilii, and interdigitation of the medial fibers of the orbicularis oculi and frontalis muscles. The procerus is the primary muscle responsible for the horizontal lines of the glabella, while the other muscles contribute to the formation of the vertical lines. Numerous injection techniques have been described with early injection incorporating electromyographic guidance to locate the muscle accurately.<sup>1,2</sup> Most clinical trials have dictated starting doses of 20 to 25 U of onabotulinumtoxinA (Botox) and 50 to 70 U of abobotulinumtoxinA for the glabella split equally into 5 injection sites for treatment of the glabellar complex. Additional or fewer injection points may be indicated in certain circumstances, such as for maintenance of a horizontal brow in men (2 additional injections) or when products have the ability to diffuse more easily (2 fewer injections)<sup>3-5</sup> (Figure 1).

Gender is particularly important regarding treatment of the glabellar complex and should be taken into

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**Figure 1.** Injection sites for the glabellar complex.

consideration, as the female brow typically is more arched (gull-wing appearance) and the male brow is classically more horizontal; additionally, women may require a lower starting dosage than men.<sup>6,7</sup> In general, men have more muscle mass and thicker sebaceous skin, which may require starting dosages approximately twice that which is used for women.<sup>8</sup> Carruthers and Carruthers<sup>9</sup> evaluated the use of Botox (total 20, 40, 60, or 80 U) in the treatment of glabellar lines in men and found a dose-dependent response rate and duration of effect, with higher doses having a more consistently superior result.<sup>10</sup>

Clinicians should evaluate the patient's facial expression at rest and during movement prior to dosing to assess any asymmetries of positioning, ptosis, and muscular mass. In general, dosage is divided among the number of injection sites but not always equally. The corrugator supercilii muscle can vary in anatomic shape and the full course of the muscle must be evaluated prior to injection. Injections performed too medial in the glabellar complex may produce an excessively arched lateral eyebrow, the so-called Spock or quizzical brow. Central immobilization results in compensatory lateral elevation. This requires additional toxin injected into the lateral frontalis above the peak. Patients seeking substantial lateral brow elevation for a "chemical brow lift" effect should be warned that additional arching may produce unwanted lateral forehead rhytides. These can be improved without lowering the brow with the addition of filling agents.

Eyelid ptosis, a result of neurotoxin migration to the upper eyelid levator muscle, generally can be prevented with accurate dose dilution and correct injection technique. In initial studies, most eyelid ptosis was found when injections were given in a downward and medial direction when treating the corrugator supercilii muscle, and it occurred in less than 2% of patients.1 To minimize the risk of eyelid ptosis, inject intramuscularly and avoid injections at or below the midbrow. Placing a fingertip against the superior orbital rim during injection helps confirm the anatomy during injection. Avoiding large-volume injections, having patients remain upright, and repeatedly using the muscle groups (by frowning) for 2 to 3 hours after treatment also may be helpful by reducing downward diffusion.<sup>11</sup> If eyelid ptosis occurs, 1 to 2 drops 3 times daily of an adrenergic agonist, such as apraclonidine ophthalmic drops 0.5%, can be used to lift the eyelid by stimulating contraction of Muller's muscle. Finally, not all glabellar folds can be treated with botulinum toxin alone, and the combination of filling agents and lasers will improve the appearance of these rhytides.

#### Frontalis Muscle

The frontalis muscle is a large, vertically oriented muscle of the forehead (originating at the galea aponeurotica and inserting into the glabellar complex and supraciliary ridge of the frontal bone) that on contraction elevates the eyebrows (especially the lower 2 cm of the frontalis) is responsible for the development of horizontal forehead lines as people age. Considerable variation exists among the structural features of the frontalis muscle between individuals. Classically, the frontalis muscle is depicted as 2 large quadrilateral vertical bands with a distinct midline separation, but in some individuals the midline fibers overlap. Forehead shape and size is variable and this anatomic disparity of features may pose difficulty for inexperienced clinicians. The major challenge is to efface

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B

Figure 2. Example of injection sites for the frontalis (A). Basic injection sites to achieve brow elevation (B).

or soften forehead rhytides while maintaining facial expression (avoiding a frozen appearance) and without creating brow ptosis, a more common complication than eyelid ptosis. Brow ptosis creates a flattened brow and, in older patients, redundant upper lid skin.

The number of injection points varies based on aesthetic goals and individual patient characteristics such as anatomic variation in forehead shape, eyebrow position, and whether an individual has single or multiple deep horizontal furrows versus fine lines. The frontalis muscle spans the entire forehead and thus requires multiple injection points (between 2-12 injection points with an average of 4-6 injection points) for effective paralysis<sup>12,13</sup> (Figure 2A). In the authors' experience, fewer injection points are necessary to achieve similar results with Dysport compared with Botox. All injections should be 1 to 2 cm above the orbital rim to reduce the potential for brow ptosis, though some patients, more often male, may accept the inevitable induction of noteable brow ptosis in exchange for more complete wrinkle reduction. 14 Guerrissi and Sarkissian 15 injected 17 participants with 14 to 20 U of Botox and achieved high-quality results for the treatment of horizontal forehead lines; however, despite avoiding injecting below 2.5 cm above the brow, 2 of 17 participants developed brow ptosis that lasted 55 to 70 days.

Most injection points are along rhytides midway between the eyebrows and the hairline and do not extend past the temporal fusion line, as the lateral extension of the frontalis muscle ends at this point. <sup>16</sup> Some clinicians ask patients to raise their eyebrows and then inject neurotoxin into the ridges between the lines, as it is believed by some that these ridges contain the most frontalis muscle. <sup>17,18</sup> Concomitant injection into the glabellar complex may achieve a brow lift, which helps reduce the risk of brow ptosis; however, treatment of the tails of the corrugator supercilii muscle also may affect the lower frontalis. The authors prefer to treat the glabellar complex 2 weeks prior to the full forehead for first-time neurotoxin patients to prevent overlap that may result in unexpected immobilization.

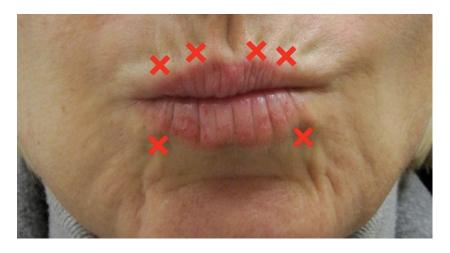
As noted previously, male patients are more likely to accept a flattened brow than female patients, for whom an arched brow is preferred. Accentuation of the midbrow arch can be obtained by a single injection of neurotoxin at the midpupillary line, staying 1 cm above the orbital rim, resulting in unopposed elevation of the midbrow by the frontalis muscle. For brow elevation, another injection of 1- to 3-U Botox or 2- to 6-U Dysport at the lateral aspect of the eyebrow into the superior lateral orbicularis oculi muscle fibers to help release the pulling force of the orbicularis on the lateral eyebrow can help in lateral lifting<sup>19-21</sup> (Figure 2B). Nonetheless, in all instances, it is best to start with low doses and distribute injections according to the observed animation of the patient and not to a preset schema. Careful planning can allow reduction of rhytides while maintaining movement, a trend that is increasingly popular with patients requesting a natural appearance.

#### Periocular

The lateral orbital wrinkles (crow's-feet) originate from movement of the orbicularis oculi muscle (with some help from the risorius and zygomaticus muscles), a muscle that encircles the eyes and functions to aid in eye closure. This sphincterlike muscle is broad, thin, and superficial, and wrinkles in this region develop from a combination of muscle activity (eye closing, facial expressions) and photoaging. The goal for treatment in this area should be to soften or improve wrinkles or help elevate the lateral eyebrow. Patients should be asked about their surgical history (blepharoplasty, laser resurfacing, chemical peels) and instructed to animate for assessment of line patterns and both static and dynamic eyebrow and cheek positions. Relatively low dosages of neurotoxins are directed into the dermal or subcutaneous plane along the outer orbital rim peripheral (1.5 cm from lateral canthus, which is 1-2 cm from orbital rim) to the lateral canthus (Figure 3). To minimize toxin diffusion and paralysis of neighboring muscles (levator labii superioris muscle), typical aliquots are distributed approximately 1 cm apart

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**Figure 3.** Injection sites for periocular rhytides: crow's feet.



**Figure 4.** Perioral injection sites: vertical lip lines.

and lateral to the outer canthus. The usual number of injections is 2 to 5 per side and the precise location of these points depends on pretreatment analysis, which takes into account the activity of the muscle and the orbital line patterns observed. Although a multipoint injection technique is more common, some clinicians have advocated a single-point injection technique ("wheal and mash") for localized lines. 16 In this case, 1 to 2 wheals of drug are injected and then massaged into the site to help distribute the neurotoxin diffusely across the orbicularis. Reducing the number of injection points, icing, and holding pressure during and after injections may help avoid ecchymosis, which is more common in this area than in the glabella. Duration of effect in this area usually is less than in the upper face and is dose dependent, with higher dosages yielding longer-lasting results. Patients also should be advised that rhytides radiating downward onto the cheek may not be improved with neurotoxin because they are a result of cheek movement. Attempts to include these rhytides in the treatment area by injecting more inferior and medial below the zygomatic arch near the zygomaticus major muscle will affect cheek position (cheek ptosis) and lip position (lip ptosis) and function, resulting in the inability to

smile effectively. Instead, combination with fillers and resurfacing techniques is often of benefit.<sup>22</sup>

For patients who desire more open eyes (increased scleral show), lower eye lateral rounding, or improvement of infraorbital rhytides, a small aliquot of toxin can be injected into the lower eyelid. 23,24 This site is contraindicated for patients with a history of symptomatic dry eye (keratoconjunctivitis sicca) because it can aggravate the condition. The lower eyelid can be treated by asking the patient to hold his or her head back and up, retracting the lid inferiorly, and injecting subdermally or subcutaneously at the midpupillary line, and then distributing the drug by rolling a cotton swab in the area.25 An additional 1 to 2 U can be injected halfway between the midpupillary line and the lateral canthus for a more rounded appearance, which may be particularly useful in Asian patients. Patients who desire eye opening should be treated with caution, as injections below the orbital rim are associated with increased risk of diplopia because of diffusion of neurotoxin into the extraocular muscles.14 Lid laxity should be evaluated with the snap-back test prior to injection to decrease the risk of developing ectropion or aggravating lower lid redundancy or bags.26

#### NEUROTOXIN UPDATE AND REVIEW





Figure 5. Injection sites for treatment of the depressor anguli oris (A). Injection site to treat the mentalis: peau d'orange chin (B).

#### MIDDLE AND LOWER FACE

#### Lips

Perioral rhytides are vertical lip wrinkles caused by the contraction of the orbicularis oris muscle. One to 2 U of Botox (total 4-10 U) or the equivalent Dysport evenly divided among each of the lip quadrants (4 sites) at the vermillion border may soften hyperfunctional lines and create upper lip fullness and eversion<sup>27,28</sup> (Figure 4). Patient selection and counseling are critical, as those who rely on their lips for their professions or hobbies (eg, musicians, singers, public speakers) may not be the best candidates. As well, many patients may have unrealistic expectations regarding the benefits of the treatment and should be counseled prior to treatment. It is suggested to start conservatively with low doses at a minimum number (4-6 units) of superficial symmetrical injections adjusted to the patterns of the lines and preference of the lip shape. Overtreatment in this area is not recommended because it may result in substantial dysfunction, such as difficulty in speech, eating or drinking, diminished proprioception, and an asymmetrical smile. Clinicians also should avoid treating more than 5 mm above the vermilion border, take care when treating the midline (Cupid's bow) of the upper lip to prevent a flattening effect, and avoid treating directly into the lip corners, which could result in paralysis of the depressor anguli oris muscle, resulting in drooling, drooping, or difficulty eating.<sup>29,30</sup>

Treatment of the depressor anguli oris muscles can lift the corners of the mouth and improve marionette lines, but only should be done by an experienced clinician. The depressor anguli oris can be located inferior to a point 1 cm lateral to the oral commissure; in some patients, this is visible during speaking and frowning as a dimple. There are 2 approaches to treating this region. Injections can be given directly into this area (10 mm lateral to the angle of the lips) or at the point where a line draws vertically downward would hit the level of the mandible (Figure 5A). Smaller volumes injected superficially and massaged laterally are preferred for the best results.

#### Mentalis Muscle

The dimpled chin (peau d'orange) is caused by the mentalis muscle, which originates on the mandible, covers the chin, and inserts below the lower lip. This muscle raises the chin and can cause baseline wrinkling or dimpling and protrusion of the lower lip, and expresses sadness, anger, disdain, or doubt.12,31 The wrinkling in this area is from a combination of constant animation, normal aging (loss of collagen and subcutaneous fat), or cumulative photodamage. One clinical trial demonstrated that Botox was an effective treatment for moderate rhytides of the mentalis for patients that exhibit strong dynamic, chin wrinkles.<sup>32</sup> One to 2 injection points can be used in this area, with a depot injection in the midline or 2 symmetrical lateral injections.<sup>29,33</sup> Pristine injection technique with a focus on small injection volumes and low dosages are of the utmost importance. Injections should not be too high, which can affect the orbicularis oris muscle leading to lower lip incompetence (drooling), or too lateral, which can affect the depressor labii and cause lower lip depression. Injections should be angled upward and massaged in a lateral direction (Figure 5B).

#### Nasalis Muscle

Contraction of the transverse portion of the nasalis muscle can result in "bunny lines," the dynamic horizontal rhytides that appear across the bridge of the nose and radiate downward. Rhytides in this area may appear in patients who regularly wrinkle or contract their nose during facial expression. A low-dosage, single, midline injection into the nasalis portion over the nasal bone is often all that is needed to soften bunny lines, but additional injections may be needed on either side of this injection to catch more radiating transverse lines. Injections should be kept superficial and high on the lateral nasal wall to avoid the levator labii superioris alaeque nasi and the levator labii superioris muscles and prevent lip ptosis. In predisposed patients, it is necessary



Figure 6. Typical injection points for the jawline and platysma.

to inject small aliquots of neurotoxin into the nasalis during glabellar treatment to avoid recruitment of this area after glabellar complex paralysis. The presence of bunny lines in the absence of glabellar frown lines often is sited as a telltale sign of toxin treatment, which may be disturbing to patients that want a natural effect. No placebo-controlled clinical trials have evaluated the use of any neurotoxin product in the treatment of this area.

#### Neck

Blitzer et al<sup>35,36</sup> were the first to report platysmal rejuvenation using botulinum toxin; since then, many clinicians have reported improvement of both platysmal bands and horizontal neck lines from neurotoxin treatment into the neck.<sup>37-40</sup> The platysma originates in the fascia of the upper chest and extends over the neck and up to the mandible interdigitating with the depressor labii, depressor anguli oris, and the mentalis muscles.<sup>41</sup> With aging and contraction (speaking, exercising, playing musical instruments), the platysma thickens, forming bands, horizontal lines, and depressions on the corners of the mouth, which all contribute to loss of definition in the neck.

A variety of techniques to treat this area have been reported in the literature, but most experts agree that the most suitable technique is to ask the patient to contract the platysma; the thickened band then is grasped by the nondominant hand and injections are given directly into the muscle belly equally spaced 1 to 2 cm apart down the course of the band from the jawline to the lower neck. 42,43 Multiple bands can be treated in a session and repeat injections can be performed with the anticipation of prolonged effects after subsequent treatments (Figure 6). Complications can include swelling, bruising, neck weakness, and headaches. Laryngeal muscle weakness, hoarseness, and dysphagia can occur at higher dosages, so each session should be limited to a few bands (2-4 bands) and no more than 75 to 100 U of total toxin when Botox is used. 10 Levy44 reported the use of botulinum toxin A for rejuvenation of the jawline in which up to 20 U of Botox was used along the jawline in multiple aliquots. He proposed this treatment gave the jawline more contour and provided a visual effect of a mini facelift. Nonetheless, neurotoxin treatments in the neck work best in younger patients with good skin elasticity and will not substitute for surgical procedures that work to correct major skin laxity. No placebocontrolled clinical trials have evaluated neurotoxins in this treatment area.

## **CONCLUSION**

The trend in the use of neurotoxin products for facial aesthetics is toward using the lowest dosage possible for natural, smooth, youthful appearances that are long lasting; thus, clinicians must have detailed knowledge of the facial anatomy and neurotoxin product characteristics, and must be able to individualize patient assessments for success. Adjunctive therapy with facial surgical procedures, cosmetic filling agents, lasers, light sources, and topical agents can enhance neurotoxin aesthetic treatment results. A topical preparation of botulinum toxin A requiring clinician application is being developed for facial aesthetics and ultimately may be an option for needle-phobic patients. The future of facial aesthetics is filled with many exciting advances, and neurotoxin products are at the forefront.

This is Part 2 of a 2-part series on neurotoxins by Drs. Waldorf and Emer. Part 1 can be found in the September 2010 issue of Cosmetic Dermatology®.

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